CORRELATION OF CD4 COUNT WITH CAROTID INTIMA

MEDIA THICKNESS IN HIV PATIENTS

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CHENNAI

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CERTIFICATE

This is to certify that the dissertation title **"CORRELATION OF CD4 COUNT WITH CAROTID INTIMA MEDIA THICKNESS IN HIV PATIENTS"** is the bonafide original work of **Dr. SIVA SHANMUGANATHAN. V.** in partial fulfilment of the requirements for M.D. Branch - I (General Medicine) Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in APRIL 2017. The Period of study was from April 2016 to September 2016.

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DECLARATION

I, **Dr. SIVA SHANMUGANATHAN V** declare that dissertation titled **"CORRELATION OF CD4 COUNT WITH CAROTID INTIMA MEDIA THICKNESS IN HIV PATIENTS "** is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during April 2016 to September 2016 under the guidance and supervision of my unit chief Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine – APRIL 2017.**

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CONTENT

INTRODUCTION

INTRODUCTION

HIV infection has been causing a pandemic all over the world and is still considered one of the most dreaded disease to be suffering from even in the advent of very effective antireteoviral therapy. Lots of research has been going on in this field. The virus is known to cause diseases of almost all systems and can cause protean manifestations that can vary from mild to life threatening complications.

HIV-infected individuals have a higher prevalence of cardiovascular disease, which has been demonstrated both using clinical end points and utilizing the high resolution ultrasound to assess carotid artery intima-media thickness(IMT) were carotid artery intima-media thickness has been used a surrogate marker for atherosclerosis**.**

The government efforts to control HIV by providing highly active anti-retroviral therapy (HAART) free of cost to all individuals will control the new incidence of tuberculosis as well. There has been tremendous outreach in providing various cART regimens to patients of different category according to their needs. WHO also started a campaign 3 by 5 in 2004 to make HAART available to resource limited areas.

HIV patients have increased risk of cardiovascular disease events. HIV-infected individuals may exhibit more rapid IMT progression in the carotid artery compared with uninfected individuals due to inflammatory state present in HIV infected .Low cd4 count has been identified as a risk factor but data has not been consistent as studies have not confirmed the reported associations of low CD4+ T-cell count with clinical or subclinical CVD .The aim of the study is to investigate the correlation between CD4 count and CAROTID INTIMA MEDIA THICKNESS as a marker of atherosclerosis in HIV patients

AIMS AND OBJECTIVES

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I. To investigate the correlation between CD4 count and CAROTID INTIMA MEDIA THICKNESS as a marker of atherosclerosis in HIV patients

II. To study the relationship between Carotid intima media thickness and the duration of antiretroviral therapy

REVIEW OF LITERATURE

REVIEW OF LITERATURE

1. SOURCE OF LITERATURE

The literature source for review of our study was taken from published studies describing the pattern of disease spread, pathogenesis, CD4 count and its relation to carotid intima media thickness (CIMT) . Priority was given to more recent studies and older studies were used when no other data is available. Articles published in English were only used. WHO site and Medline were the main electronic data used for the review of literature.

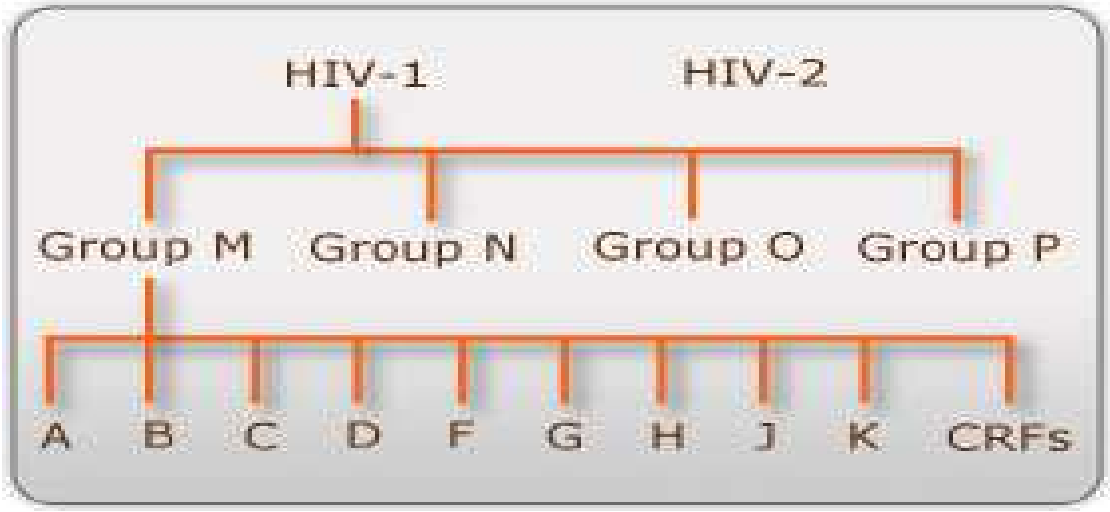
Indian studies were given priority and global scenario was used for comparison. Studies about atherosclerosis in HIV were appraised from few articles. The aim of selecting the literature review was to fill the gaps in knowledge regarding atherosclerosis in HIV. The main limitations were the lack of convincing studies from India regarding incidence of atherosclerosis in HIV patients and with regards to ART duration.

2 . INTRODUCTION

HIV or human immunodeficiency virus belongs to the family - human retroviridae and subfamily – lentiviruses. The virus is unique in its way because of its ability to convert its RNA genome into DNA to get incorporated into host genome by the enzyme reverse transcriptase. The Acquired immunodeficiency syndrome (AIDS) was first described in United States in 1981 in homosexual men who presented with Kaposi sarcoma and Pneumocystis jiroveci. The causative virus was isolated in 1983. ELISA TEST was developed to detect the antibodies in 1985. Since then there has been enormous turnabout of events and expanding information and paradigm shift in treatment approaches in HIV patients.[1]

Phylogenetic analysis of certain earlier isolates show that HIV 1 was prevalent even before the AIDS pandemic. HIV 1 the common infectious agent is further sub classified into M, N and O. M type causes the global burden of HIV. It is further subdivided into A-D, F-H and K subgroups. HIV 2 is commonly found in west Africa. HIV 1 virus has supposedly come from chimpanzee and probably gorilla whereas HIV 2 is believed to be originated from the mangabeys. The worldwide pandemic of AIDS is caused by M group HIV 1 viruses. Other group viruses only cause a localized epidemics. [2]

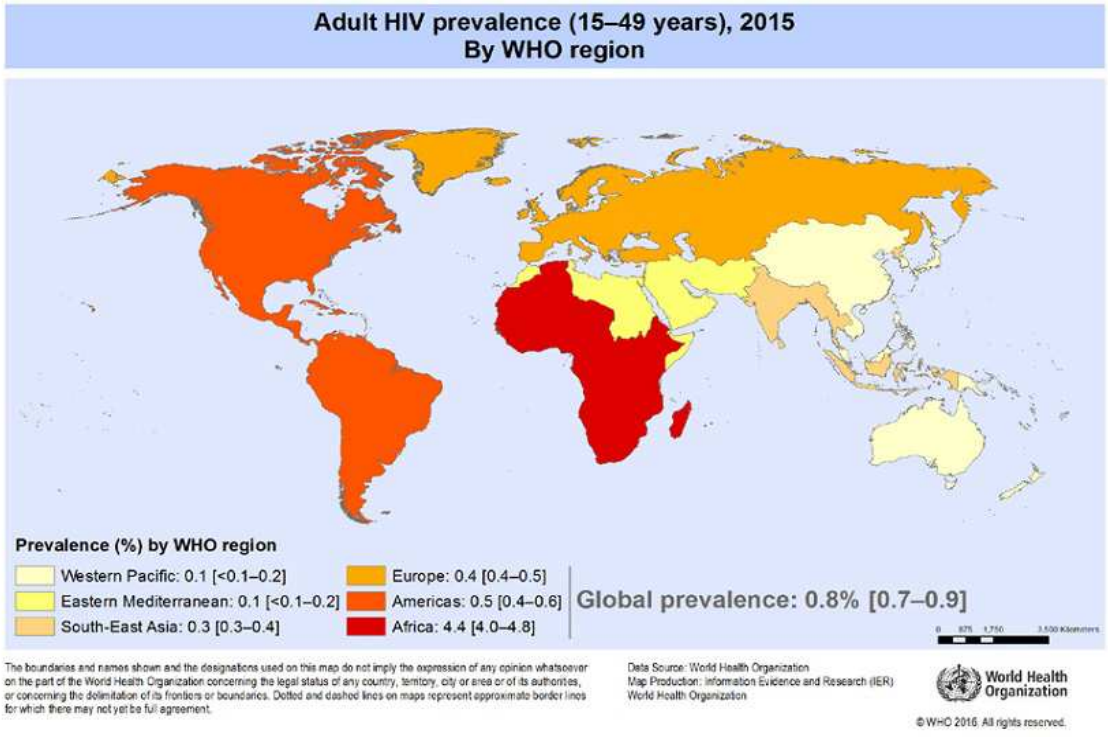
Subtype C is responsible for almost half of the HIV-1 infections worldwide and is predominantly found in southern Africa and India . Subtype B predominates in North America, western as well as central part of Europe, the Caribbean islands, and Latin America.[5]



3. EPIDEMIOLOGY

The present global HIV epidemic is quite different from that first recognized among a small number of homosexual men as early as the 1981. The epidemic has reached almost every country all over the world and nearly all populations throughout the world. The spread of the HIV pandemic has been particularly alarming in resource-limited countries, especially the sub-Saharan part of Africa and southeast Asia, but continues to threaten other population in eastern part of the Europe, Latin America, and the Caribbean islands.[3,4]

36.7 million of ad ults and children all over the world were diagnosed with HIV/AIDS and 2.1 million people had been infected newly with HIV in the year of 2015. About 1.1 million people died of AIDS in the same year. The global prevalence rate was 0.8 percent worldwide in patients of age 15 – 50 years . Incidence of new HIV viral infections represents a decline of 38 percent in 2015 when compared to 2001.

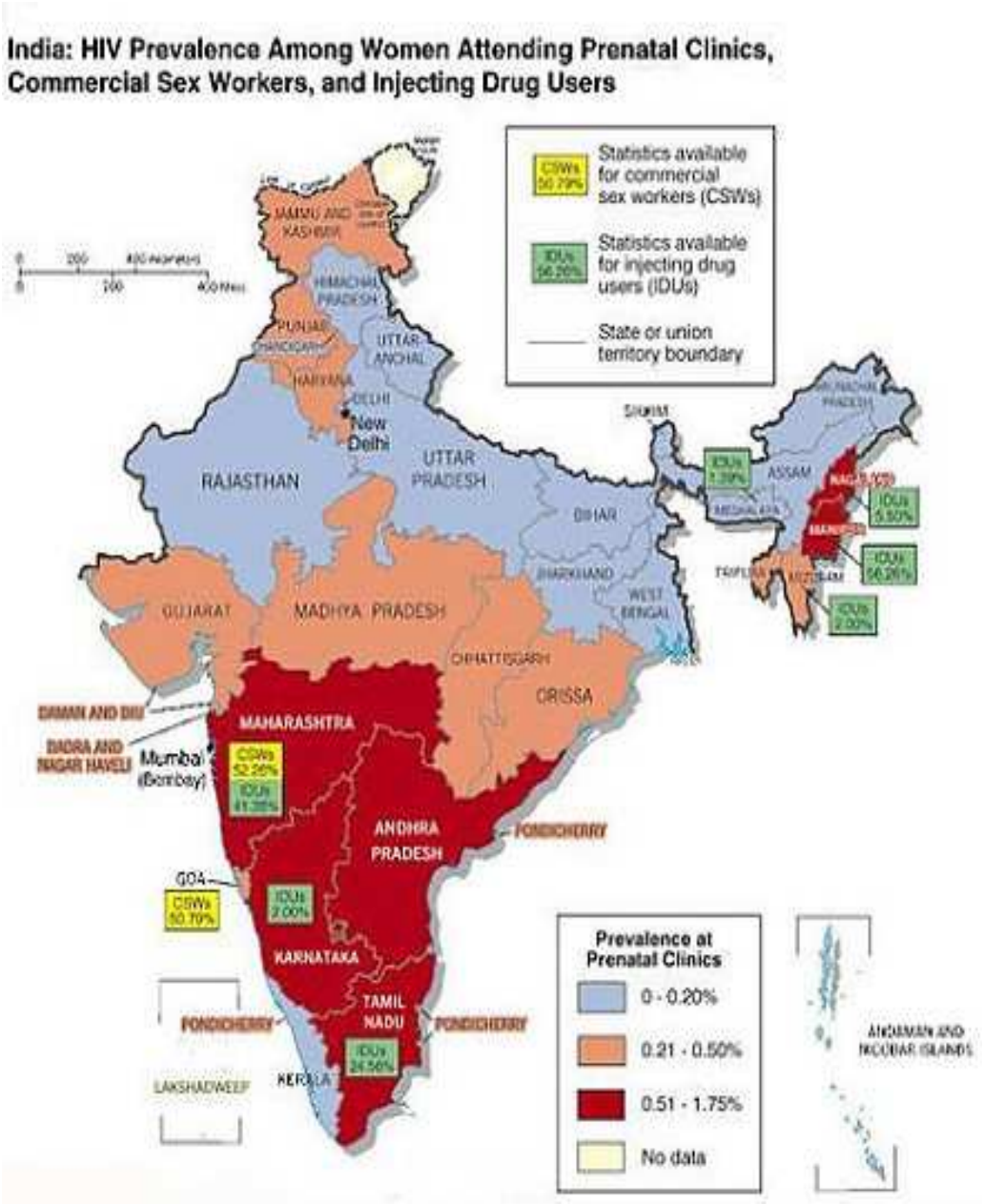


Children constitute a majority of persons who are infected and about 3.3 million children are HIV positive. Seventy five percent of the HIV infected individuals live in AFRICA particularly sub sahara region.

The prevalaence rate varies according to the region ranging from less than 0.1 percent in middle east to 5 percent in African countries.

HIV has occurred in various countries as cycles and the most affected region is sub Saharan Africa . The seroprevalence rate is very high in the rank of more than 10 % of the population . Heterosexual mode of transmission is most common in Africa.

Even though overall prevalence rates of HIV load in Asia is slightly low, that is approximately 0.6 percent , this still results in a substantial burden of disease, as the region accounts for about half of the the world's population. Of the estimated 5.1 million HIV-infected persons living in Asia, nearly half live in India. Approximately 85 percent of HIV transmission in India is postulated to be through sexual transmission. Barriers to control of the epidemic is due to fact that acceptance of condoms is very less and enforcing laws that make homosexuality illegal and punishable by imprisonment. MSM prevalence rate in India is estimated to be 18 percent which is higher when compared to neighbouring countries.[6 7]



In central asia 1 million people had HIV and The Russian federation and Ukraine had majority of the cases. In South America 2 million had HIV and in that Brazil had highest number of HIV patients. But incidence there has reduced to due to successful prevention efforts. In north America ,2.5 million people were affected and men who had sex with men constituted the majority of the patients. [8]

4.TRANSMISSION

Four distinct risk groups have been identified in the category of non-occupational exposure to HIV infection, including men who have sex with men (MSM), male and female heterosexuals, injection drug users (IDUs), and also persons exposed to HIV through other routes of transmission like human bites .[9, 10]

Worldwide sexual transmission constitutes the majority of the cases occurring due to viral transmission. Anal mucosa being more fragile leads on to more infection rates compared to infections in the vaginal mucosa. And also to be noted is receptive sex suffer from more transmission rates than insertive sex which in turn supports the fact that femalehavemuch higher rates of infection than men. The female to male transmission rate was 0.04% whereas the male to female transmission rate was found to be 0.08% .

Anal mucosa gets infected by the virus either by direct inoculation or by infection of the langerhans cells presnt in mucosa . HIV is demonstrated to be present both cell free as well as within mononuclear cells. Presense of other sexually transmitted infections also increase the rate of viral infection. So treating other STIs in addition reduces incidence of acquiring HIV Iinfection[12]. Circumcision in men is protective against acquiring infection because the foreskin which

provides moist environment for microbes as well as high number of langerhans cell is got rid of in circumscribed men. Rate of transmission is more in early stages of infection and also in advanced stages which reinforces the fact that HIV RNA load is directly proportional to rates of transmission.[11]

Male to female transmission is more effective because of prolonged exposure of vagina to seminal secretions as compared to men genitalia where the female secretion contact time is less. Oral contraceptive pills use increases infection as cervica mucosa is vulnerable. Adolescent girls have exposed columnar epithelium in cervix which favours infection.

Type of exposure (from a source known to be HIV positive)	Risk of HIV transmission per exposure
Accidental needlestick injury	0.2%-0.4%
Mucosal membrane exposure	0.1%
Receptive oral sex	From 0 to 0.04%
Insertive vaginal sex	≤ 0.1%
Insertive anal sex	≤ 0.1%
Receptive vaginal sex	0.01%-0.15 %
Receptive anal sex	≤ 3%
IDUs sharing needle	0.7%
Transfusion	90-100%

Transmission through IDU or injection drug users occurs when sharing needles, cotton, syringes. They can infect by not only intravenous route but also subcutaneous and muscular route as well . The per act risk of transmission is about 0.58%

The risk of transmission is less with other bodily fluids or secretions. In case of saliva it has HIV specific immunoglobulins as well as soluble factors in saliva like SLPI (secretory leucocyte protease inhibitor) .

In case of mother to child transmission it can occur during antenatal period , labour period ,and breast feeding . in this highest share is in lobour period when upto 65 % transmission occurs. The rate of transmission is about 30 % in underdeveloped countries . Risk Factors for increased transmission includes HLA mismatch , prolonged ruptured membranes , chorioamnionitis , episiotomy and other invasive procedures

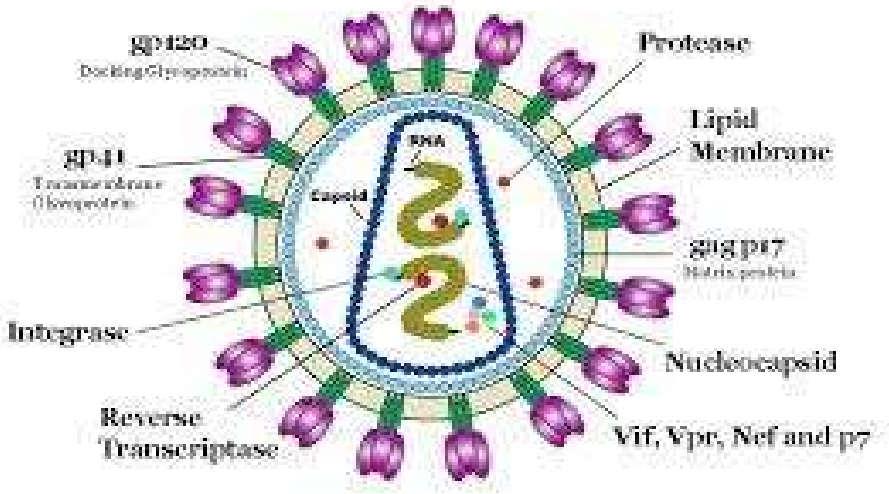
In breastfeeding women , mastitis , high viral load , HIV present in milk , low CD 4 counts all favor infection of the baby. Early c ART and cesarean section all decreases incidence of infection to child.

Occupational exposure to health care workers constitutes about 1000 cases per year . Rates of transmission for needle injury is 0.3% and in case of mucous membrane it is 0.09%. Non intact skin exposure is less

compared to mucous membrane . Risk factors for infection include deep injury ,prolonged exposure , big bore needle ,large quantity of blood ,advanced stages of AIDS . Early instituition of PEP (POST – EXPOSURE PROPHYLAXIS) has very much reduced infection rates if given within 24 hours of exposure . other potential infectious fluids include cerebrospinal fluid , semen , vaginal secretions , pleural fluid , pericardial fluid , amniotic fluid .

5.VIRUS STRUCTURE

The virus has a diameter of 100-120 nanometer with a spherical morphology. It has a truncated core with a lipid core. The viral core contains 2 copies of single stranded RNA, along with the enzymes protease, integrase and reverse transcriptase. The viral genome is 9.2 kilo base pairs long and contains 3 structural, 2 envelope and 3 genes for enzymes. It is a single- stranded and positive sense RNA. Their ends are covered by polyadenylated caps which prevents it from enzyme degradation. There is an element called tyrosine RNA which acts as a primer of viral RNA



HIV-1 virus consists of two copies of non-covalently linked and, positive-sense , unspliced and single-stranded RNA which is surrounded by a conical capsid composed of the virus protein called as p24, which is typical of lentiviruse family . The RNA component is 9749 nucleotides long and bears a 5’ cap (Gppp), a 3’ poly(A) tail. The RNA has many open reading frames (ORFs). Viral structural proteins are encoded by long ORFs, whereas smaller ORFs encode regulators of the viral life cycle that is attachment, replication, membrane fusion, and assembly .

HIV GENOME

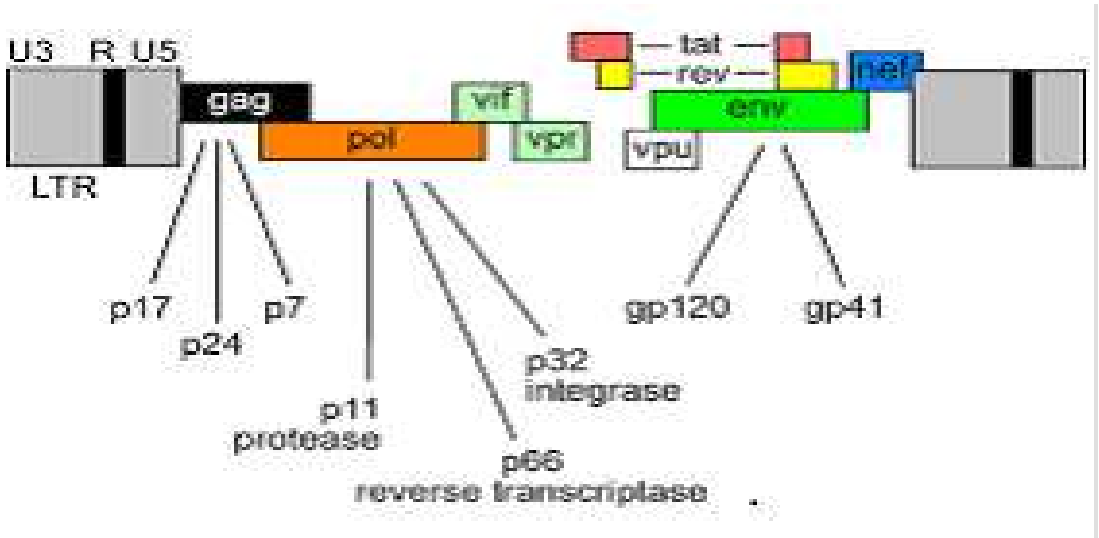
The Human immunodeficiency virus contains the genes called the regulatory genes. These help the virus to produce proteins and help the virus from infection and replication.

TAT gene –

(Tran's activator of transcription) ie p14 is a regulatory gene which is encoded by 2 different exons. It codes for a protein which is 102 Amino acid long which acts through TAT receptor binding which activates viral transcription. When it is shed into circulation, there is a chance of development of antibody to this protein. It however induces apoptosis of both CD4 cells which are infected and those which are not infected. It can act as a neurotoxin, which is shown in vitro experiments. Therefore it enhances RNA pol elongation of viral genome.

REV gene–

It is another regulatory gene which forms an essential accessory protein the function of which is to transport mRNA. Rev dependent RNA transport is important for early and late phases of viral replication



VIF gene –

Also known as the viral infectivity factor . It produces a 23 kilo Dalton protein found in the cytoplasm. It helps the virus to infect cells which contain CD4 receptors. The mechanism of action is less clear. Thought to overcome inhibitory effects of APOBEC3 preventing viral DNA degradation. The significance of Vif gene is the viruses with no Vif gene infect other cells at least 25 times slower than other viruses.

NEF gene –

Negative factor, produces a 27 kiloDalton protein. It helps in downregulation of the receptor expression and enhances infectivity of the virus. Nef Phenotypes of the viruses are present but not understood to a large extent.

VPU gene –

Viral protein U, It produces a protein which is 81 amino acids long. It is a membrane protein which also encodes envelope and controlled by Rev. It helps in release of virus from plasma membrane of infected cell and degrades the CD4+ cells in the endoplasmic reticulum.

VPR gene –

Viral protein R, produces a protein which is 96 amino acids long one more protein 14kDa responsible for G2 phase cell cycle arrest . This will indirectly improve viral replication by increasing transcription from LTR. Vpr expression causes breaks in the structure of nuclear lamin, which will weaken nuclear envelope and intrudes with DNA synthesis thus cause cell cycle arrest prior to mitosis. It also supports infection of non-dividing cells, mostly macrophages. Vpr also functions to connect the pre-integration complex along with the cellular nuclear import-machinery.

Structural proteins are encoded by three genes called as gag , pol, env . Gag encodes for the proteins that will form the core including the p24; Pol encodes the enzymes responsible for protease that is responsible for processing of viral proteins, reverse transcriptase ,and integrase ; and Env encodes the envelope proteins.

However, HIV-1 is much more complex than other retroviruses , especially that of the nonprimates, in that it also contains at least six other genes t(rev,tat, vif,nef, vpr, and vpu), which will code for proteins that is needed for the modifying of the host cell to enhance virus growth . LTRs or long terminal repeats has the regulatory genes that is involved in gene expression .The major difference between HIV 1 and HIV 2 is the fact

that HIV 2 does not have vpu gene and has a vpx gene not contained in HIV 1.

6.HIV REPLICATION CYCLE

The replication cycle begins when the gp 120 binds via the V1 region to the CD4 molecule. It is present mainly on the CD4 subset of lymphocytes and also on the surface of monocytes or macrophages , dendritic or Langerhans cells. After binding to CD4, gp120 protein undergoes a conformational change that cause the binding to one of two major co-receptors. CCR5 and CXCR4 are two major co-receptors for HIV-1.

Both receptors belong to 7-transmembrane domain G protein–coupled receptors (GPCR) family, and the use of these receptors by the virus for entry into the host cell is an very important determinant for the tropism of the hiv virus. Certain dendritic cells (DCs) will express a variety of C-type lectin receptors on their surface, for example ,DC-SIGN which binds with the HIV gp120 envelope protein, allowing DCs to facilitate virus infection to CD4+ T cells. Following binding of the gp120 to the CD4+ molecule along with the above mentioned conformational change in the viral envelope gp120, fusion with the host plasma cell membrane occurs via the newly exposed gp41 . This helps in penetrating

the plasma membrane of the target cell and then coiling upon itself to bring the viarl particle and target cell together.[16]

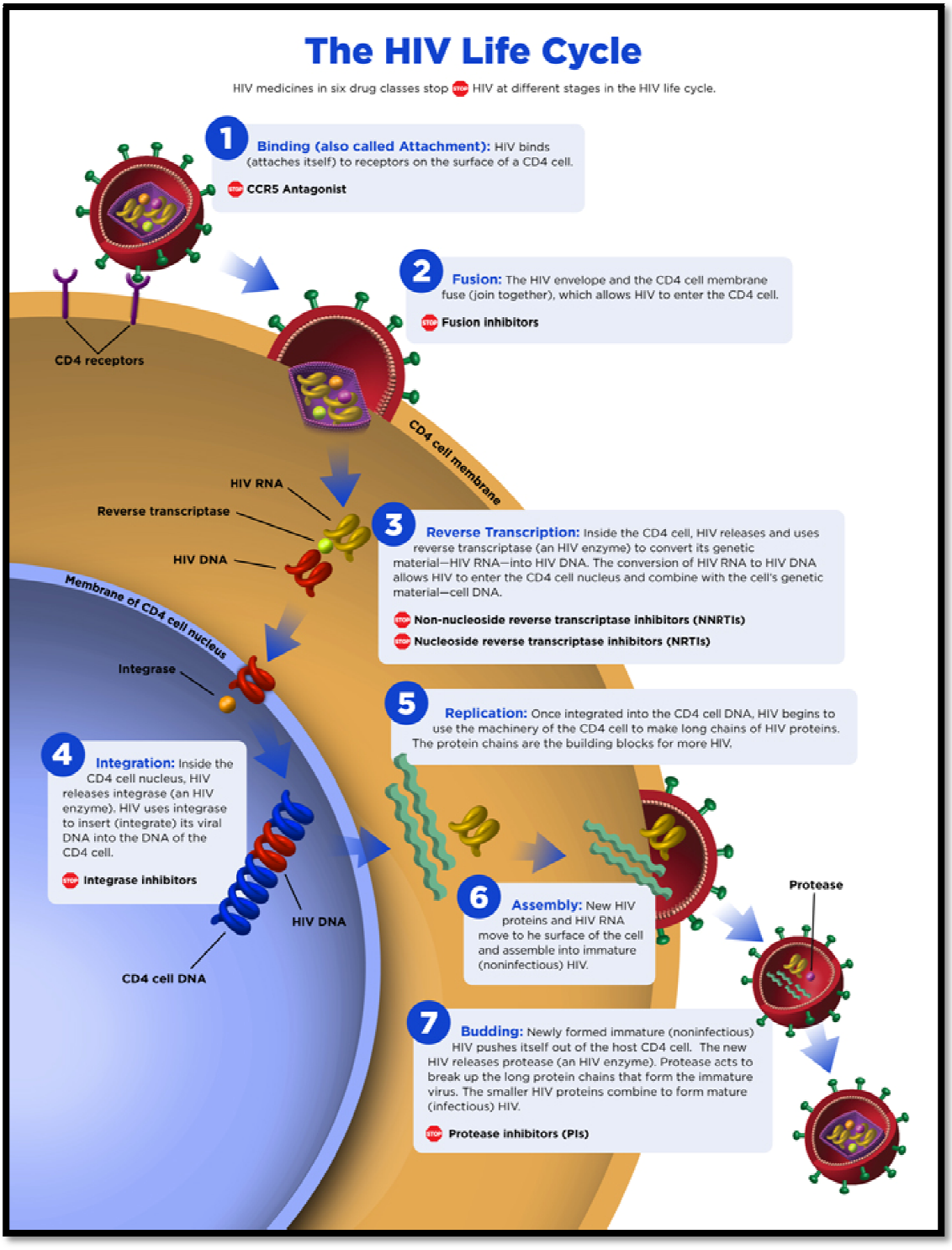
Following fusion of virus and host cell, uncoating of the capsid protein shell is started that facilitates reverse transcription and leads to the subsequent formation of the preintegration complex, composed of viral RNA, enzymes, and accessory proteins and surrounded by capsid proteins . As the preintegration complex transports across cytoplasm reverse transcriptase converts RNA to DNA.

When the cell is activated , the viral DNA can enter inside nucleus through the nuclear pore and is transported from the cytoplasm to the nucleus, where it is integrated into the host cell genome through the action of important enzyme called as integrase . HIV provirus (DNA) integrates into the nuclear DNA preferentially within introns rather than exons of genes and hotspots within specific region. This provirus may remain transcriptionally inactive or it may lead on to varying levels of gene expression, up to the level of even active production of virus.[14 15]

Activation of host cell is needed for transcription of the proviral DNA that was previously integrated into host DNA . After transcription the mRNA is translated into various structural proteins. Infectious virus particle is formed by assembly of various proteins ,enzymes, RNA at the

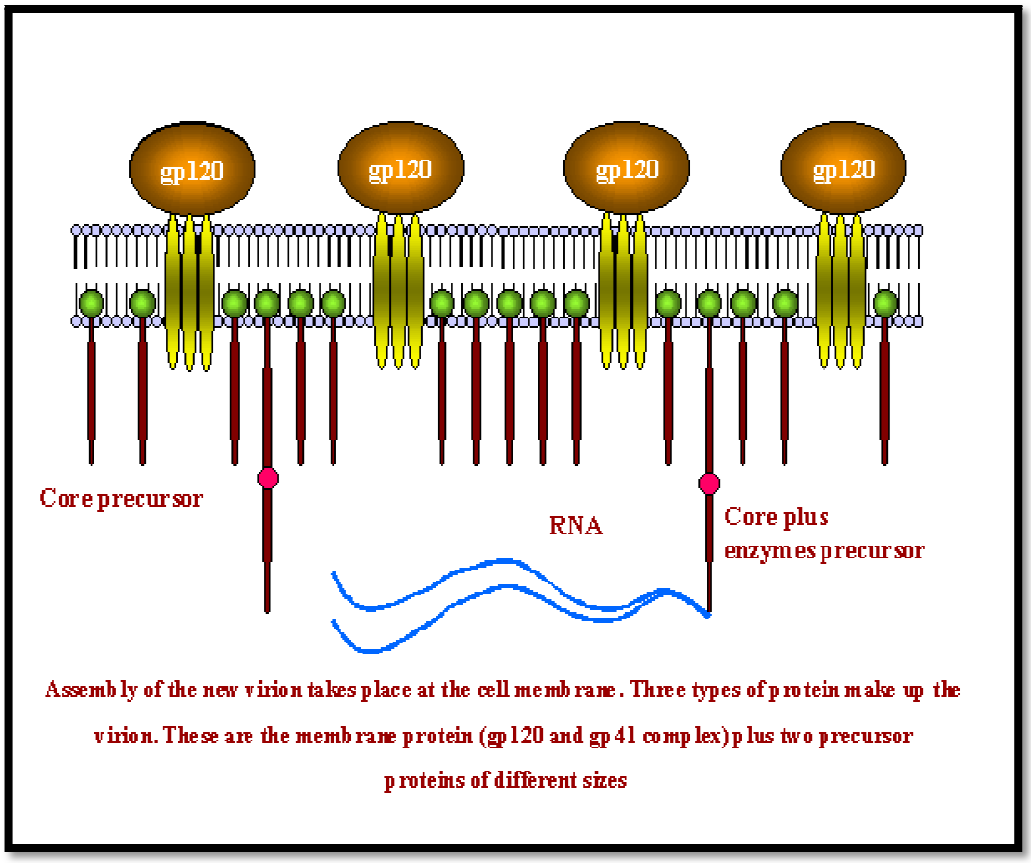
outer membrane of cells. Budding of virus through lipid bilayer is when the core acquires the external envelope. The protease enzyme causes breakdown of gag pol precursor to yield mature virus particle.

There are number of host cell factors that help prevent viral replication for example, tetherin interferes with virion detachment ,TRIM5-a and APOBEC3 family of proteins also inhibits viral progression in the cytoplasm. The beauty of HIV virus lies in the fact that the virus is able overcome these factors and replicate.[14]



The reverse transcriptase enzyme has no proofreading activity and accumulates mutation at a rate of $10^{4} - 10^{6}$ and each time it replicates it

destroys nearly 2 billion CD4 cells per day. The half-life of a HIV virus is six to eight hours approximately



Assembly of the new virion takes place at the cell membrane. Three types of protein make up the virion. These are the membrane protein (gp120 and gp41 complex) plus two precursor proteins of different sizes

7.CLINICAL FEATURES

The Human immunodeficiency virus can have variety of manifestations, wherin the symtomatology can range from completely asymptomatic patients to completely debilitated patients. Patients can be asymptomatic without any significant symptoms for ranging from eight to ten years. This is because of the long incubation period of HIV. As HIV advances depleting the CD4 cells, the first manifestations may be the initial Opportunistic infections. These diseases are not very common in any normal or immunocompetent individual.

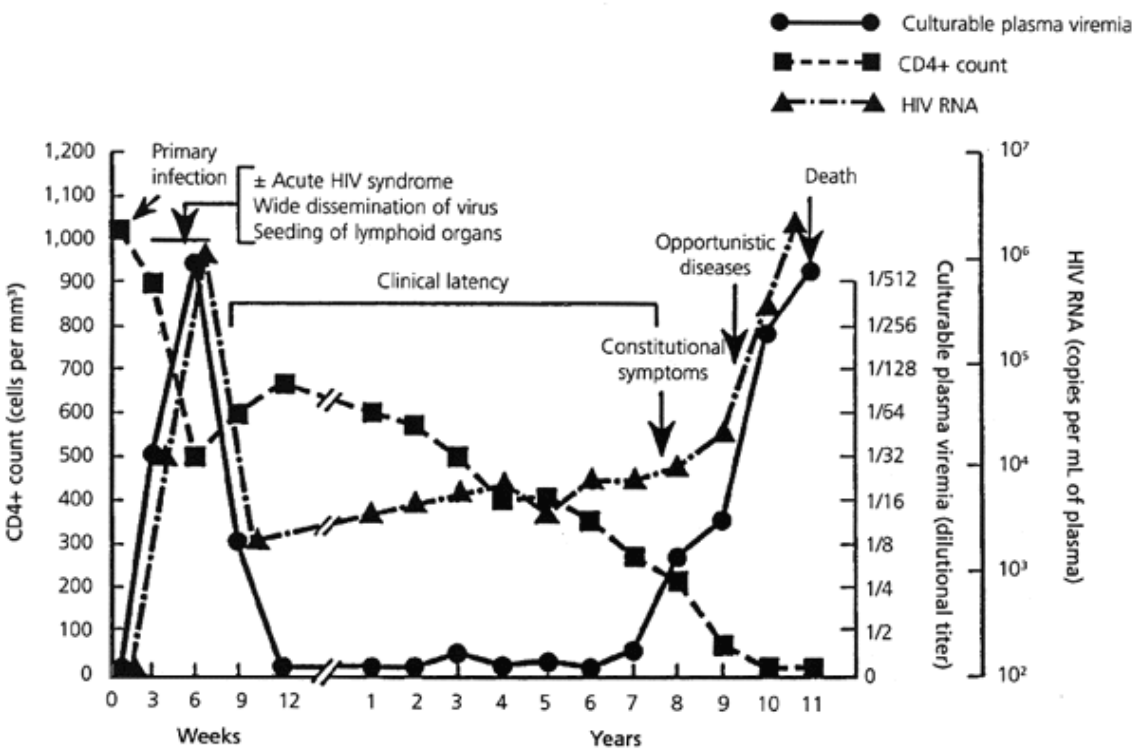
Human immunodeficiency virus per se can cause severe debilitation and death. Opportunistic infections includes both infective and cancerous conditions. The better term to use would be opportunistic conditions. [15]

The infections seen in HIV infection are protean that they include an entire spectrum.. They can be classified as bacterial, viral, parasitic and fungal. The frequency of opportunistic infections are dependent on the geographic conditions. Overall Tuberculosis is the commonest opportunistic infections. Other common infections[16]

CLINICAL STAGE	SYMPTOMS
Stage 1	Asymptomatic Lymphadenopathy
Stage 2	Hepatosplenomegaly Papular pruritic eruptions Fungal nail infection Angular chelitis Lineal gingival erythema Extensive wart virus infection Extensive molluscum contagiosum Recurrent oral ulcerations Parotid enlargement Herpes zoster Chronic upper respiratory tract infections
Stage 3	Malnutrition Persistent diarrhea Persistent fever Persistent oral cordiasis Oral hairy leukoplakia Necrotizing ulcerative gingivitis or periodontisis Lymph node tuberculosis Pulmonary tuberculosis Recurrent bacterial pneumonia Lymphoid interstistial pneumonitis Lung disease (such as brochiectasis) Anemia or chronic thrmobocytopaenia
Stage 4	Severe wasting, stunting, or malnutrition Pneumocystis pneumonia Severe bacterial infections Chronic herpes simplex infection Esophageal candidiasis Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection Central nervous system toxoplasmosis Extrapulmonary cryptococcosis (including meningitis) HIV encephalopathy Disseminated endemic mycosis Disseminated non-tuberculous mycobacterial infection Chronic cryptosporidiosis (with diarrhoed) Chronic isosporiasis Cerebral or B-cell non-Hodgkin lymphoma Progressive multifocal leukoencephalopathy Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

seen are pneumocystis jirovecii, CNS infections which are common are Tuberculoma, tuberculous meningitis and Primary CNS lymphoma. Visceral leishmania are common in some areas of Bihar. According to degree of immunosuppression clinical phases can be differentiated into primary, early, intermediate and advanced HIV infection.[17]

Active replication occurs throughout the process of disease along with continued immunological deterioration .Except for the rare virus controllers the disease will keep on progressing even in the latent stages of the disease .[17]

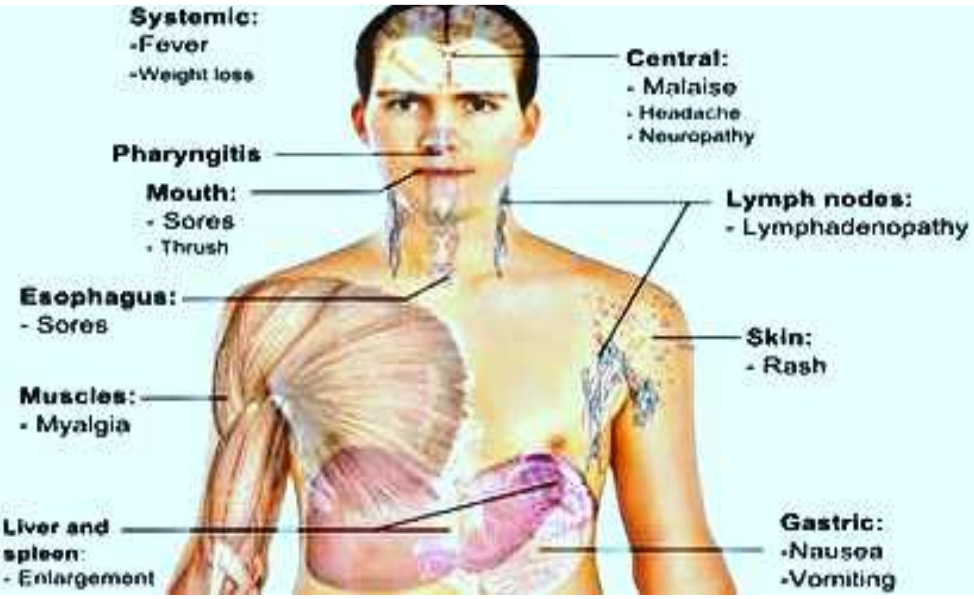


Acute HIV infection

During this phase patients are extremely infectious. This is of no clinical value. Patient usually doesn't come to hospital at this stage as there is no significant clinical deterioration.

The initial presentation of HIV infection is similar to an ordinary viral infection. Fever, skin rash, headache and diarrhea are the most common presentations. As soon as viral replication occurs, there is a

drastic fall in CD4 cell count and at the same time the viral load increases rapidly and forms a set point.[18]



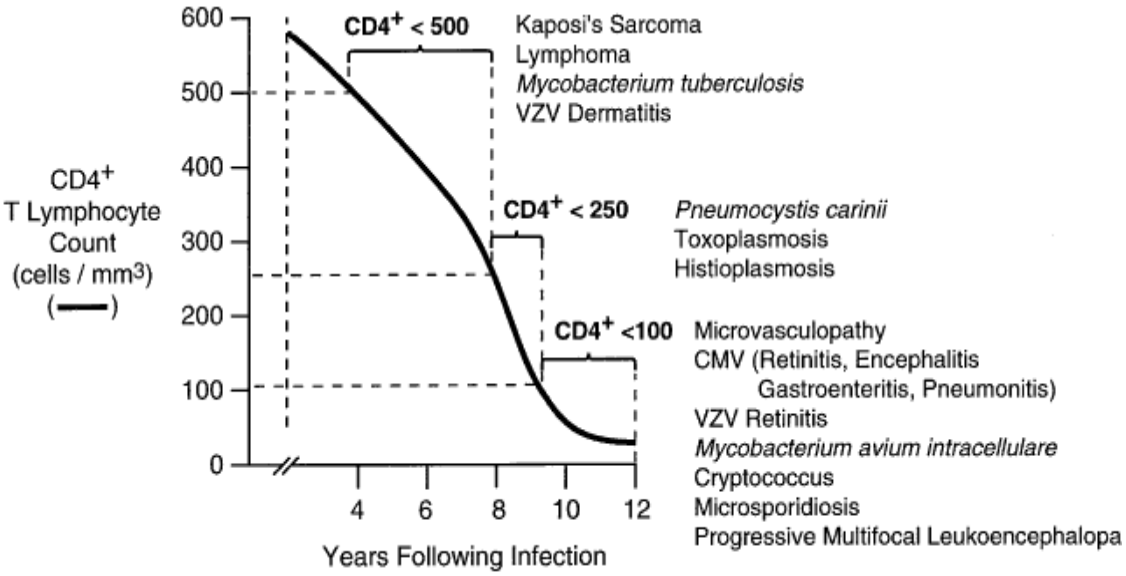
The acute clinical syndrome lasts for 3 to 6 weeks. If at all there is a symptomatic seroconversion patient is prone for accelerated disease progression. Severity is more by sexual route of transmission than by injection drug users .there is a reversal of the CD4+/CD8+ ratio such that CD4+ cells are reduced and the CD8+ cells are increased. 10% of them can have a fulminent course. The primary infection is followed a prolonged period of clinical latency.[18]

GENERAL	SKIN	CNS	GIT	LUNG
Fever Pharyngitis Enlarged lymph nodes Arthalgia Myalgia Fatigability Loss of appetite /weight	Erythematous rashes Mucocutaneous ulceration Alopecia	Photophobia Headache Kernig's sign Peripheral neuropathy GBS Cognitive disorders	Candidiasis Nausea/ vomiting Diarrhea	Dry Cough

Patients with CD4 count <500 cells/cubic millimeter are considered usually more to be vulnerable to autoimmune diseases and neurological illness such as diseases like Bell's palsy, acute inflammatory demyelinating polyneuropathy or guillain barre syndrome, chronic inflammatory demyelinating polyneuropathy and Bell's palsy have seemed to occur.

Primary infection lead to acute syndrome in 3 to 6 weeks when there is viremia and retrafficking of lymphocytes . After the acute syndrome , immune response to HIV occurs in 1 week to 3 months when

the plasma viremia is controlled as well as a chronic latent infection is established in the lymphoid tissue which subsequently lead to clinical latency.



ASYMPTOMATIC STAGE

This stage progresses for a median period of about 10 years that is from acute infection to the clinically overt immunocompromised manifestations. Patients who have very high levels of HIV RNA levels will progress to symptomatic disease very quickly when compared to others.

When the level of RNA copies is less than 50 copies / ml then those patients are called as elite non – progressors as they may not have a drastic fall in CD4+ counts when compared to the usually delirious

progressive course in other patients. The rate of decline of immunological status is estimated to be around 50 / microliters per year.[18]

SYMPTOMATIC STAGE

The clinical stage of AIDS is made in patients who are 6 years and more and with CD4+ counts less than 200 per microliter and anyone who has HIV associated diseases.[19]

This stage is dictated by clinical opportunistic conditions like pneumocystis jiroveci , mycobacteria , cytomegalovirus and many other organisms that seldom cause diseases in immunocompromised individuals. In addition to mortality due to AIDS defining illness that accounts for less than 50% of deaths in HIV patients non – AIDS defining illnesses like cardiovascular events ,malignancies and liver diseases accounts for about 15% each for the deaths in HIV patients.

In general, it should be emhasized that a key element in the treatment of complications of HIV infection, even if they are primary or secondary, is to aim for good control of HIV virus replication through the use of antiretroviral therapy and starting primary and secondary prophylaxis for opportunistic infections as and when needed. This approach has indeed changed the lives of millions of people suffering from this disease.[20]

8.LABORATORY DIAGNOSIS

Testing is taken from a source which is meant for the State government. It is offered to all people who approach the centers counselling called ICTC. The centers follows the national AIDS program algorithm. The first guidelines were given in 1989 for the diagnosis of HIV by the Centre of disease Control.

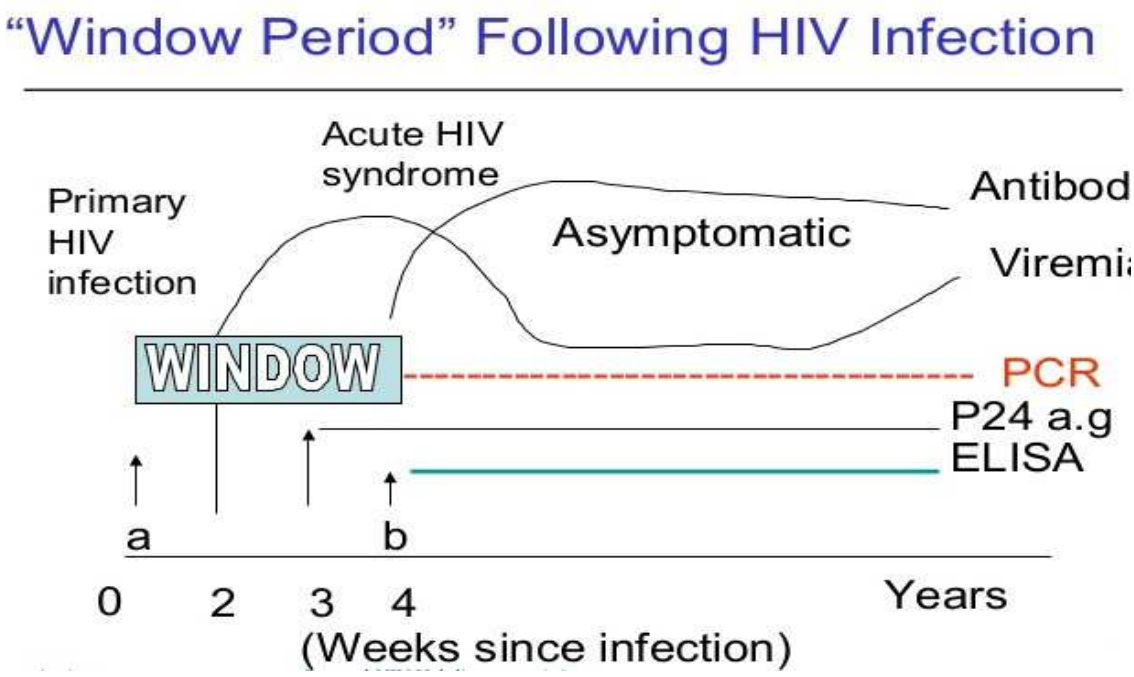
Blood screening started in march 1985.They also started testing for HIV 2 but was not useful for our country. This was started in the year 1992. The most recent international update regarding this was started in the year 2014. The updates include tests for HIV antigens and newer antibodies. HIV nucleic acid tests are included specially. This is to prevent the people who may be in window period, in an area of high prevalence, this is very important as this percentage might contribute to a huge amount of people[21]

The rationale behind testing for HIV infection is as follows. After viral infection occurs , first antigenemia is observed. It is only after 3 to 8 weeks that patient will start developing antibodies. Antibodies of IgM and IgG are produced subsequently. The period before the production of antibody where only the antigen persists is called Window period. The first antigens to rise are the protein products of p55 and p24 that are actually products of the gag gene. P24 levels continue to rise along with

concomitant progression of the disease to AIDS. Antibodies will however persist throughout infection.

The diagnostic ability of tests have improved so much such that detection of window period has reduced from 22 days for antibody tesing to 16 days for p24 antigen testing to 12 days with nucleic acid testing (NAT).

The standard screening tests include enzyme immunoassay (EIA) with a sensitivity of 99.5%. the fourth generation EIA combine combine antibodies detection along with p 24 antigen detection . The tests are said to be either positive or indeterminate or negative. False positive results occur in pregnancy ,blood transfusions previously, influenza vaccination, acute viral infection ,hepatic disease ,transplantation. [22]



Those who test positive are to undergo a confirmatory testing whereby Western blot is widely accepted. When antibodies to all the gene products namely gag , pol, env is all present it is a conclusive test then . The FDA approved positive test for Western blot is if two of the following three antibodies to gp41, p24 ,gp120/160 is all present. If at all the test turns out to be indeterminate the test is repeated after a month. Also other tests like HIV-RNA PCR or p24 capture assay can be done.

If a person tests positive for enzyme immunoassay that is done twice and turned out to be positive a third confirmatory test like western blot is done to confirm the diagnosis. [22]

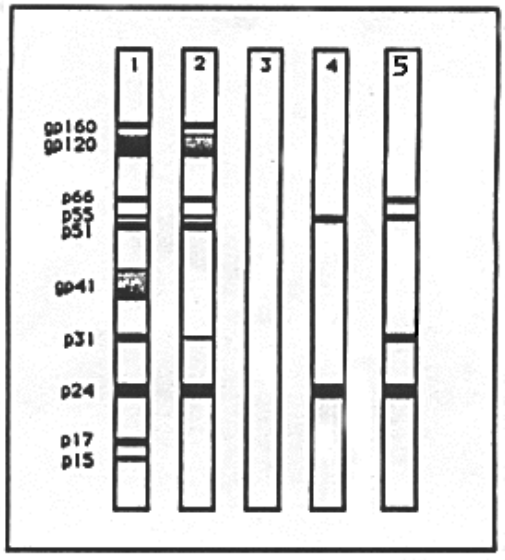


Figure:

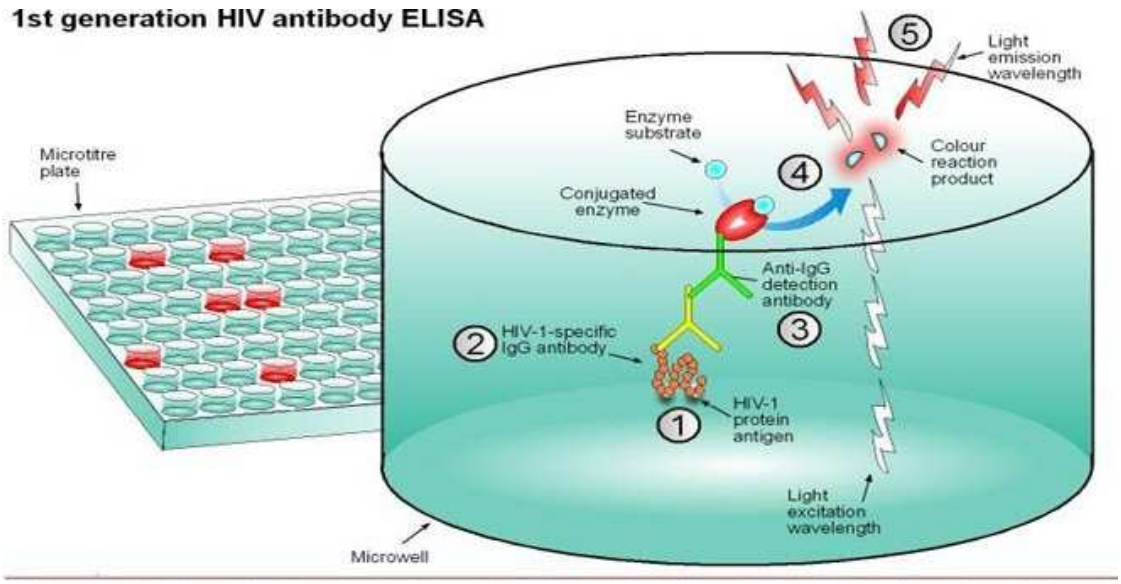
Examples of reactions by an HIV-1 Western blot:

1. Positive control (strong)
2. Positive control (weak)
3. Negative control
4. Indeterminate profile
5. Indeterminate profile (highly suggestive)

Next step if the western blot test turnss negative , HIV -2 is tested for. If the test is indeterminate repeat the test within 4 to 6 weeks. There are certain rapid tests like oraquick rapid HIV 1 antibody test and home-access HIV-1 test system. These can provide results in 1 - 60 min. It has a sensitivity and specificity of 99%

The p24 capture assay is very useful to detect acute HIV syndrome because of the fact that lots of antigen is present prior to immunological development of antibodies. The fourth generation assays that detect both antigen and antibody have replaced the p24 capture assay. Four assays are available for this of which RT – PCR Is well accepted test. The RNA detection tests have a sensitivity of 50 – 1800 copies per milliliter of blood. As they tests are highly sensitive some false positive results do occur. For this reason it's the enzyme immunoassay and western blot that is still the gold standard.[22]

RT PCR is used for finding out drug resistance, prognosis, in patints where serology testing is not proper (like in hypogamma globulinemia and advanced AIDS) and also only when the standard serological testing has not produced a confirmed result.



9.CD4 COUNT

The core brunt of the HIV infection and the primary lesion will be involving the CD4+ CELLS. Both a qualitative as well as a quantitative defect occurs proving the fct that these group of cells are very important in immune regulation. Even when the count is normal there can be a qualitative dysfunction of these cells that can demonstrated. In the GALT the CD4+ T_H1 cells are affected first which are the cells that maintain the mucosal defence mechanism and these cells do not recover even after prolonged antiretroviral therapy. In the lymph nodes , TF_H cells are infected but in contrast these cells will increase in number more so in patients who are viremic. The CD4+ cells that produce IL – 2 are depleted much earlier than compared the cells which will produce IFN .

The CD4+cells also expree co stimulatory molecules such as CD28 which is important for early activation. But in HIV infected cells this is not expressed instead late markers of activation like HLA-DR,CD45 and CD38 are expressed.[23]

The T- regulatory cells or the t-regs is important in regulating the aberrant immune activation that facilitates the viral infection. The CD4 is important for the fact that it is by this receptor the gp120 binds along with co stimulatory molecules CXCR4 and CCR5 which facilitates in virus entry and replication.

The CD4 cell count becomes resistant to antiretroviral therapy after a certain stage ,that is the counts will not rise even after therapy . This is because of the destruction of the thymic precursor cells and also destruption the the lymph node micro environment. It is also found that IL -7 is increased in level because the respective receptor for it, that is, CD127 is damaged leading to reduced use of the cytokine and further increase in its levels.

The CD4+ T cell count is a laboratory test that is widely accepted as the reliable indicator of the immediate status of immunological competence of the patient with HIV disease. The CD4+ count can be determined either directly or it can be calculated as the product of percentage of CD4+ T cells and the total lymphocyte count . The CD4

cells percentage can be counted by flow cytometry and the total lymphocyte count can be determined by the white blood cell count multiplied by the differential percentage of the lymphocytes.[23]

The CD4+ count derived has been proven to correlate very well with the level of immunological competence that it is used for monitoring the therapy effects as well. Patients with CD4+ cell count <200/microlitre are at high risk to acquire Pneumocystis jiroveci and patients with CD4+ cell count <50/microlitre can develop infections due to Cytomegalovirus , Mycobacterium avium complex, Toxoplasma gondii. If the CD4 cell count is <200/microliter, patients should be started on for *P.* jiroveci prophylaxis, and if the CD4 count is <50/microliter , prophylaxis for MAC is to be given. It is always prudent to take two definite values prior to any significant changes in patient management based on CD4+ T cell count alone.

Patients with HIV infection should have CD4+ count performed at time of diagnosing and then after every three to six months thereafter. More frequent measurements of the values should be made if at all a declining trend is noted. For patients who have been on antiretroviral therapy for a minimum of 2 years and those with HIV RNA levels persistently <50 copies/ microliter , the monitoring of the CD4 count can be optional. [24]

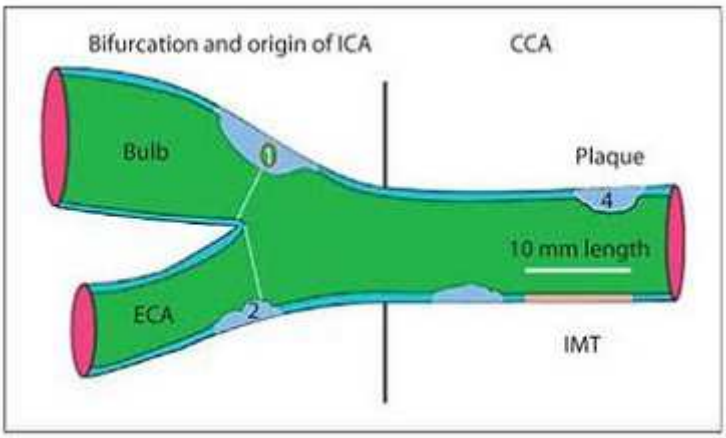
There are a number of clinical situations in which the CD4 cell count may be falsely increased or decreased . Patients with both HTLV and HIV co-infection may have a falsely elevated CD4+ cell counts that can give a false picture of good immunological status eve when the patient is deteriorating. In patients with hypersplenism or those who have had previous history of splenectomy, and in patients taking drugs that suppress the bone marrow cells such as IFN-α, the CD4+ cell percentage may be a more helpful and prudent marker of immune function than the CD4+ T cell count. A CD4+ T cell percentage of fifteen is equivalent to a CD4+ T cell count of 200/ microlitre .[24]

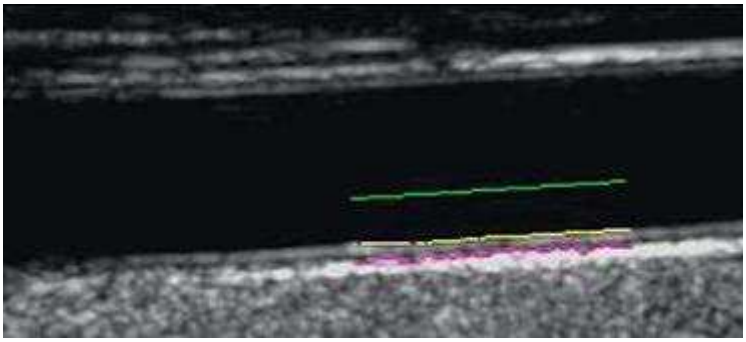
10. CAROTID INTIMA MEDIA THICKNESS

The first structural change that can be detected in atherosclerosis is an increase in intima media thickness. Intima-media thickness is an important atherosclerotic risk marker. There can be smooth muscle cells hyperplasia and fibrocellular hypertrophy leading to medial hypertrophy and compensatory arterial remodeling. Therefore this process may be an adaptive response to changes in flow, wall tension, or lumen diameter. The uniform thickening progresses in straighter arterial segment of vessels as the patient ages and all known atherosclerotic risk

factors accelerate this process. Therefore IMT is an important atherosclerotic risk marker [25]

IMT is a marker of subclinical atherosclerosis that is asymptomatic organ damage and should be evaluated in every asymptomatic adult or hypertensive patient at moderate risk for cardiovascular disease. Intima-media thickness values of more than 0.9 mm (ESC- European Society of Cardiology) or over the seventy fifth percentile (ASE- American Society of Echocardiography) should be considered abnormal. Carotid artery ultrasound scan is the method of choice and results are quite reliable provided certain standards are followed.[26]





Examination of the carotid wall gives every clinician an opportunity to evaluate for the subclinical changes in wall structure that precede as well as predict future cardiovascular clinical events. B-mode ultra sonography is a noninvasive, reproducible, sensitive, safe, easily performed, relatively inexpensive and widely available method for detection of early stages of atherosclerosis and is accepted as one of the best methods for evaluation of arterial wall structure.

IMT is defined as a double-line pattern visualised by echo 2D on both walls of the common carotid artery (CCA) in a longitudinal view. The two parallel lines (leading edges of two anatomical boundaries) form it: lumen-intima and media-adventitia interfaces .[25]

Which IMT values should be considered as abnormal is controversy. The relationship of IMT with cardiovascular risk is continuous and determining a threshold IMT value would be not

correct as it is a dichotomy. Nevertheless, it should be noted that in the ESH / ESC hypertension guidelines , carotid IMT > 0.9 mm has been said as a marker of asymptomatic organ damage, although it has been proven that in middle-aged and elderly patients the threshold values indicating high cardiovascular risk are higher

The American Society of Echography (ASE) Task force recommends that IMT ≥ seventh fifth percentile is considered high and indicative of increased cardiovascular risk. Values from the twenty five to seventy fifth percentile are considered average and indicative of unchanged cardiovascular risk. Values ≤ twenty fifth percentile are considered low and indicate lower than the expected cardiovascular risk.

High-resolution B-mode system (B-mode imaging is preferred over M-mode), equipped with a linear array transducer >7 MHz with minimal compression and footprint of at least 3 cm. Use of a zoom function is discouraged . IMT measurement is done at a distance of at least 5 mm below the distal end of CCA , along a segment of the artery free of atherosclerotic plaque with clearly defined lumen-intima and media-adventitia interface .10-mm-in-

length straight arterial segment is required and the far wall of the common carotid artery is preferred.[26]

The following table gives the IMT values – median (P50), 25th and 75th percentile (P) IMT values for men and women at different age categories of which values more than P75 are significant.

	P25	P50	P75
MEN <30	0.39	0.43	0.48
MEN 31-40	0.42	0.46	0.50
MEN 41-50	0.46	0.50	0.57
MEN >50	0.46	0.52	0.62
WOMEN <30	0.39	0.40	0.43
WOMEN 31-40	0.42	0.45	0.49
WOMEN 41-50	0.44	0.48	0.53
WOMEN >50	0.50	0.54	0.59

11.CARDIOVASULAR EFFECTS OF HIV

HIV infection per se may promote atherosclerosis either by activating the vascular endothelium directly, or by systemic cytokine release by the virus indirectly . Higher rates of sub-clinical atherosclerosis are seen in HIV-1-infected patients, and, these can also be due to the classical cardiovascular risk factors and due to the side effect profile of cART [30].Recent studies have suggested that viral factors, in addition to the traditional cardiovascular risk factors,

have independent negative effects, possibly by causing abnormalities in lipid levels, monocyte attraction and migration into the intima of vessels and a state of chronic inflammation[31] . Effects of vascular alterations in patients with HIV can be secondary to direct effects of the HIV virus on vascular function, including direct alteration in endothelial function, inflammation, and modification of aortic wall vascular smooth muscle cell behaviour and extracellular matrix composition changes.[32]

Studies have shown that HIV patients have elevated levels of hsCRP , IL-6, TNF- alpha. Studies also suggest that chronic inflammation in HIV infection may partially underlie the reduced vascular function and premature atherosclerosis[33]

Endothelial dysfunction is a common feature of atherosclerosis .There is a increasing evidence to suggest HIV itself may have deleterious effects on endothelial function. Patients with HIV have been shown to have reduced vascular reactivity similar to patients type 2 diabetes mellitus. Increased secretion of monocyte chemoattractant protein 1 as well as increased expression of adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1) , intercellular adhesion molecule 1 and E-selectin is present [34].

Vascular endothelium from patients with HIV have increased monocyte adherence and its migration into the intima during plaque development. In addition, several HIV proteins, notably Tat and gp120 are causing endothelial cell activation and increased expression of the cell adhesion molecules . [35]

This along with the fact that HIV infection affects lipid processing and is associated with lower HDL cholesterol, lower apolipoprotein B levels and smaller LDL cholesterol particles, this environment provides an atherogenic milieu. Although few studies have shown that ART may reduce endothelial activation, it does not appear to completely ameliorate the effects of HIV infection, suggesting that even during complete virological suppression, endothelial dysfunction continues to promote atherosclerosis in HIV patients.[36]

MATERIALS AND METHODS

MATERIALS AND METHODS

SETTINGS

The study was conducted in the Institute of Internal medicine and ART centre at Madras Medical College and Rajiv Gandhi Government General Hospital.

ETHICAL COMMITTEE APPROVAL

The study was approved by the Institutional Ethics Committee of Madras Medical College, Chennai

STUDY DURATION

This study was done for a duration for a period of six months.

STUDY POPULATION

Patients attending ART center OPD and medical wards with HIV infection.

TYPE OF STUDY

Observational study of 100 patients

SAMPLE SIZE

100 patients recruited from Institute of Internal medicine and Antiretroviral center from Rajiv Gandhi Government General Hospital Chennai.

INCLUSION CRITERIA

Patients who are HIV infected as evidenced by ELISA and western blot Reactivity

EXCLUSION CRITERIA

1. Patients with history of diabetes mellitus
2. Patients with history of hypertension
3. Patients with coronary artery disease
4. Patients with chronic kidney disease
5. Patients with history of smoking

DATA COLLECTION AND METHODS

We examined 100 patients recruited from Institute of Internal Medicine, and Anti-retroviral center at Madras Medical College and Rajiv Gandhi Government General Hospital. Patients were selected for clinical study as per inclusion/exclusion criteria and demographic data , past medical history , ART drug history ,duration of illness was collected from patients .CD4 T cell count is measured. Carotid artery intima media thickness is measured using B-mode ultrasound . Informed consent was obtained from each patient and relatives in necessary cases. They were given a questionnaire and were subjected to thorough clinical examination. Patients were asked to take routine blood investigations like renal function tests, liver function tests, CD4 cell count. All the data was entered in the proforma (enclosed). Data was analyzed using Excel data analysis software and p value was calculated using paired T test

OBSERVATION AND RESULTS

STASTISTICS

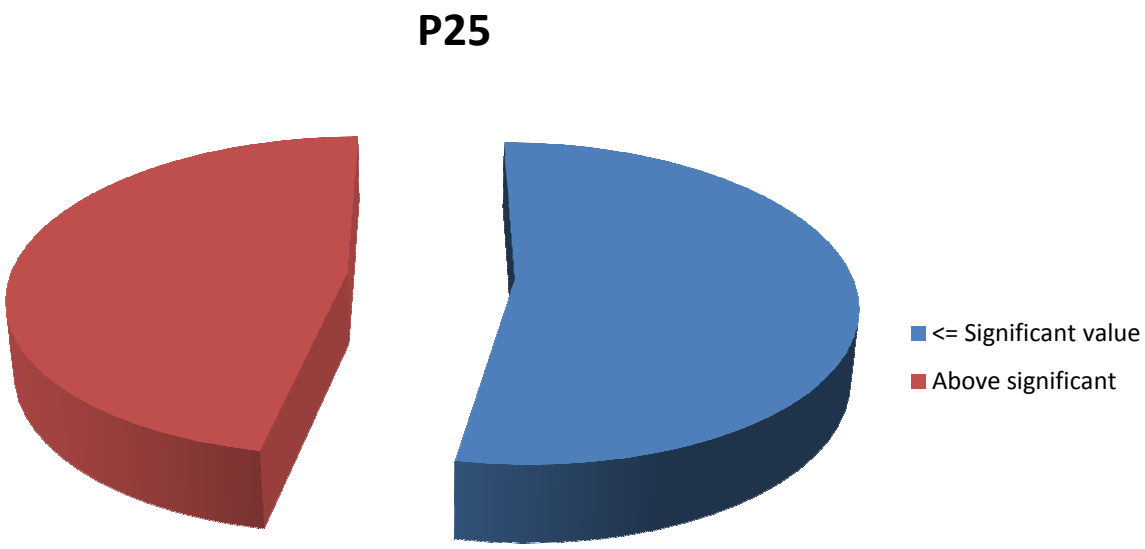
AGE WISE DISTRIBUTION OF CIMT

				CIMTMEAN			
				Mean	Percentile 25	MedianP 50	Percentile 75
age_group	<30	SEX	Male	.38	.20	.30	.60
			Female	.41	.35	.43	.48
	31-40	SEX	Male	.39	.35	.35	.45
			Female	.43	.30	.40	.50
	41-50	SEX	Male	.47	.40	.45	.55
			Female	.42	.30	.40	.50
	Above 50	SEX	Male	.61	.38	.48	.90
			Female	.42	.30	.35	.50

The above table shows the shows that the mean CIMT was more in females in age groups <30 and 31-40 and was more in men in 41-50 and >50 age groups. The distribution is similar upto p50 and there is increased values in CIMT for men above p75 except in the 31 – 40

PERCENTILE 25(P25)

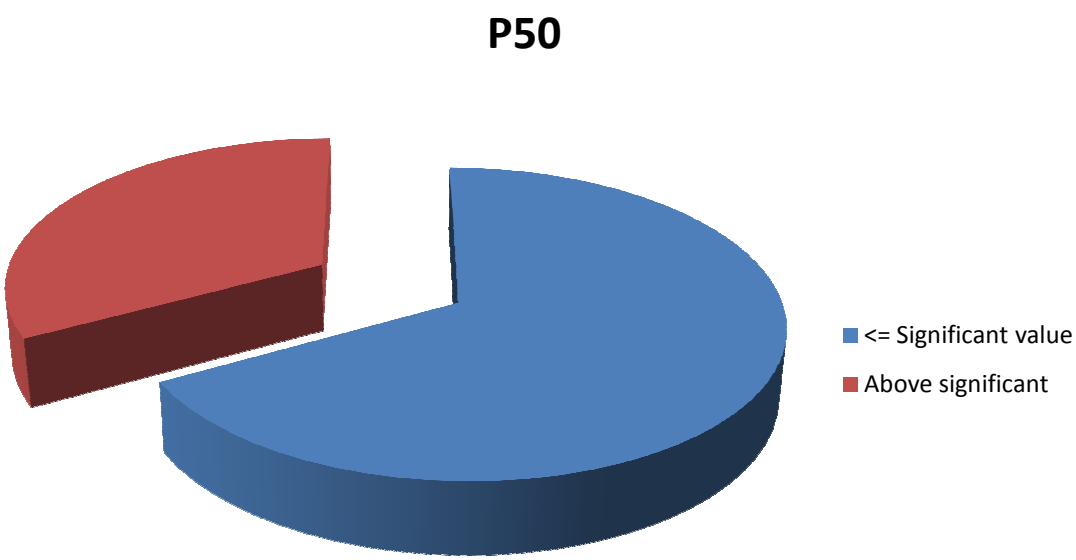
		Frequency	Percent
Valid	<= Significant value	53	53.0
	Above significant	47	47.0
	Total	100	100.0



The pie chart shows that 47 percent of them had significant values of CIMT at p25

PERCENTILE 50 (P50)

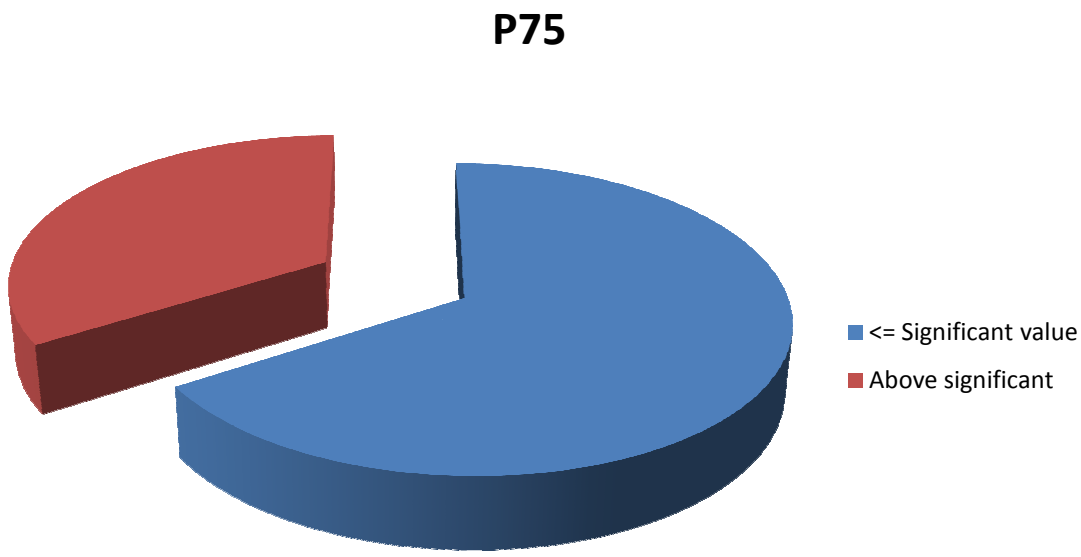
		Frequency	Percent
Valid	<= Significant value	67	67.0
	Above significant	33	33.0
	Total	100	100.0



The pie chart shows that 33 percent of them had significant values of CIMT at p50

PERCENTILE (P75)

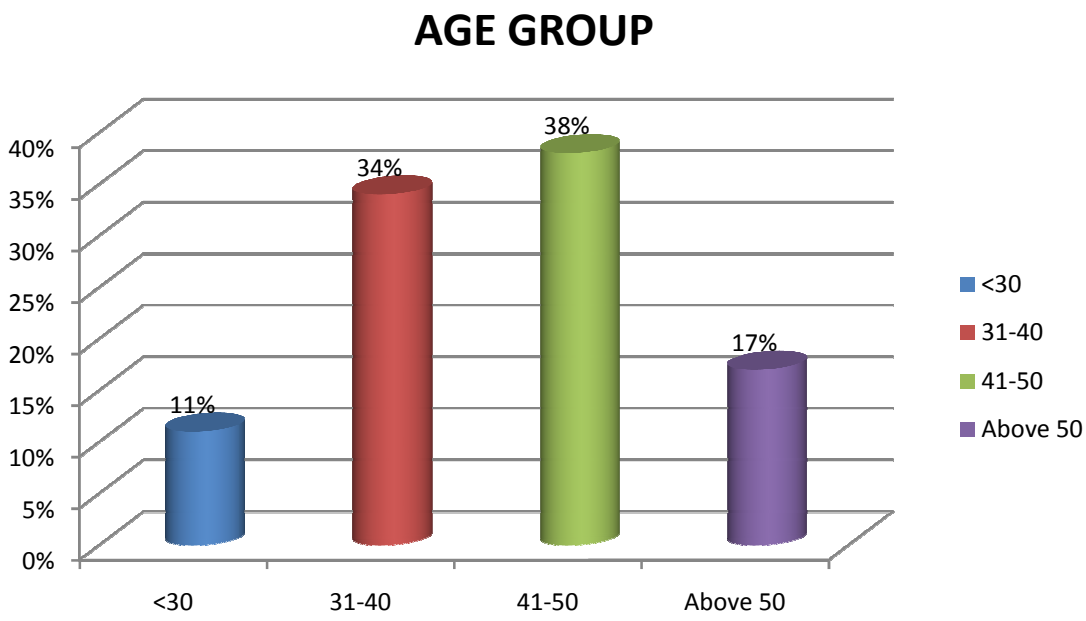
		Frequency	Percent
Valid	<= Significant value	66	66.0
	Above significant	34	34.0
	Total	100	100.0



The pie chart shows that 34 percent of them had significant values of CIMT at p75

AGE GROUP DISTRIBUTION

Age		Frequency	Percent
Valid	<30	11	11.0
	31-40	34	34.0
	41-50	38	38.0
	Above 50	17	17.0
	Total	100	100.0



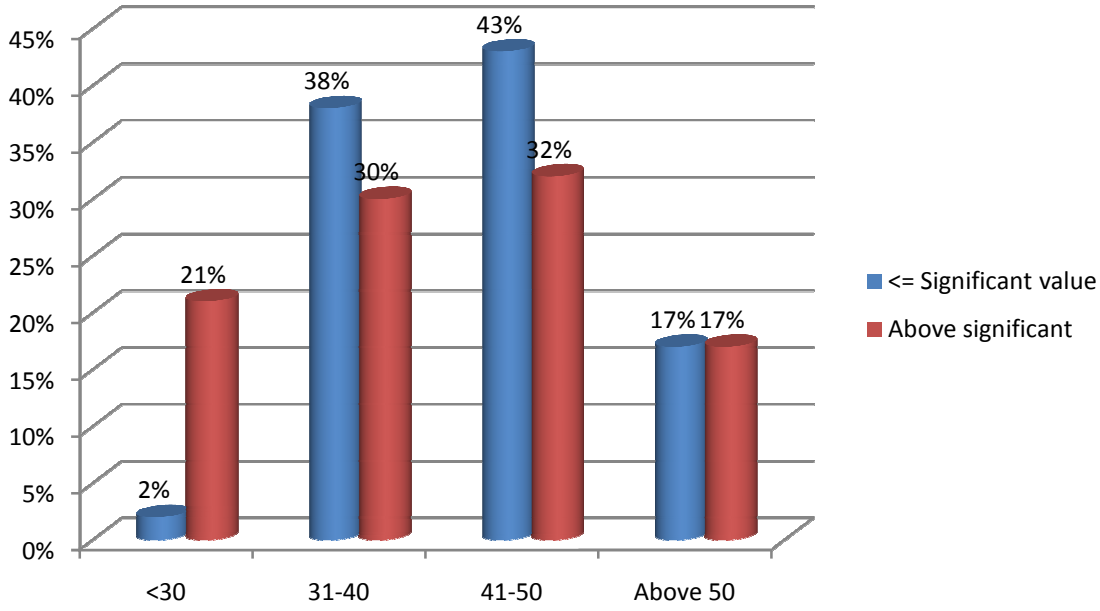
The x axis shows age groups in ranges and y axis has percentage in each

CROSSTAB SHOWING THE SIGNIFICANT CIMT VALUES ABOVE P25 DISTRIBUTED BY AGE GROUPS

Crosstab

			p25		Total
			<= Significant value	Above significant	
age_group	<30	Count	1	10	11
		% within p25	1.9%	21.3%	11.0%
	31-40	Count	20	14	34
		% within p25	37.7%	29.8%	34.0%
	41-50	Count	23	15	38
		% within p25	43.4%	31.9%	38.0%
	Above 50	Count	9	8	17
		% within p25	17.0%	17.0%	17.0%
Total		Count	53	47	100
		% within p25	100.0%	100.0%	100.0%

Pearson Chi-Square =9.841* p=0.020



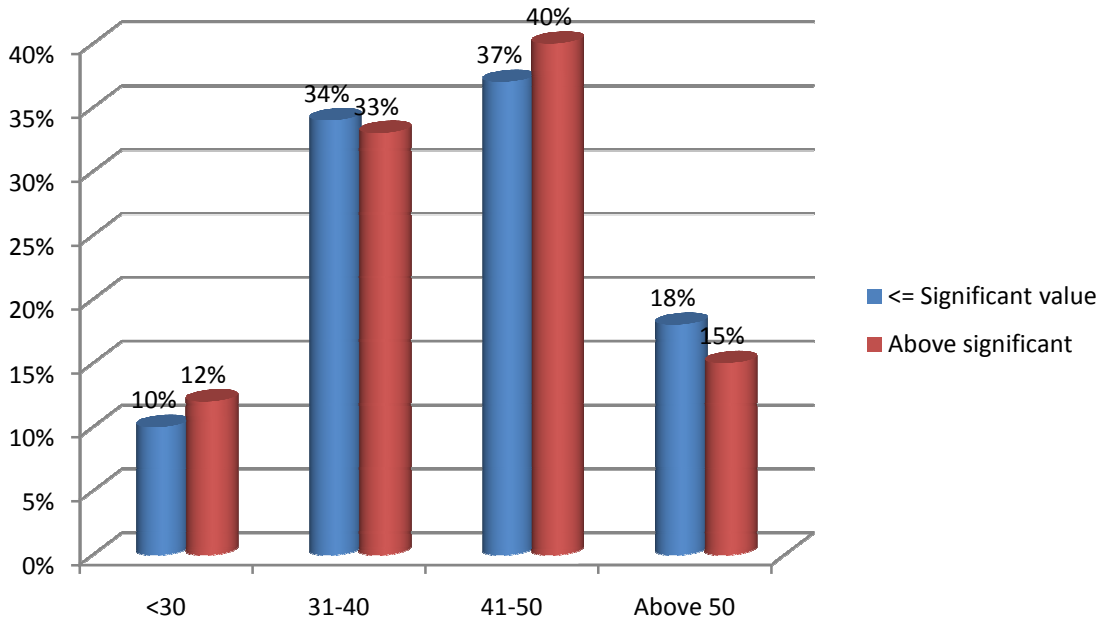
The above graph shows that the CIMT values at p25 distributed to age groups was significant , p =0.020

CROSSTAB SHOWING THE SIGNIFICANT CIMT VALUES ABOVE P50 DISTRIBUTED BY AGE GROUPS

Crosstab

			p50		Total
			<= Significant value	Above significant	
age_group	<30	Count	7	4	11
		% within p50	10.4%	12.1%	11.0%
	31-40	Count	23	11	34
		% within p50	34.3%	33.3%	34.0%
	41-50	Count	25	13	38
		% within p50	37.3%	39.4%	38.0%
	Above 50	Count	12	5	17
		% within p50	17.9%	15.2%	17.0%
Total		Count	67	33	100
		% within p50	100.0%	100.0%	100.0%

Pearson Chi-Square =0.187 p=0.980



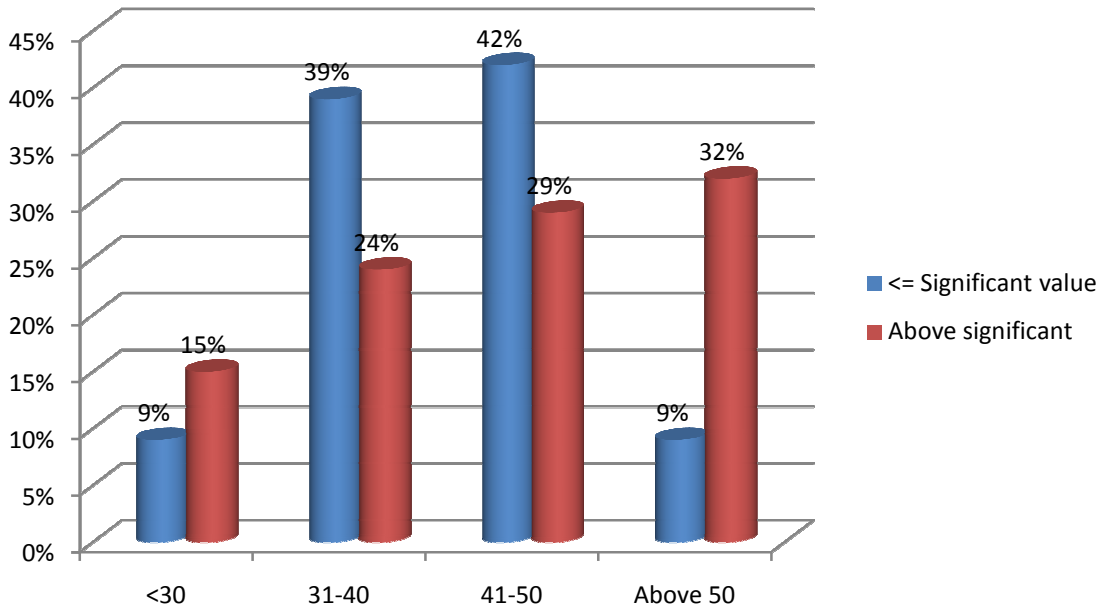
The above graph shows that the CIMT values at p50 distributed to age groups was not significant , p =0.980

CROSSTAB SHOWING THE SIGNIFICANT CIMT VALUES ABOVE P75 DISTRIBUTED BY AGE GRUOPS

Crosstab

			p75		Total
			<= Significant value	Above significant	
age_group	<30	Count	6	5	11
		% within p75	9.1%	14.7%	11.0%
	31-40	Count	26	8	34
		% within p75	39.4%	23.5%	34.0%
	41-50	Count	28	10	38
		% within p75	42.4%	29.4%	38.0%
	Above 50	Count	6	11	17
		% within p75	9.1%	32.4%	17.0%
Total		Count	66	34	100
		% within p75	100.0%	100.0%	100.0%

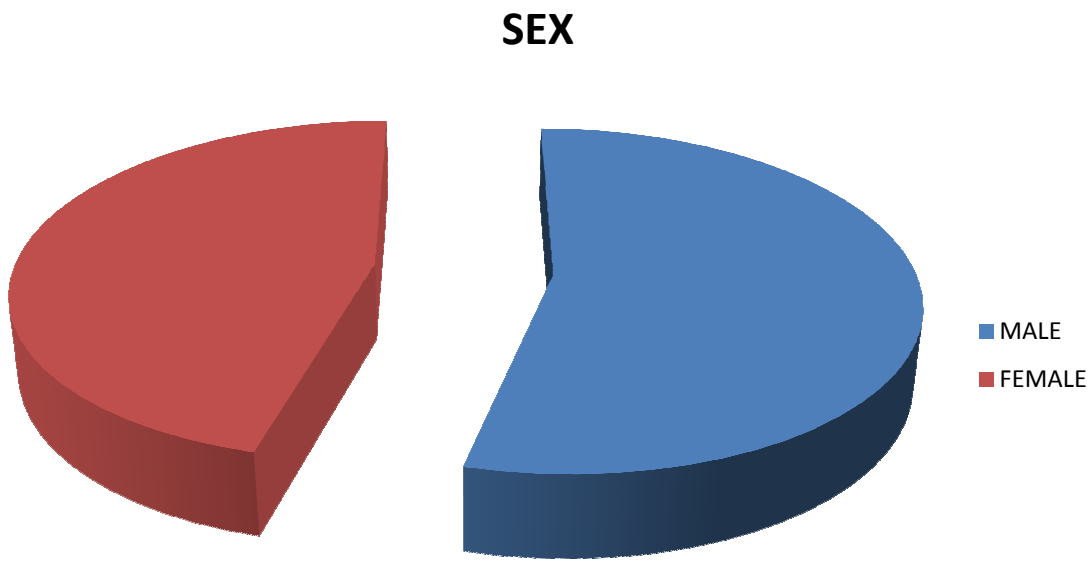
Pearson Chi-Square =10.447* p=0.015



The above graph shows that the CIMT values at p75 distributed to age groups was significant , p =0.015. The CIMT was more <30,>50 groups.

SEX DISTRIBUTION

		Frequency	Percent
Valid	Male	54	54.0
	Female	46	46.0
	Total	100	100.0



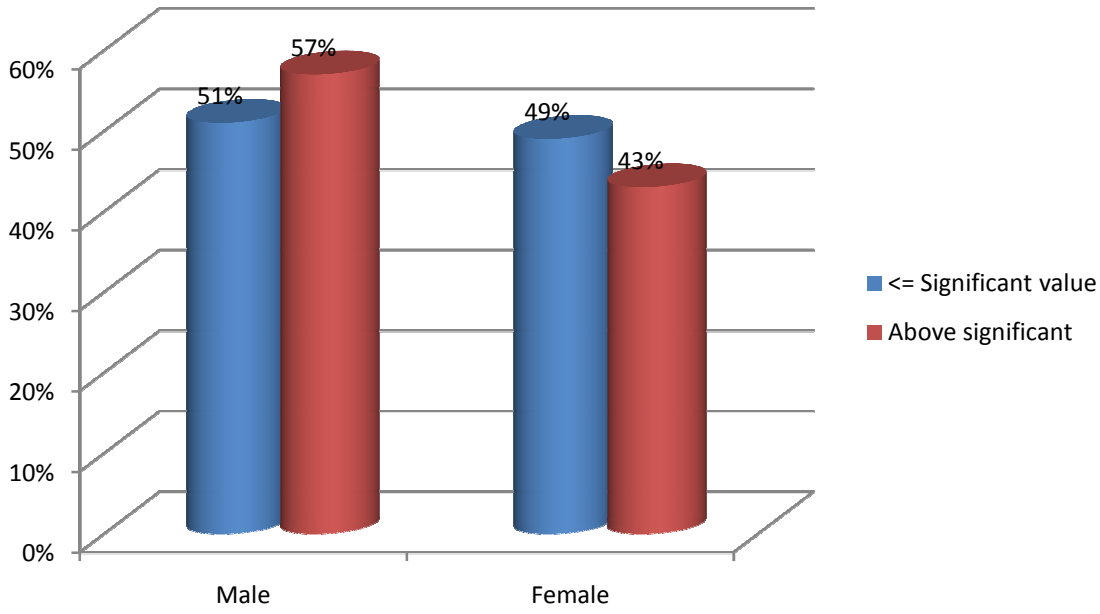
Males constituted 54 percent and females 46 percent of the total cases

CROSSTAB SHOWINGTHE SIGNIFICANT CIMT VALUES ABOVE P25 DISTRIBUTED FOR THE SEXES

Crosstab

			p25		Total
			<= Significant value	Above significant	
SEX	Male	Count	27	27	54
		% within p25	50.9%	57.4%	54.0%
	Female	Count	26	20	46
		% within p25	49.1%	42.6%	46.0%
Total		Count	53	47	100
		% within p25	100.0%	100.0%	100.0%

Pearson Chi-Square =0.424 p=0.515



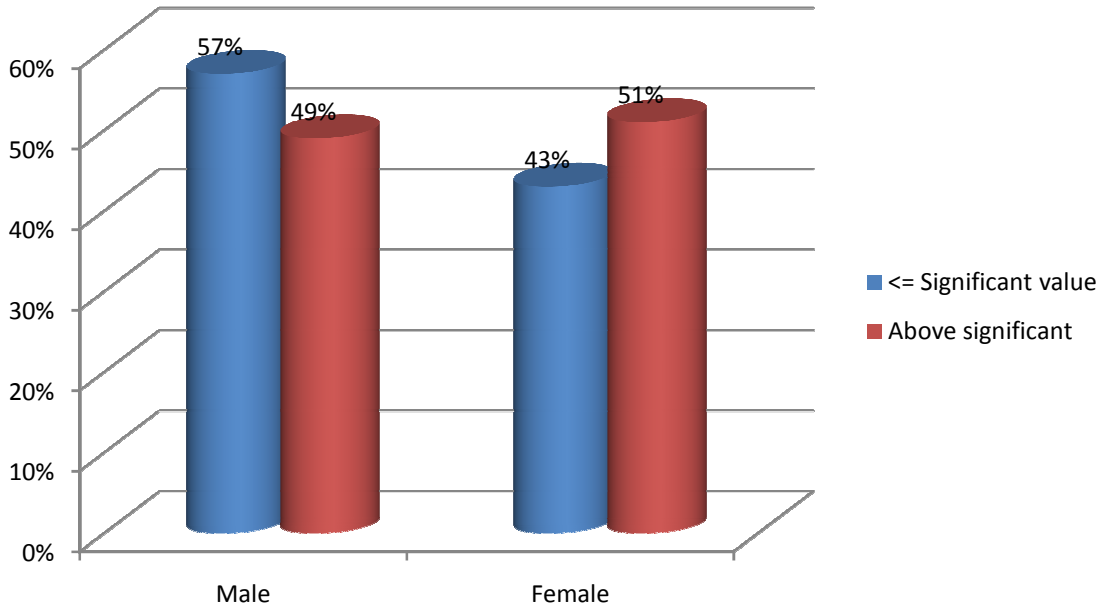
The above graph shows that the CIMT values at p25 distributed for sexes was not significant , p =0.515

CROSSTAB SHOWINGTHE SIGNIFICANT CIMT VALUES ABOVE P50 DISTRIBUTED FOR THE SEXES

Crosstab

			p50		Total
			<= Significant value	Above significant	
SEX	Male	Count	38	16	54
		% within p50	56.7%	48.5%	54.0%
	Female	Count	29	17	46
		% within p50	43.3%	51.5%	46.0%
Total		Count	67	33	100
		% within p50	100.0%	100.0%	100.0%

Pearson Chi-Square =0.603 p=0.437



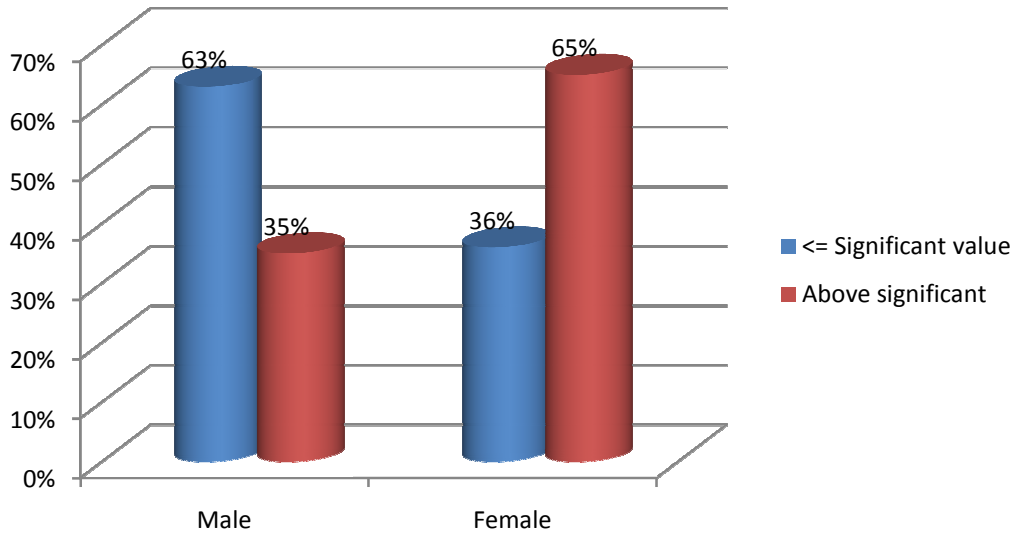
The above graph shows that the CIMT values at p50 distributed for the sexes was not significant , p =0.437

CROSSTAB SHOWINGTHE SIGNIFICANT CIMT VALUES ABOVE P75 DISTRIBUTED FOR THE SEXES

Crosstab

			p75		Total
			<= Significant value	Above significant	
SEX	Male	Count	42	12	54
		% within p75	63.6%	35.3%	54.0%
	Female	Count	24	22	46
		% within p75	36.4%	64.7%	46.0%
	Total	Count	66	34	100
		% within p75	100.0%	100.0%	100.0%

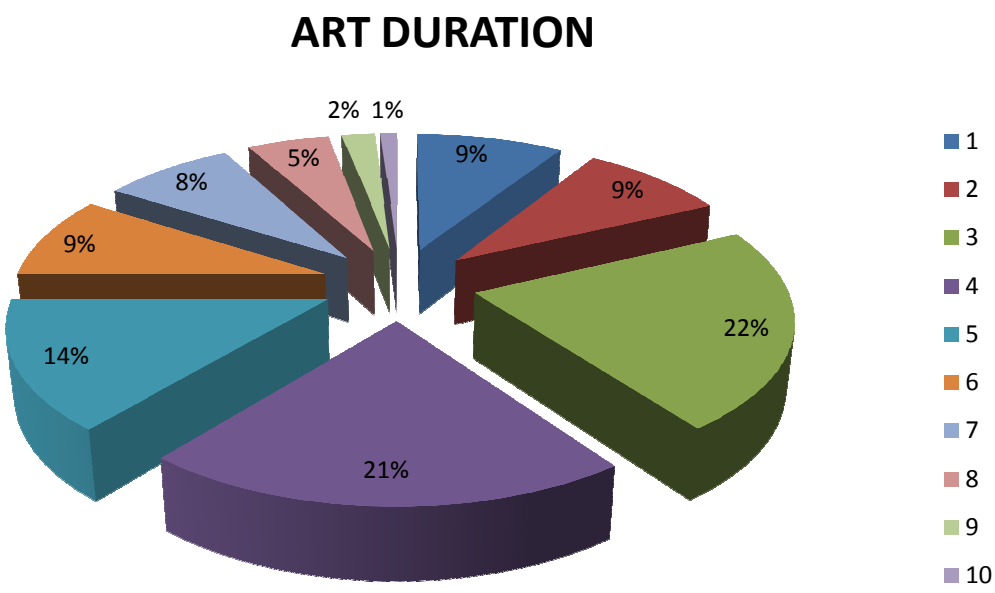
Pearson Chi-Square =7.257* p=0.007



The above graph shows that the CIMT values at p75 distributed for the sexes was significant , p =0.007 indicating that females had more significant increase in CIMT than males above the significant values

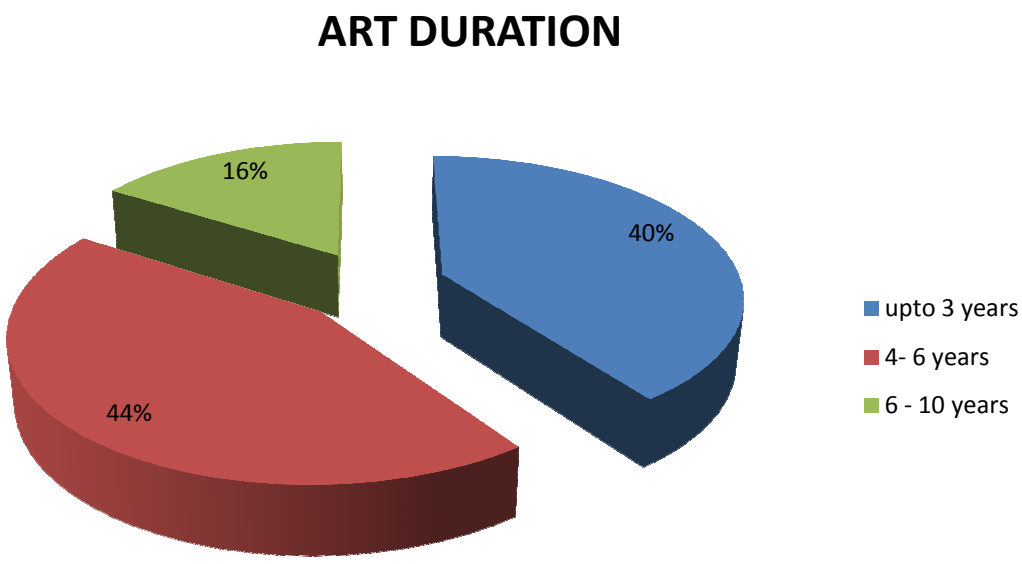
ART DURATION YEARWISE DISTRIBUTION

		Frequency	Percent
Valid	1.00	9	9.0
	2.00	9	9.0
	3.00	22	22.0
	4.00	21	21.0
	5.00	14	14.0
	6.00	9	9.0
	7.00	8	8.0
	8.00	5	5.0
	9.00	2	2.0
	10.00	1	1.0
	Total	100	100.0



ART DURATION YEAR RANGE DISTRIBUTION

		Frequency	Percent
Valid	upto 3 years	40	40.0
	4- 6 years	44	44.0
	6 - 10 years	16	16.0
	Total	100	100.0

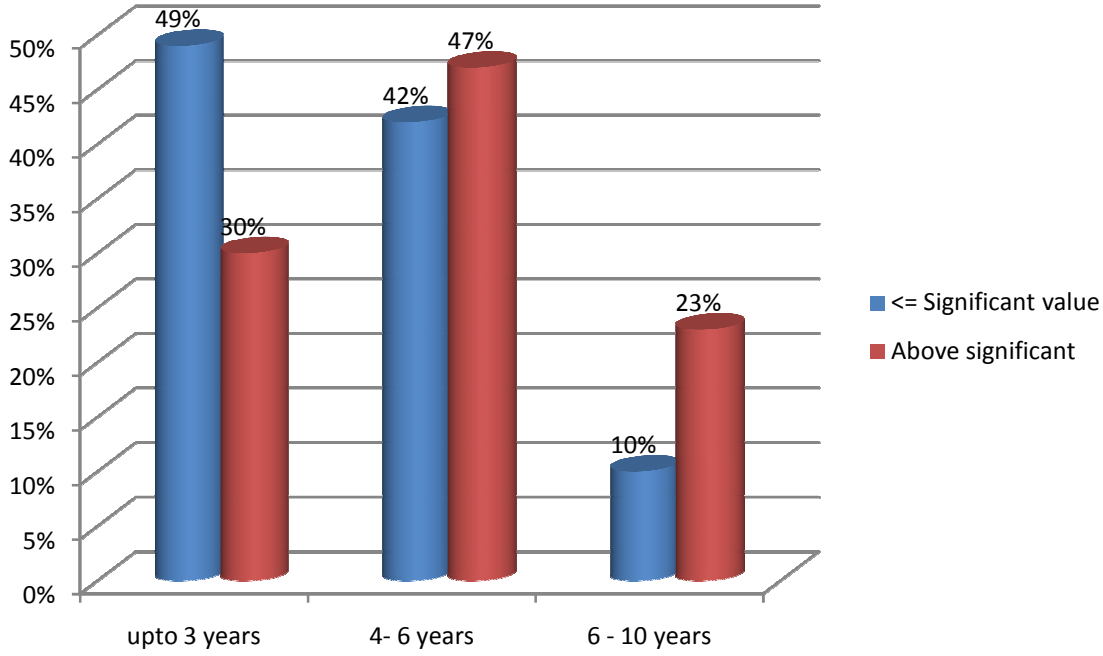


CROSSTAB SHOWING THE SIGNIFICANT CIMT VALUES ABOVE P25 COMPARED TO ART DURATION

Crosstab

			p25		Total
			<= Significant value	Above significant	
art	upto 3 years	Count	26	14	40
		% within p25	49.1%	29.8%	40.0%
	4- 6 years	Count	22	22	44
		% within p25	41.5%	46.8%	44.0%
	6 - 10 years	Count	5	11	16
		% within p25	9.4%	23.4%	16.0%
Total		Count	53	47	100
		% within p25	100.0%	100.0%	100.0%

Pearson Chi-Square =5.510 p=0.064



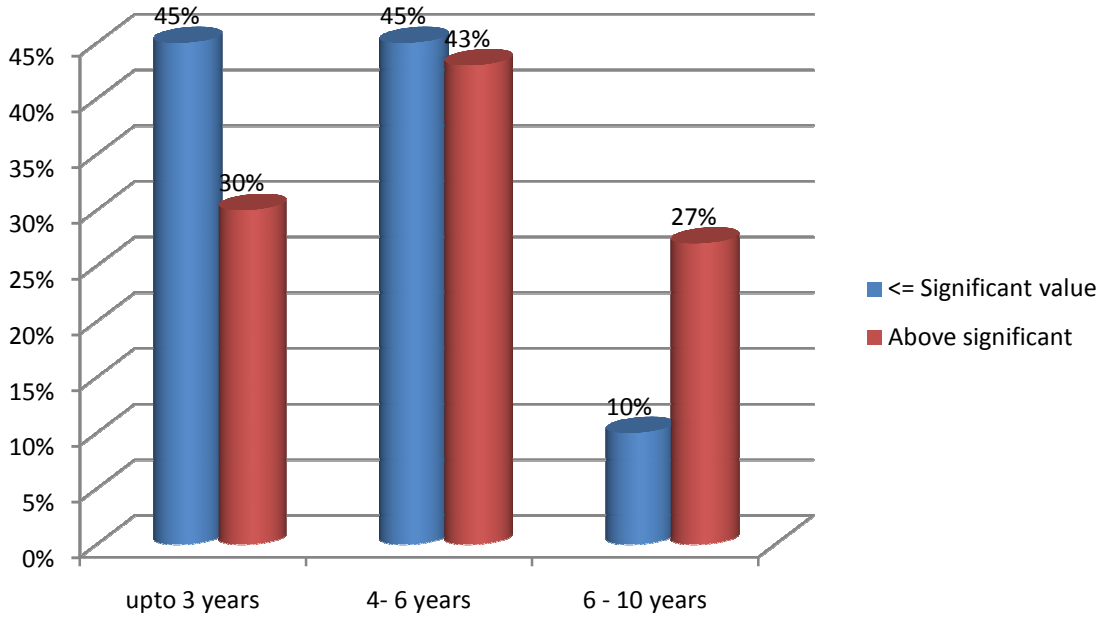
The above graph shows that the CIMT values at p25 compared to ART duration was not significant , p =0.064

CROSSTAB SHOWING THE SIGNIFICANT CIMT VALUES ABOVE P50 COMPARED TO ART DURATION

Crosstab

			p50		Total
			<= Significant value	Above significant	
art	upto 3 years	Count	30	10	40
		% within p50	44.8%	30.3%	40.0%
	4- 6 years	Count	30	14	44
		% within p50	44.8%	42.4%	44.0%
	6 - 10 years	Count	7	9	16
		% within p50	10.4%	27.3%	16.0%
Total		Count	67	33	100
		% within p50	100.0%	100.0%	100.0%

Pearson Chi-Square =5.097 p=0.078



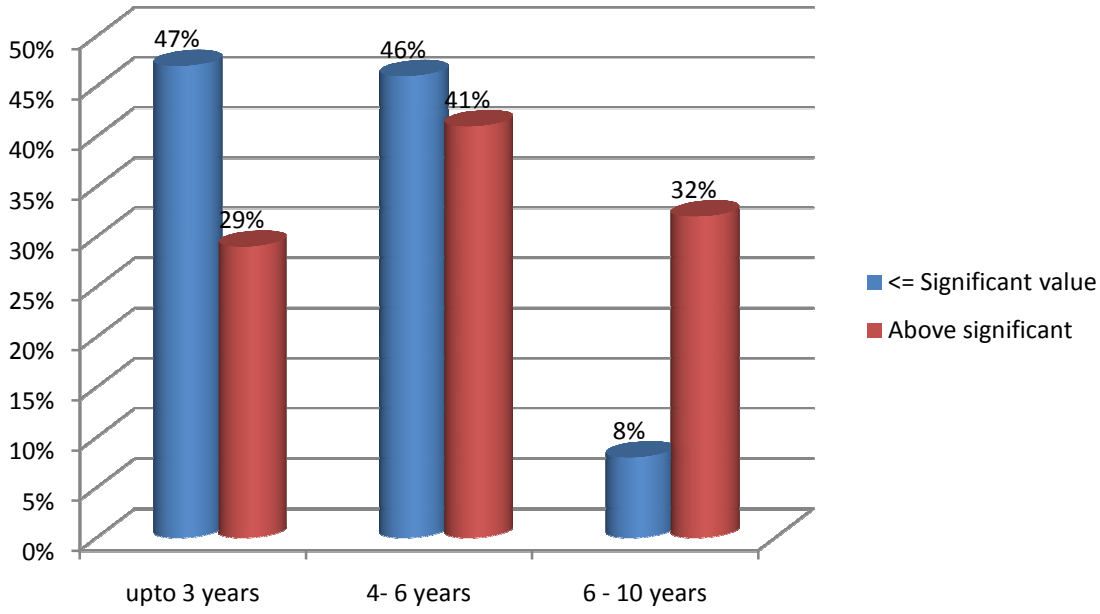
The above graph shows that the CIMT values at p50 compared to ART duration was not significant , p =0.078

CROSSTAB SHOWING THE SIGNIFICANT CIMT VALUES ABOVE P75 COMPARED TO ART DURATION

Crosstab

			p75		Total
			<= Significant value	Above significant	
art	upto 3 years	Count	31	9	40
		% within p75	47.0%	26.5%	40.0%
	4- 6 years	Count	30	14	44
		% within p75	45.5%	41.2%	44.0%
	6 - 10 years	Count	5	11	16
		% within p75	7.6%	32.4%	16.0%
Total		Count	66	34	100
		% within p75	100.0%	100.0%	100.0%

Pearson Chi-Square =11.061* p=0.004



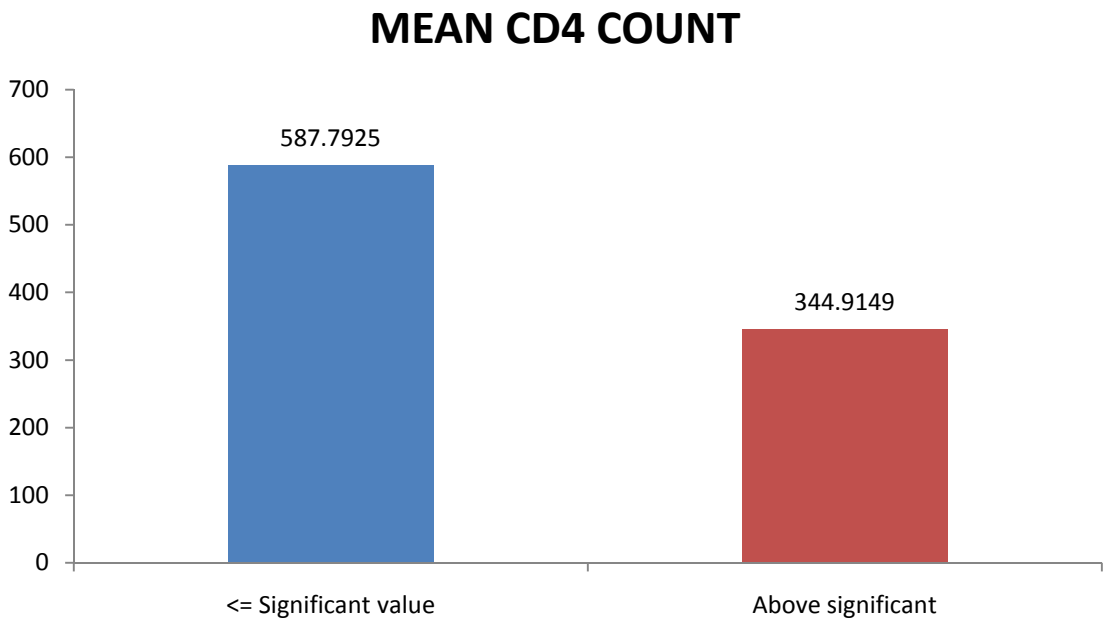
The above graph shows that the CIMT values at p75 compared to ART duration was significant , p =0.004 indicating that patients on ART for 6-10 years had more CIMT values

GROUP STATISTICS SHOWING MEAN CD4 COUNT FOR P25

Group Statistics

	p25	N	Mean	Std. Deviation	Std. Error Mean
CD4_COUNT	<= Significant value	53	587.7925	221.27127	30.39395
	Above significant	47	344.9149	200.88801	29.30253

t value =5.719 * p<0.001



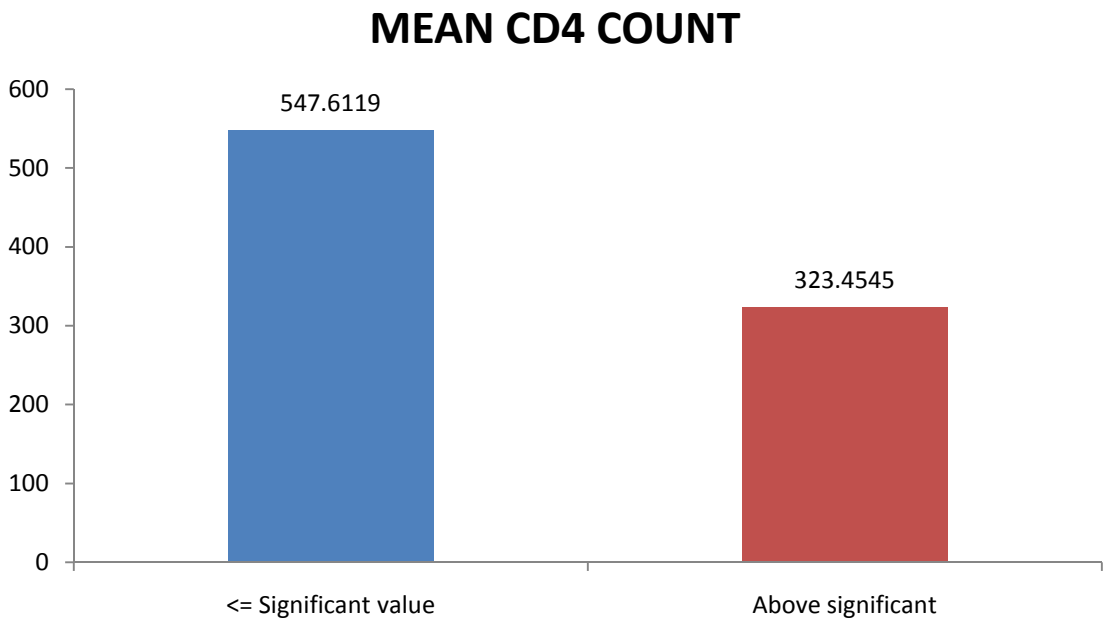
The above graph shows that the significant mean cd4 count was 344 for patients with cimt above p25 ,p <0.001

GROUP STATISTICS SHOWING MEAN CD4 COUNT FOR P50

Group Statistics

	p50	N	Mean	Std. Deviation	Std. Error Mean
CD4_COUNT	<= Significant value	67	547.6119	233.39010	28.51314
	Above significant	33	323.4545	190.86499	33.22533

t value =4.782 * p<0.001



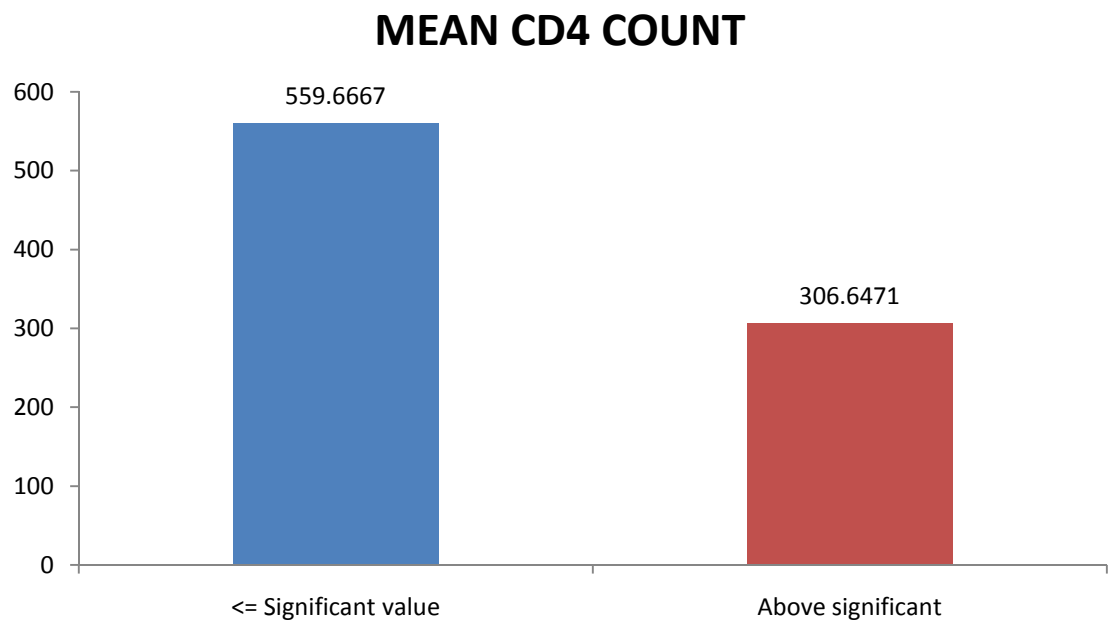
The above graph shows that the significant mean cd4 count was 323 for patients with cimt above p50 ,p <0.001

GROUP STATISTICS SHOWING MEAN CD4 COUNT FOR P75

Group Statistics

	p75	N	Mean	Std. Deviation	Std. Error Mean
CD4_COUNT	<= Significant value	66	559.6667	228.76507	28.15903
	Above significant	34	306.6471	176.97079	30.35024

t value =5.634 * p<0.001



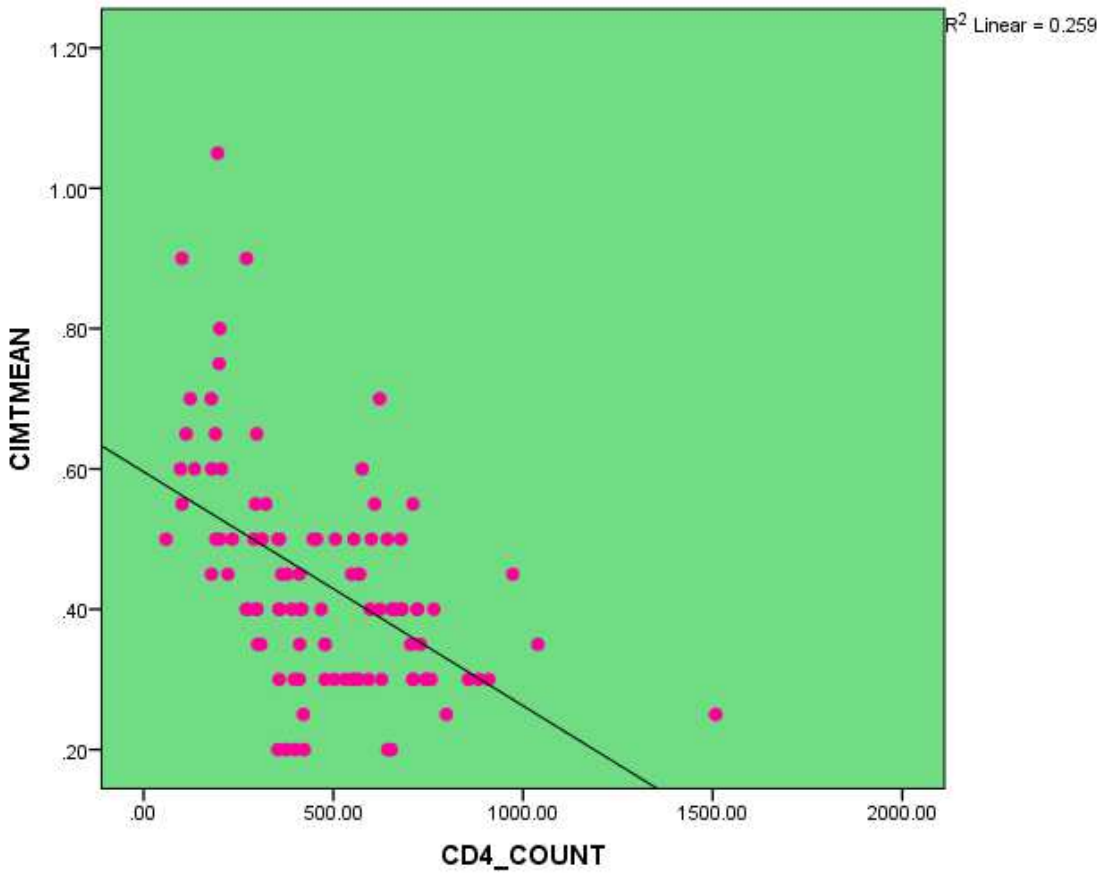
The above graph shows that the significant mean cd4 count was 306 for patients with cimt above p75 ,p <0.001

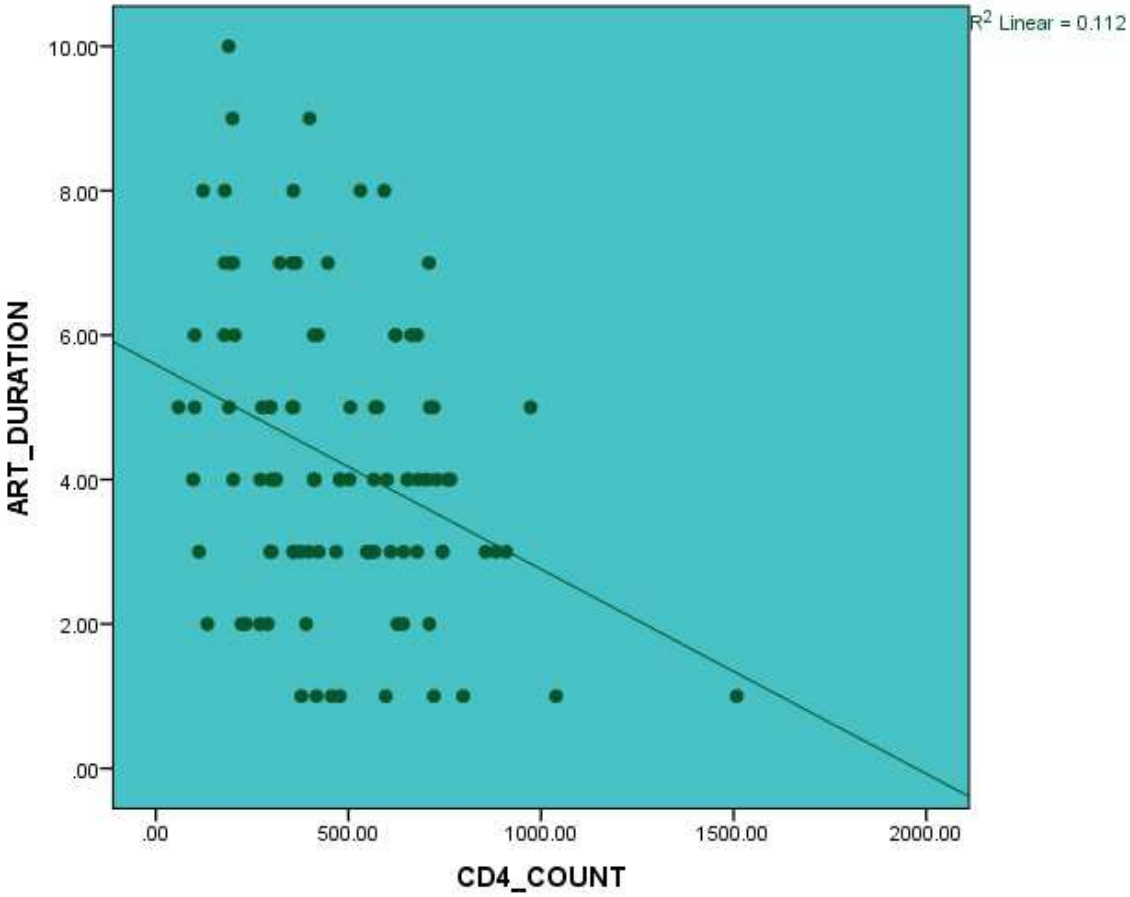
CORRELATIONS OF CD4 COUNT WITH CIMT AND ART DURATION

Correlations

		CIMTMEAN	ART DURATION
CD4_COUNT	Pearson Correlation	-.509**	-.335**
	Sig. (2-tailed)	.000	.001
	N	100	100

**. Correlation is significant at the 0.01 level (2-tailed).





The above graphs show there is a negative correlation between CD4 count and CIMT values as well as between CD4 count and ART duration.

RESULTS

The results obtained were compared to age adjusted normal values for CIMT . It was found that the following number of patients had significant values according to percentiles. At p25 the number of patients was 47 , p50 the number of patients was 33 , p75 the number of patients was 34.

AGE DISTRIBUTION

In our present study, the distribution of patients as follows : below 30 years was 11 , 31-40 years was 34 , 41-50 years was 38 , above 50 years was 17. At p75 significant values of CIMT was noted for age adjusted values and it was found that values are more in age groups below 30 years and above 50 years .

SEX DISTRIBUTION

54 % of the study population were males and 46 % were females. The CIMT values at p75 distributed for the sexes was significant , p =0.007 indicating that females had more significant increase in CIMT than males above the significant values

ART DURATION

The graphs show that the CIMT values at p75 compared to ART duration was significant at p75 , p =0.004 indicating that patients on ART for 6-10 years had more CIMT values compared to other age groups.

MEAN CD4

The mean CD4 counts was found to be in decreasing trend with increasing percentile of CIMT . The count was 344, 323, 306 for p25 , p50 , p75 respectively and was significant with p value < 0.001.

CORRELATIONS

The crux was to find out if there is a correlation between CD4 count and CIMT and it was found to have a negative correlation (the Correlation is significant at the 0.01 level (2-tailed). meaning that the CIMT values were increasing in trend when there was a fall in mean CD4 count.

There was also a negative correlation between CIMT values and ART duration indicating that CIMT was more for patients who are on prolonged ART.

DISCUSSION

DISCUSSION

The aim of the study was to investigate if the degree of immune suppression as indicated by a reliable marker , the CD4 count , was correlating with atherosclerosis which in turn can be assessed by CIMT (carotid intima media thickness).CIMT is considered a surrogate marker for atherosclerosis.

Among HIV patients, low CD4+ T-cell count has been identified as a risk factor for atherosclerosis. However, the data has not been consistent as few studies have not confirmed the reported associations low CD4+ T-cell count with clinical or subclinical cardiovascular disease (CVD). Several potential mechanisms have been described that can explain HIV and its treatment with increased risk of vascular disease. Individuals with untreated Human retroviral infection have reduced levels of high-density lipoprotein cholesterol (HDL-C) and increased levels of triglycerides, which happen to be risk factors for vascular disease. Initiatng antiretroviral therapy will normalize the lipid parameters (total cholesterol, LDL-C and triglycerides, but not HDL-C) . Protease inhibitors (PI), can have adverse effects on LDL-Cholesterol and triglyceride levels, blood pressure, and diabetes . The study did not include patients taking protease inhibitors .Circulating markers of

inflammation such CRP may be increased among patients with HIV , especially when AIDS occurs.

Values of CIMT was noted for age adjusted values and it was found that values are more in age groups below 30 years and above 50 years . There are not sufficient studies in this regard for age adjusted atherosclerosis risk distribution although multiple confounding factors can contribute to these results , patients with any known co morbid conditions predisposing to atherosclerosis were effectively screened and excluded from the study

It was also found that female had more incidence of higher CIMT values than men. Insufficient studies are present in this parameter although in one study women had increased prevalence of mean CIMT, compared with healthy controls and histology was similar to women with systemic lupus erythematosus and rheumatoid arthritis . Histologic studies of carotid plaques in HIV-infected individuals show extensive inflammatory infiltration of the vascular wall, more similar to arteritis than to classical atheroma, which is further evidence of an atypical vascular disease phenotype in the HIV-infected patients consistent with the above findings.

In this study it was also found that the CIMT was more in patients on prolonged antiretroviral therapy which can indicate the disease activity has overtaken the effects of the drug therapy leading on to accelerated atherosclerosis along with a decreased CD4 count

Previous studies have revealed that the prevalence of carotid lesions was higher in HIV patients who had a CD4+ T-cell count measurement below 200 cells/mm3 when compared to HIV uninfected persons , consistent with evidence that low CD4+ T-cell count may increase risk of CVD in HIV populations. The main results from SMART (Strategies for Management of Antiretroviral Therapy) trial appear to be consistent with the current finding that immunosuppression (low CD4 count) was associated with increased atherosclerosis. The association between low CD4+ T-cell count may plausibly be explained by chronic inflammation or specific pathogen exposures in immunosuppressed HIV patients.

LIMITATIONS OF THE STUDY

1. The data was collected from a single center.
2. The sample size is small for HIV infected population.
3. Potential for Bias and hence inaccuracy.
4. Factors have to be reduced more
5. This was a study of subclinical atherosclerosis measures rather than hard cardiovascular disease events.

Large multi-centric studies in future prospective studies are needed to fully ascertain the accuracy of the above findings.

CONCLUSION

CONCLUSION

It was found that HIV-infected patients with a low CD4+ T-cell count had a significantly increased prevalence of subclinical carotid artery lesions in the form of increased carotid intima media thickness (CIMT) indicating that there is increased atherosclerosis in these immunocompromised group of patients.

It was also found that CIMT was increased in older age group compared to younger age group HIV infected. HIV infected females had increased CIMT values than men which can indicate a inflammatory pathology. Prolonged duration of ART was associated with increased values of CIMT.

These findings emphasize that the association of antiretroviral therapy use and other HIV related variables with atherosclerosis is in need of further study. Further studies are needed in this regard to know the exact pathogenesis of atherosclerosis in HIV patients as well as to know the effectiveness of the antiretroviral therapy in controlling atherosclerosis. More research is needed for developing newer drug therapy for atherosclerosis in HIV as well as to evaluate the effectiveness of current lipid lowering agents in treatment of the HIV infected patients. Prospective studies to reduce chronic inflammation beyond HAART are

required to investigate whether or not this improves vascular inflammation and function and ultimately reduces atherosclerotic risk in patients with HIV

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BIBILIOGRAPHY

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ANNEXURES

ABBREVIATIONS

HIV	-	Human Immunodeficiency Virus
AIDS	-	Acquired Immunodeficiency Deficiency Syndrome
ART	-	Antiretroviral Therapy
WHO	-	World Health Organization
CD	-	Cluster of Differentiation
TNF	-	Tumor Necrosis Factor
NK	-	Natural Killer Cells
NOS	-	Nitric Oxide Synthase
ELISA	-	Enzyme Linked Immuno Sorbant Assay
LAC	-	Link ART Center
CIMT	-	Carotid intima media thickness
TNF	-	Tumor necrosis factor
NAT	-	Nucleic acid testing

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

IP/OP NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

PAST HISTORY : Diabetes mellitus:

Systemic hypertension:

Chronic Kidney Disease:

Coronary artery disease:

TREATMENT HISTORY :

PERSONAL HISTORY : Smoking :

Alcohol:

GENERAL EXAMINATION

Pallor: Icterus: Cyanosis: Clubbing:

Lymphadenopathy: Odema:

External markers of HIV :

VITALS : Pulse Rate: BP: Respiratory rate: Temperature:

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM :

RESPIRATORY SYSTEM :

ABDOMEN :

CENTRAL NERVOUS SYSTEM :

CIMT by ultrasound :

CD4 cell count(s) :

Other investigations :

Hemogram: Renal Function Test:

Liver Function Test:

CERTIFICATE OF APPROVAL

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Siva Shanmuganathan.V.
Post Graduate in M.D. (General Medicine)
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr. Siva Shanmuganathan.V.,

The Institutional Ethics Committee has considered your request and approved your study titled **"CORRELATION OF CD4 COUNT WITH CAROTID INTIMA MEDIA THICKNESS IN HIV PATIENTS "** - **NO.(II) 14032016.**

The following members of Ethics Committee were present in the meeting hold on **22.03.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
5.Dr.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
6.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
7.Prof.Srinivasagalu,Director,Inst.of Int.Med.,MMC,Ch-3	: Member
8.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

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

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

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE.
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

MADRAS MEDICAL COLLEGE
31 MAR 2016
CHENNAI-600 003

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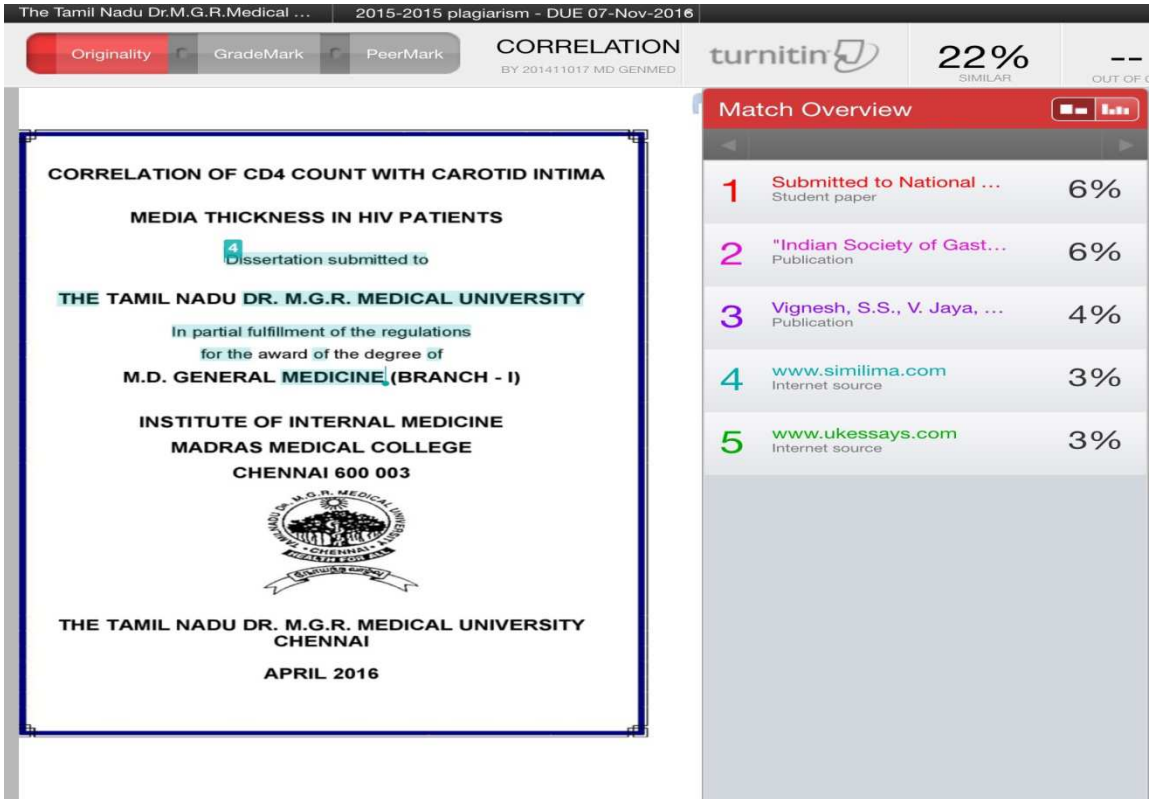

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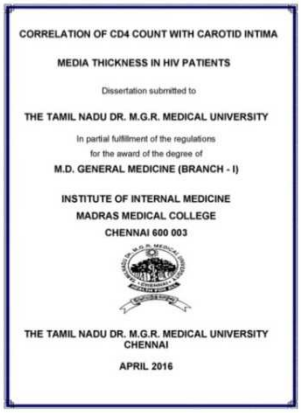

CORRELATION OF CD4 COUNT WITH CAROTID INTIMA

MEDIA THICKNESS IN HIV PATIENTS

Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations
for the award of the degree of
M.D. GENERAL MEDICINE (BRANCH - I)

INSTITUTE OF INTERNAL MEDICINE
MADRAS MEDICAL COLLEGE
CHENNAI 600 003

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI

APRIL 2016

1

INFORMATION SHEET

We are conducting a study on " CORRELATION OF CD4 COUNT WITH CAROTID INTIMA MEDIA THICKNESS IN HIV PATIENTS" among patients attending Rajiv Gandhi Government General Hospital, Chennai Chennai and for that your co-operation to undergo ultrasound neck and your blood sample may be valuable to us.

The purpose of this study is to investigate " correlation between CD4 count and CAROTID INTIMA MEDIA THICKNESS as a marker of atherosclerosis in HIV patients"

We are selecting certain cases and if you are found eligible, we may be using clinical profile, lab test reports and radiological reports for study purposes which does not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator

Signature /left thumb fingerprint of Participant

Date :
Place :

ஆராய்ச்சி தகவல் தாள்

சென்னை இராஜிவ் காந்தி அரசு பொது மருத்துவமனையில் பற்றிய ஒரு ஆராய்ச்சி நடைபெற்று வருகிறது.

எச்.ஐ.வி நோயினால் பாதிக்கப்பட்டோரின் இரத்த நாளங்களில் ஏற்படும் அடைப்பிற்கும் வெள்ளை இரத்த அணுக்களுக்கும் இடையே உள்ள தொடர்பினை அறிவதே இந்த ஆராய்ச்சியின் நோக்கமாகும்.

அதற்கு வெள்ளை இரத்த அணுக்களின் எண்ணிக்கை மற்றும் கழுத்து பகுதி ஸ்கேன் அவசியம் அதற்கு தங்கள் ஒத்துழைப்பு தேவை

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருத்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

PATIENT CONSENT FORM

Study detail : CORRELATION OF CD4 CELL COUNT WITH CAROTID CAROTID INTIMA MEDIA THICKNESS IN HIV PATIENTS

Study centre : INSTITUTE OF INTERNAL MEDICINE , Madras Medical College and Rajiv Gandhi Government General Hospital

Patient's Name :

Patient's age :

Identification number :

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ❑

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

I understand that sponsor of the clinical study, others working on the sponsor's behalf , the ethical committee and the regulatory authorities will not need my permission to look my health records , both in respect of current study and any further research that may be conducted in relation to it , even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published , unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

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

I hereby consent to participate in this study ❑

I hereby give permission to undergo complete clinical examination , biochemical and radiological tests ❑

Signature of Investigator
Study Investigator's Name:
DR. SIVA SHANMUGANATHAN V

Signature/thumb impression
Patient's Name and Address:

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு:

எச்.ஐ.வி நோயினால் பாதிக்கப்பட்டோரின் இரத்த நாளங்களில் ஏற்படும் அடைப்பிற்கும் வெள்ளை இரத்த அணுக்களுக்கும் இடையே உள்ள தொடர்பினை பற்றிய ஆராய்ச்சி.

பெயர்: தேதி:

வயது: உள்நோயாளி எண்:

பால்: ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் வெள்ளை இரத்த அணுக்களின் எண்ணிக்கை மற்றும் கழுத்தில் உள்ள இரத்த நாளங்களில் ஏற்படும் அடைப்பினை கண்டறியும் ஸ்கேன் பரிசோதனைகளைப் பற்றியும் ஆராய்ச்சியாளர் கூற முழுவதும் விளங்கப்பெற்றேன்.

மேற்கொண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

கையொப்பம் /இடது கட்டைவிரல் இரேகை

MASTER CHART

S.NO	AGE	SEX	CD4 COUNT	CIMT-R	CIMT-L	CIMT-MEAN	ART DURATION
1	48	F	758	0.3	0.3	0.3	4 YEARS
2	45	F	554	0.5	0.5	0.5	3 YEARS
3	35	M	597	0.4	0.4	0.4	1 YEAR
4	32	M	322	0.5	0.6	0.55	7 YEARS
5	48	M	189	0.6	0.7	0.65	10 YEARS
6	54	M	1039	0.3	0.4	0.35	1 YEAR
7	49	F	134	0.6	0.6	0.6	2 YEARS
8	22	F	297	0.4	0.4	0.4	3 YEARS
9	34	F	642	0.5	0.5	0.5	2 YEARS
10	53	M	478	0.3	0.3	0.3	1 YEAR
11	37	F	609	0.6	0.5	0.55	3 YEARS
12	42	M	1508	0.2	0.3	0.25	1 YEAR
13	54	F	600	0.5	0.5	0.5	4 YEARS
14	47	M	710	0.5	0.6	0.55	2 YEARS
15	39	M	301	0.3	0.4	0.35	3 YEARS
16	47	F	681	0.4	0.4	0.4	4 YEARS
17	37	F	722	0.4	0.4	0.4	1 YEAR
18	38	F	556	0.3	0.3	0.3	3 YEARS
19	26	M	97	0.6	0.6	0.6	4 YEARS
20	52	F	199	0.8	0.7	0.75	9 YEARS
21	44	M	643	0.2	0.2	0.2	3 YEARS
22	34	M	721	0.4	0.4	0.4	5 YEARS
23	31	M	410	0.3	0.3	0.3	4 YEARS
24	24	F	627	0.3	0.3	0.3	2 YEARS
25	35	F	276	0.4	0.4	0.4	5 YEARS
26	52	F	357	0.3	0.3	0.3	8 YEARS
27	40	F	205	0.6	0.6	0.6	6 YEARS
28	26	M	112	0.6	0.7	0.65	3 YEARS
29	42	M	178	0.7	0.7	0.7	6 YEARS
30	32	M	711	0.3	0.3	0.3	5 YEARS
31	35	F	179	0.4	0.5	0.45	8 YEARS
32	43	M	399	0.2	0.2	0.2	9 YEARS
33	32	M	478	0.4	0.3	0.35	4 YEARS
34	37	M	744	0.3	0.3	0.3	3 YEARS
35	42	M	299	0.4	0.4	0.4	4 YEARS
36	32	F	312	0.5	0.5	0.5	4 YEARS
37	45	M	569	0.5	0.4	0.45	5 YEARS
38	54	M	101	0.9	0.9	0.9	6 YEARS
39	24	F	59	0.5	0.5	0.5	5 YEARS
40	51	F	531	0.3	0.3	0.3	8 YEARS
41	40	M	364	0.5	0.4	0.45	7 YEARS
42	63	M	295	0.6	0.5	0.55	5 YEARS
43	45	M	359	0.4	0.4	0.4	3 YEARS
44	43	F	410	0.5	0.4	0.45	6 YEARS
45	47	M	201	0.5	0.5	0.5	4 YEARS
46	39	F	653	0.2	0.2	0.2	4 YEARS
47	46	F	397	0.3	0.3	0.3	3 YEARS
48	54	F	356	0.4	0.4	0.4	3 YEARS
49	38	F	709	0.3	0.3	0.3	7 YEARS

50	32	F	412	0.4	0.4	0.4	4 YEARS
51	34	M	309	0.4	0.3	0.35	4 YEARS
52	41	M	505	0.5	0.5	0.5	5 YEARS
53	42	M	576	0.6	0.6	0.6	5 YEARS
54	33	M	704	0.3	0.4	0.35	4 YEARS
55	45	F	101	0.5	0.6	0.55	5 YEARS
56	47	F	623	0.4	0.4	0.4	6 YEARS
57	43	M	654	0.4	0.4	0.4	4 YEARS
58	32	F	744	0.3	0.3	0.3	3 YEARS
59	43	M	201	0.8	0.8	0.8	7 YEARS
60	46	M	622	0.7	0.7	0.7	6 YEARS
61	53	M	271	0.9	0.9	0.9	4 YEARS
62	37	F	179	0.6	0.6	0.6	7 YEARS
63	44	F	798	0.2	0.3	0.25	1 YEAR
64	44	F	123	0.7	0.7	0.7	8 YEARS
65	32	F	663	0.4	0.4	0.4	6 YEARS
66	42	M	390	0.4	0.4	0.4	2 YEARS
67	36	M	729	0.4	0.3	0.35	4 YEARS
68	24	M	376	0.2	0.2	0.2	3 YEARS
69	61	M	195	1	1.1	1.05	7 YEARS
70	38	M	456	0.5	0.5	0.5	1 YEAR
71	29	F	222	0.5	0.4	0.45	2 YEARS
72	49	F	548	0.4	0.5	0.45	3 YEARS
73	53	F	354	0.5	0.5	0.5	7 YEARS
74	27	M	503	0.3	0.3	0.3	4 YEARS
75	29	M	423	0.2	0.2	0.2	3 YEARS
76	41	F	551	0.3	0.3	0.3	3 YEARS
77	51	F	411	0.3	0.4	0.35	4 YEARS
78	54	M	468	0.4	0.4	0.4	3 YEARS
79	46	F	593	0.3	0.3	0.3	8 YEARS
80	37	F	190	0.5	0.5	0.5	5 YEARS
81	39	F	298	0.6	0.7	0.65	5 YEARS
82	45	F	447	0.5	0.5	0.5	7 YEARS
83	52	M	678	0.4	0.4	0.4	3 YEARS
84	48	M	883	0.3	0.3	0.3	3 YEARS
85	23	M	234	0.5	0.5	0.5	2 YEARS
86	26	M	354	0.2	0.2	0.2	5 YEARS
87	38	F	421	0.2	0.3	0.25	6 YEARS
88	57	F	567	0.3	0.3	0.3	3 YEARS
89	50	F	270	0.4	0.4	0.4	2 YEARS
90	47	M	378	0.4	0.5	0.45	1 YEAR
91	45	F	910	0.3	0.3	0.3	3 YEARS
92	39	M	856	0.3	0.3	0.3	3 YEARS
93	35	M	566	0.4	0.5	0.45	4 YEARS
94	43	M	678	0.5	0.5	0.5	6 YEARS
95	46	M	765	0.4	0.4	0.4	4 YEARS
96	39	M	973	0.5	0.4	0.45	5 YEARS
97	51	F	478	0.3	0.4	0.35	4 YEARS
98	43	M	417	0.4	0.4	0.4	1 YEAR
99	44	M	291	0.5	0.5	0.5	2 YEARS
100	37	M	358	0.5	0.5	0.5	5 YEARS