A PROSPECTIVE STUDY TO EVALUATE THE IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON CD_4 T CELL COUNT

Dissertation submitted to
The Tamilnadu Dr. M.G.R. Medical University
Chennai - 600 032.

In partial fulfillment of the
regulations for the award of the Degree of
MD (General Medicine)
Branch I, Part II

Kilpauk Medical College
Chennai - 600 010.

MARCH 2007

CERTIFICATE

This is to certify that Dr. V. MADHAVAN, post graduate student (April 2004 to March 2007) in the Department of Medicine, Kilpauk Medical College, Chennai - 600 010, has done this dissertation " **A PROSPECTIVE STUDY TO EVALUATE THE IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON CD_4 T CELL COUNT** " under my guidance and supervision in fulfillment of the regulation laid down by THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY for the award of MD Degree in General Medicine. (Branch I, Part II)

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ACKNOWLEDGEMENT

I owe my thanks to the Dean, Govt. Kilpauk Medical College and Hospital. **Dr. Thiagavalli Kirubakaran, MD** for allowing me to avail the facilities needed for my dissertation work.

I am extremely grateful to **Prof. Dr. S.R. Sakuntala, MD Professor and Head of the Department of Medicine,** Govt. Kilpauk Medical College and Hospital for permitting me to do the study and for her constant encouragement and guidance.

I express my gratitude to the Medical Registrar **Dr. Raghunandhan, MD** and Assistant Professors **Dr. R. Kulothungan MD, Dr. Gunasekaran MD,** for their encouragement and guidance.

I am also thankful to **Dr. E. Suresh DCH** ART Centre Medical Officer, KMCH, for his cooperation in this study.

Last, but not the least, my sincere thanks to all the patients who cooperated for this study, without whom this study could not have been undertaken.

CONTENTS

INTRODUCTION

Human Immunodeficiency Virus, the cause of AIDS, continues to spread, being described as a global health emergency by the world health organization. HIV type 1 is the etiologic agent of most cases of AIDS[1,2]. The epidemic of HIV-1 infection continues to expand globally, with more than 40 million humans currently infected by the virus[3]. HIV disease has claimed more than 20 million lives worldwide[4]. The recent estimate done by National AIDS Control organization reports 5.1 million HIV infected people in India.

India has the second highest HIV / AIDS burden in the world next to south Africa. It is a disease that is acquired, for which no permanent cure has been found till date, and consequently has a great impact on the quality of life of a patient. HIV/AIDS infection results in a wide range of clinical consequences from asymptomatic carriage to life threatening opportunistic diseases. In persons infected with HIV, ongoing viral replication produces a sequential decline in and ablation of cell mediated immunity, giving rise to diverse manifestations of opportunistic disease. The acquired immuno deficiency syndrome is the most advanced stage of this illness, in which the infected host can no longer control opportunistic organisms or malignancies, that rarely cause illness in immuno competent individuals. The interactions between the human immuno deficiency virus and the human immune system are extraordinarily complex, as evidenced by the highly variable rates of disease progression observed in HIV infected individuals.

HIV subverts the immune system by infecting $CD4^+$ T cells that normally orchestrate immune responses and by activating the immune system and inducing a cytokine milieu that the virus uses to its own replicative advantage. The discovery that certain chemokine receptors function as HIV Co-receptors of HIV entry into target cells has expanded the scope of host factors that play a role in the pathogenesis of HIV-induced disease. The lack of recognizable correlates of protective immunity in HIV infection continues to hamper vaccine development and immunotherapeutic approaches. It remains unclear why the vast majority of HIV infected patients experience inexorable immunodeficiency and disease progression despite the presence of these robust antiviral immune responses.

The progress that has been made to date in understanding the pathogenesis of HIV infection is unparalleled. The recent availability of effective combination antiretroviral therapy has had extraordinary clinical benefits for patients and has also provided important insights into the immunologic and virologic factors associated with control of HIV infection and disease progression. It is clear that HIV induces dysfunction of nearly all elements of the immune system and that the pathogenesis of HIV disease is multifactorial, causing $CD4^+$ T cell depletion and dysfunction. And the prevalence and morbidity due to opportunistic infections can be controlled by improving the general condition and immune status of the individual.

In this study the impact of antiretroviral therapy on $CD4^+$ cell count was evaluated in patients suffering from HIV / AIDS at Govt. Kilpauk Medical College, Chennai.

AIM OF THE STUDY

AIM:

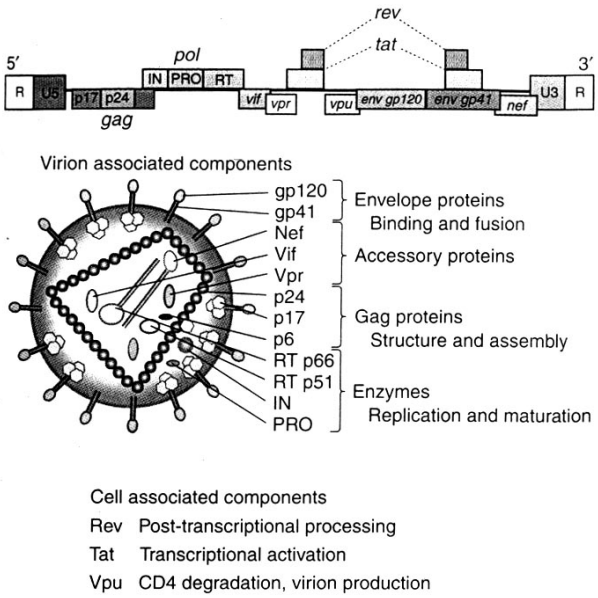
The aim of the study which was conducted on patients attending antiretroviral therapy centre (ART Centre) of Govt. Kilpauk Medical College Hospital was to evaluate the impact of highly active antiretroviral therapy on CD4 T cell count.

REVIEW OF LITERATURE

DEFINITION:

HIV belongs to the lentivirus group of the retrovirus family. There are at least two types, HIV - 1 and HIV - 2. AIDS definition has varied widely, the most widely used being the Centre for Disease Control (CDC) classification of 1993. Since 1993, the definition of AIDS has differed between USA and Europe. The USA definition includes individuals with CD4 count below 200/μl or CD4 percentage of total lymphocyte count of <14 % in addition to the clinical classification based on the presence of specific indicator diagnosis called as AIDS - defining conditions. In Europe, the definition remain based on the diagnoses of specific clinical conditions with no inclusion of CD4 lymphocyte count.

GENETIC ORGANIZATION OF HIV - 1



HIV-1 is an enveloped retrovirus with a plus - stranded ribonucleic acid (RNA) genome that contains genes for proteins with structural, enzymatic, and regulatory functions.

PREVALENCE AND CLASSIFICATION:

The global epidemiologic pattern of human immuno deficiency virus has changed dramatically from North America and Western Europe to Sub-Saharan Africa and Asia, that includes countries like Nigeria, Ethiopia, India, Russia and China. The disease has evolved into an epidemic of mainly heterosexual transmission, disproportionately affecting those most socially and economically vulnerable sections, resembling the 'classic' infectious diseases. It is estimated that one third of those currently living with HIV/AIDS are between of the ages of 15 and 24. In India, the epidemic seems to be following the so called 'type 4' pattern, where the epidemic shifts from the highest risk group (commercial sex workers, drug users) to bridge population (clients of sex workers, STD patients and partners of drug users) and then to general population.

Estimate at the national level is that there are about 5.1 million people suffering from HIV infection at the end of 2004. States such as Tamilnadu, Andhra Pradesh, Manipur, Maharashtra, Nagaland and Karnataka are reporting high levels of infection (between 1-2 percent in antenatal women).

CLASSIFICATION OF AIDS:

1993 AIDS SURVEILLANCE CASE DEFINITION:

Bacterial infections, multiple or recurrent.

Candidiasis of bronchi, trachea, or lungs

Candidiasis, esophageal

Cervical cancer, invasive

Coccidioidomycosis, disseminated or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (>1 month's duration)

Cytomegalovirus disease (other than liver, spleen or nodes)

Cytomegalovirus retinitis (with loss of vision)

Encephalopathy, HIV related

Herpes simplex, chronic ulcer (>1 month's duration) or bronchitis, pneumonitis, or esophagitis

Histoplasmosis, disseminated or extrapulmonary

Isosporiasis, chronic intestinal (>1 month's duration)

Kaposis sarcoma

Lymphoid interstitial pneumonia and/or pulmonary lymphoid hyperplasia

Lymphoma, Burkitt's (or equivalent term)

Lymphoma, immunoblastic (or equivalent term)

Lymphoma, primary of brain

Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)

Mycobacterium avium - intracellulare complex or Mycobacterium kansasii (disseminated or extrapulmonary)

Pnemocystis jirovecii pneumonia

Pneumonia, recurrent

Progressive multifocal leukoencephalopathy

Salmonella septicemia, recurrent

Toxoplasmosis of brain

Wasting syndrome of HIV infection

1993 REVISED CLASSIFICATION SYSTEM FOR HIV INFECTION AND EXPANDED AIDS SURVEILLANCE CASE DEFINITION FOR ADOLESCENTS AND ADULTS[5]

CLINICAL CATEGORIES

	A	**B**	**C**
$CD4^+$ T Cell Categories	**Asymptomatic, Acute (Primary) HIV, or PGL**	**Symptomatic, Not A or C Conditions**	**AIDS-Indicator Conditions**
1. ≥500/μL	A1	B1	C1
2. 200-499/μL	A2	B2	C2
3. <200/μL AIDS indicator T-cell count	A3	B3	C3

Clinical conditions in category C are listed in the 1993 Aids Surveillance Case Definition.

CLASSIFICATION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION (WHO CLINICAL STAGING SYSTEM)

Clinical Stage 1

Asymptomatic

Persistent generalized Lymphadenopathy (PGL)

Performance scale 1 : asymptomatic, normal activity

Clinical Stage 2

Weight loss, < 10% of body weight

Minor mucocutaneous manifestations

Herpes zoster, within the last 5 years

Recurrent upper respiratory tract infections (e.g bacterial sinusitis)

And/or performance scale 2 : symptomatic, normal activity

Clinical stage 3

Weight loss, >10% of body weight

Unexplained chronic diarrhea, > 1 month

Unexplained prolonged fever (intermittent or constant), >1 month

Oral candidiasis (thrush)

Oral hairy leukoplakia

Pulmonary tuberculosis, within the past year

Severe bacterial infections (e.g pneumonia, pyomyositis)

And/or performance scale 3 : bedridden, >50% of the day during the last month

Clinical stage 4

HIV wasting syndrome,

Pneumocystis jirovecii pneumonia

Toxoplasmosis of the brain

Cryptosporidiosis with diarrhea, > 1 month

Cryptococcosis, extrapulmonary

Cytomegalovirus (CMV) disease of an organ other than liver, spleen, or lymph nodes

Herpes simplex virus (HSV) infection, mucocutaneous >1 month, or visceral any duration.

Progressive multifocal leukoencephalopathy (PML)

Any disseminated endemic mycosis (e.g histoplasmosis, coccidioidomycosis)

Candidiasis of the esophagus, trachea, bronchi, or lungs

Nontyphoid Salmonella septicemia

Extrapulmonary tuberculosis

Atypical mycobacteriosis, disseminated

Lymphoma

Kaposis' sarcoma (KS)

HIV encephalopathy

And/or performance scale 4 : bedridden, >50% of the day during the last month.

MODES OF TRANSMISSION:

Worldwide, HIV infection is basically a sexually transmitted infection. Unprotected heterosexual intercourse accounts for the large majority of cases of HIV infection in the developing world. The low efficiency of penile vaginal intercourse for transmission of HIV has now been well documented especially for transmission from women to men. Factors that may enhance the efficiency of heterosexual transmission of HIV include higher viremia or more advanced immuno deficiency in the infecting partner, anal intercourse,

sex during menses and presence of other Sexually Transmitted Diseases. Viral load of HIV has been shown to be the primary determinant of heterosexual transmission in HIV - discordant couples[6]. Other factors that may increase the risk of heterosexual transmission are traumatic sexual intercourse, cervical ectopy etc[7].

FACTORS INFLUENCING THE SPREAD OF THE HUMAN IMMUNODEFICENCY VIRUS:

Sexual behaviour is undoubtedly the most important determinant of HIV spread. In general men have more partners than women. The behaviour of one's partner is as relevant for the risk of HIV infection as is one's own behaviour. Sexual practices in particular the frequency of anal intercourse, which is the most efficient mode of sexual transmission of HIV. Last, but not least, the rate of condom use plays a major role in the extent of HIV spread.

NATURAL HISTORY OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION:

The clinical spectrum of HIV infection includes primary infection (the acute retroviral syndrome), asymptomatic infection, early symptomatic infection, and advanced immunodeficiency with opportunistic complications.

Viral load or viremia is monitored by measurement of HIV RNA in plasma, and immunologic status is reflected in the absolute number of CD4.

Plasma viremia declines precipitously with antibody seroconversion and the development of an anti-HIV immune response usually reaching a steady-state level within 6 to 12 months[8,9].

In most untreated asymptomatic patients, the CD4 cell count declines gradually over several years. The slope of decline is a function of the plasma viral load. Plasma viremia increases, accompanied by a more rapid decline in CD4 cell count before the onset of symptomatic disease. As the viral load increases and CD4 cell count falls the risk of opportunistic infections, malignancies, wasting, neurologic complications, and death increases substantially.

There is considerable variation in the progression of HIV disease, with some individuals progressing from infection to AIDS in less than 5 years[10] and so-called long-term nonprogressors remaining asymptomatic without treatment or evidence of immunologic decline for many years[11,12].

A number of laboratory tests have been correlated with progressive immunodeficiency, the development of AIDS and mortality. Taken together, however, the CD4 lymphocyte count and plasma viral load are the best prognostic markers for subsequent disease course in an HIV-infected individual. The CD4 lymphocyte count, a specific test for cellular immunocompetence, is a sensitive predictor of the development of symptomatic HIV infection and AIDS in the near term as it reflects current

immunologic capacity[13]. Conversely the plasma viral load (HIV-1 RNA) is an extremely useful predictor of disease course over a more extended period of time and is strongly associated with the rate of subsequent CD4 cell count decline. A more rapid decline in CD4 count, faster clinical progression and decreased survival are all associated with a higher baseline viral load. Baseline plasma viral load was a stronger predictor of progression and mortality than CD4 count.

In addition the average annual decline in the CD4 count of HIV infected men varied according to their initial viral load, decreasing by 36 CD4 cells/year among men with baseline HIV-1 RNA less than 500 copies/mL, and by 77 $CD4^+$ cells/year among men with baseline HIV-1 RNA greater than 30,000 copies/mL[14]. Using the viral load and $CD4^+$ count together, however, gives the best prognostic estimate of subsequent clinical course.

Put in the context of HIV pathogenesis, the viral load measures the replicative rate of the infection and its destructive potential for the cellular immune system, and the $CD4^+$ count gauges the extent of immune compromise and the present risk of opportunistic disease. Subsequent studies revealed that survival after diagnosis of AIDS was directly related to the CD4 cell level at diagnosis. In most studies before the availability of combination antiretroviral therapy, median survival after the diagnosis of AIDS was estimated to be between 12 and 18 months[15]. The mean survival time after a $CD4^+$ count of $200/mm^3$ was 38 to 40 months[16,17].

Other markers of HIV disease progression that have been validated in clinical studies include the HIV p24 antigen, serum β2-microglobulin, neopterin, acid-labile interferon-α, anti-p24 antibody, and soluble CD8. These so-called surrogate markers are measures of either viral markers or host immune responses to HIV. Many of these measures do not provide prognostic information independent of the viral load. However the heat-denatured p24 antigen assay does provide prognostic information independent of HIV-1 RNA and could also be used in lieu of viral load or $CD4^+$ lymphocytes as a marker of subsequent disease progression[18,19].

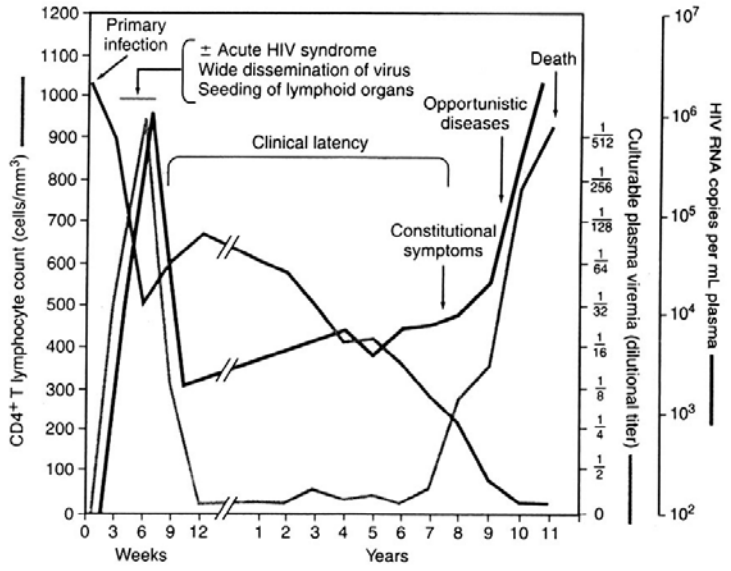
Other low-cost predictors of disease progression include total lymphocyte count and hemoglobin[20,21,22]. The probability of a HIV- infected individual developing opportunistic disease is influenced by several factors. First, immunocompetence is a critical determinant of whether an infected individual can contain a potential pathogen. As discussed later, the $CD4^+$ cell count appears to be the most clinically useful measure of host cellular immunocompetence and plays a central role in the staging of HIV disease. Second, exposure to potential pathogens is required before disease can result. Third, the relative virulence of the pathogen.

Although the range of $CD4^+$ cell counts for some conditions is broad, most patients with truly opportunistic infections had $CD4^+$ counts less than $100/mm^3$. HIV-1 infection increases susceptibility to tuberculosis[23]. Malaria

is also endemic in increased frequency and severity in HIV-infected persons, particularly during pregnancy.

Clinical findings may also predict disease progression in seropositive subjects. Oral candidiasis and oral hairy leukoplakia are early clinical markers of immunosuppression and herald the development of AIDS in many patients[24]. Generalized lymphadenopathy is also a clinical marker of HIV infection but does not predict progression to AIDS. Most opportunistic diseases increase the risk of death independently of the $CD4^+$ cell count[25].

NATURAL HISTORY OF HUMAN IMMUNODEFICIENCY VIRUS (HIV)



CLINICAL PRESENTATION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION:

HIV infection causes disease manifestations that include, an acute viral illness seen in the initial weeks of infection and associated with a high viral load and an intense host immune response, immunologically mediated process and opportunistic disease resulting from impaired host responses as the cellular immune system is damaged or ablated.

Potent antiretroviral therapy has added two new categories of clinical manifestations that may be commonly encountered in patients with HIV infection namely immune reconstitution syndromes with exacerbations of previously silent or adequately treated infections, especially mycobacterial infections, and a syndrome of lipodystrophy with fat loss and redistribution, elevated serum triglycerides and cholesterol, and insulin resistance seen in patients receiving HAART, especially with protease inhibitors.

CLINICAL FINDINGS:

Acute Retroviral Syndrome

The initial manifestation of HIV infection in one half to two thirds of recently infected individuals is a mononucleosis like illness referred to as the acute retroviral syndrome. The incidence of the acute retroviral syndrome is not precisely known. Overall this syndrome is probably underreported. The

clinical features of the acute retroviral syndrome are nonspecific and variable. The onset of the illness ranges from 1 to 6 weeks after exposure to the virus but peaks at 3 weeks. Fever, sweats, malaise, myalgias, anorexia, nausea, diarrhea, and a nonexudative pharyngitis are prominent symptoms[26].

Physical examination frequently reveals cervical, occipital, or axillary lymphadenopathy, rash and less commonly hepatosplenomegaly. Their occurrence is probably due to the depression of the $CD4^+$ cell count that generally accompanies acute HIV infection.

Laboratory evaluation of patients with the syndrome reveals a reduced total lymphocyte count, elevated sedimentation rate, negative heterophile antibody test, and elevated transaminase and alkaline phosphatase levels[26].

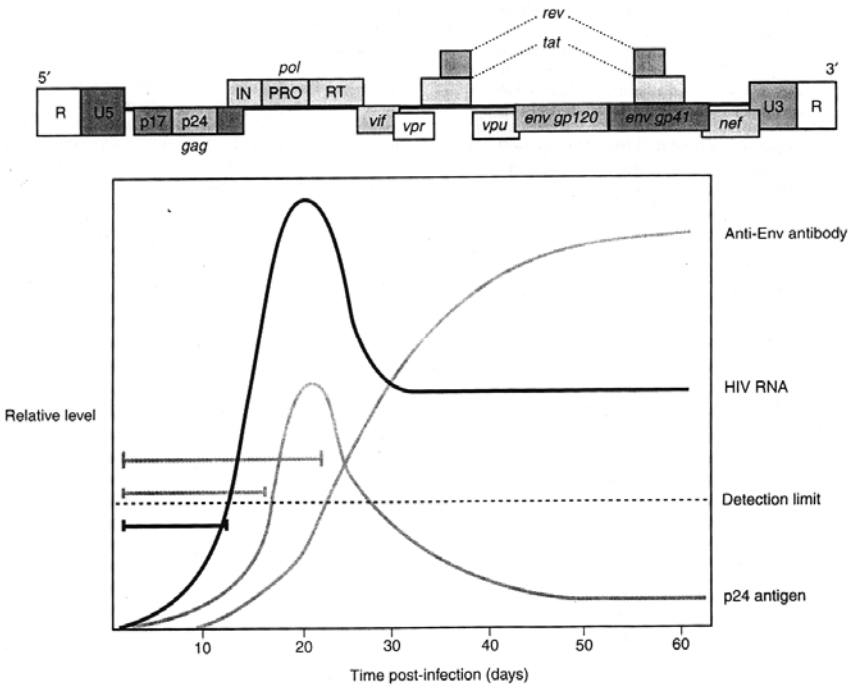
Initially, the total lymphocyte count, including both $CD4^+$ and $CD8^+$ cells decreases with a normal ratio of $CD4^+$ to $CD8^+$ cells. Within several weeks, both the $CD4^+$ and $CD8^+$ cell populations begin to increase. The rise in $CD8^+$ cell numbers is relatively greater than that in $CD4^+$ cells, and the CD4/CD8 ratio is inverted. In the weeks that follow, the $CD8^+$ cell population increase rather markedly because of HIV specific $CD8^+$ Tlymphocytes. The ratio of $CD4^+$ to $CD8^+$ cells usually remains inverted as the acute illness resolves (primarily because of excess numbers of $CD8^+$ cells)

HIV p24 antigen may be detected in the serum and cerebrospinal fluid in about 75% of patients with primary HIV infection within 2 weeks of

exposure. The most sensitive marker for acute HIV infection, however, is plasma HIV RNA, which is markedly elevated in most patients[27]. Typical RNA levels range from 10^5 to more than 10^6 copies/mL of plasma. High level viremia is virtually diagnostic of acute infection in the absence of anti-HIV antibodies.

There is increasing interest in treating acute HIV with combination antiretroviral therapy, as there is evidence that this may both lower the viral setpoint and lead to enhanced $CD4^+$ and $CD8^+$ HIV-specific responses[28]. However early treatment does not appear to prevent establishment of reservoirs of latently infected resting $CD4^+$ cells and may not provide any long term benefit[29].

HIV INFECTION PROFILE



PERSISTENT GENERALIZED LYMPHADENOPATHY:

The pathogenesis of generalized lymphadenopathy is related to the rapid infection of $CD4^+$ cells in lymph nodes by HIV after initial infection. The syndrome of PGL is defined as the presence of two or more extrainguinal sites of lymphadenopathy for a minimum of 3 to 6 months for which no other explanation can be found. The most frequently involved node groups are the posterior and anterior cervical, submandibular, occipital, and axillary chains. Epitrochlear and femoral nodes may also be enlarged. Physical examination usually reveals symmetrical, mobile, rubbery lymph nodes ranging from 0.5 to 2 cm. Pain and tenderness are uncommon. Mediastinal and hilar adenopathy is not characteristic of the syndrome.

The natural history of HIV infection in individuals with PGL does not differ significantly from that of HIV infection without PGL. In patients treated with HAART, previously involuted lymph nodes may again enlarge as HIV-specific and other T cells are replenished. In addition, focal lymphadenitis with constitutional symptoms may occur in patients with previously silent mycobacterial infections, 1 to 2 months after starting HAART. These 'reversal reactions' or immune reconstitution syndromes are reminiscent of reversal reactions seen in multibacillary forms of leprosy, heralding a return of pathogen specific T-cell responses.

CONSTITUTIONAL DISEASE AND WASTING:

Severe wasting with loss of more than 10% of body weight is generally a finding of advanced HIV disease. The exact incidence of constitutional symptoms, fatigue, and weight loss is not known, and the etiology is varied and often multifactorial. Elevated levels of myostatin-immunoreactive protein, a muscle catabolic agent, have been found in men with HIV and wasting[30]. Weight loss has remained an important predictor of mortality even in the era of HAART[31]. In patients with more advanced HIV disease with high viral loads and severe depletion of $CD4^+$ cells, constitutional disease (fatigue, weight loss, malaise, fever) usually heralds the onset of opportunistic infections or malignancies.

The definition of wasting syndrome in the United States is the presence of unexplained constitutional disease for more than 1 month with a temperature greater than 38.3^{o}C, diarrhea, and loss of more than 10% of baseline body weight.

IMMUNE RECONSTITUTION SYNDROMES:

HAART (regimens that include a HIV protease inhibitor or non nucleoside reverse transciptase inhibitor together with nucleoside reverse transciptase inhibitors) is associated with dramatic reductions in HIV-1 RNA and increase in CD4 lymphocyte counts. They are sometimes associated with paradoxical worsening of underlying opportunistic infections[32]. Not every

patient who has immunologic improvement with antiretroviral therapy experience paradoxical worsening. But it has been noted in Mycobacterium tuberculosis, Mycobacterium avium Complex Disease, Cytomegalovirus, Varicella-Zoster virus, Viral Hepatitis.

THE IMMUNOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION:

HIV subverts the immune system by infecting $CD4^+$ T cells. It is clear that HIV induces dysfunction of nearly all elements of the immune system and that the pathogenesis of HIV disease is multifactorial[33].

HUMAN IMMUNODEFICIENCY VIRUS ENTRY:

CD4 was identified as the major cellular receptor for HIV fusion and entry in 1984[34]. Transfection of the CD4 gene into CD-4 negative (CD-4) human cells rendered them infectable with HIV[35]. However, transfection of the human CD4 gene into murine cell lines did not render these cells susceptible to HIV infection despite glycoprotein (gp) 120 binding to CD4, suggesting that other factors were necessary for HIV fusion and entry. The protein, called fusin, together with CD4, was required for T-tropic envelope fusion to target cells.

DISSEMINATION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION:

It remains unclear which cell type in the blood, lymphoid tissue, spleen, or mucosa is the first to actually become infected with HIV. However in studies of macaques exposed to SIV intravaginally, bone marrow-derived dendritic cells (DCs) in the vaginal mucosa are the first cells to contain SIV DNA which is detectable 2 days after exposure.

Recently, it has been shown that dendritic cell-specific intracellular adhesion molecule (ICAM) 3-grabbing nonintegrin (DC-SIGN)[36,37], a protein expressed on DCs in the T-cell area of tonsils, lymph nodes, spleen and in the lamina propria of mucosal tissues, may be important in the attachment of HIV to DCs and may be an important factor in the transmission of HIV from DCs to T cells. It is likely that DCs carry HIV from tissues in which the initial rounds of viral replication occur to the regional lymph nodes, where $CD4^+$ T cells become infected after contact with DCs. This leads to subsequent rounds of virus replication and spread in the absence of HIV-specific immune responses. Thus, lymphoid tissue plays a key role in the initiation and dissemination of HIV infection.

HUMORAL IMMUNE RESPONSES:

Antibodies that bind HIV proteins, including the viral surface envelope glycoprotein, can be detected in the plasma within weeks of HIV infection coincident with the decline of plasma viremia[38,39].

Both the CD4 and co-receptor binding sites are well conserved among known viral isolates and are not glycosylated. For these reasons they are thought to be important targets of neutralizing antibodies.

CELLULAR IMMUNE RESPONSES:

Cytotoxic T-Lymphocytes

MHC class I-restricted, HIV-specific $CD8^+$ cytotoxic T-lymphocyte (CTL) responses are found in the peripheral blood within the first few months of HIV infection and are detected during the chronic phase of infection in the majority of HIV infected individuals[40]. First the temporal association of the peak of the HIV-specific CTL response with the decline of viremia during acute infections is thought to represent the effect of virus-specific CTL in restricting HIV replication in humans[40,41]. HIV-specific $CD8^+$ T cells falls due to a lack of $CD\text{-}4^+$ T-cell help[42].

CD-4^{+} T-Cell Responses

Unlike most other infections of humans, HIV infection is characterized by the absence of HIV-specific CD4^{+} T-cell proliferative responses in the vast majority of untreated patients[43]. Because HIV infects CD4^{+} T-cell, it was believed that the early loss of HIV-specific proliferative responses may be the result of infection and deletion of HIV-specific CD4^{+} T cells in the lymphoid tissues on encountering the virus. Thus, there is now general agreement that HIV-specific CD4^{+} T cells persist in patients with progressive disease.

RESERVOIRS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION:

There is unequivocal evidence from several lines of investigation that there is ongoing HIV replication despite effective ART. The most powerful demonstration of the inability of ART to eradicate HIV infection comes from in vivo studies of individuals who began ART during the chronic stage of HIV infection, achieved and maintained suppression of plasma HIV RNA for up to 2 years and subsequently interrupted therapy. Interruption of ART resulted in a rapid rebound of plasma viremia in 95% of individuals[44]. It has been demonstrated that an evolution in HIV envelope and protease genes occurs in individuals who have been effectively treated with ART, indicating persistent HIV replication despite adequate therapy[45]. Finally it has been demonstrated using ultrasensitive assays with a limit of detection of less than

3 copies/mL that many individuals with "undetectable" (<50 copies/mL) plasma HIV by standard assays have persistent low-level plasma viremia[46]. Thus there are reservoirs of ongoing HIV replication that persist in the presence of effective ART. Important HIV reservoir sites include lymphoid tissue and resting $CD4^+$ T cells that circulate in the blood.

RESTING CD4 T CELLS:

It has been clearly demonstrated that the pool of resting $CD4^+$ T cells that carry replication-competent HIV persisted in essentially all infected individuals who were receiving ART[29, 47,48]. This HIV reservoir is established during the earliest stages of HIV infection. The initiation of ART as early as 10 days following infection with HIV does not prevent the establishment of the resting $CD4^+$ T-cell reservoir of HIV. Therefore, the pool of HIV-infected resting $CD4^+$ T cells is a clinically relevant reservoir of HIV.

LYMPHOID TISSUE:

Lymphoid tissue is a major site of HIV replication and plays a role in the progression of disease throughout all stages of infection. The significant role of lymphoid tissue in ongoing HIV replication during all stages of disease in the absence of ART suggests that this compartment may play a significant role in ongoing HIV replication in the presence of ART. There is a rapid decrease in lymph node viral burden following the initiation of ART, within 24 weeks, the majority of HIV RNA detected by in situ

hybridization is eliminated and it is uncommon to detect HIV RNA in the germinal centers[49]. There is a commensurate decrease in HIV RNA as quantified by reverse transcription - polymerase chain reaction per gram of tissue or in isolated lymph node mononuclear cells. Lymphoid tissue other than lymph nodes may serve as important reservoirs of HIV infection. Gastrointestinal lymphoid tissue harbors HIV that is not completely cleared with ART. However, the precise contribution of non-lymph node lymphoid tissue to persistent HIV replication in the presence of ART remains unknown.

MECHANISMS OF $CD4^+$ T-CELL DEPLETION :

Effective ART has provided fundamental insights into the understanding of the potential contributions of increased destruction, decreased production, and redistribution as mechanisms for $CD4^+$ T-cell depletion in HIV-infected individuals.

a) Increased Destruction

1. **Direct Infection :** The observations that $CD4^+$ T cells are the principal targets of HIV infection in vivo[34] and that HIV infection of $CD4^+$ T cells in vitro causes cytopathicity[50,51] led to a reasonable assumption that direct infection of $CD4^+$ T cells in vivo results in their depletion. However quantitative studies of the frequency of HIV infected cells in vivo suggest that single cell killing by direct infection with HIV may not be the predominant mechanism of $CD4^+$ T cell depletion.

2. **Apoptosis :** Apoptotic cell death is characterized by plasma membrane blebbing, nuclear condensation, DNA fragmentation and release of cellular contents in the form of small, dense apoptotic bodies. Ingestion of apoptotic bodies by phagocytes completes the apoptotic death process without the inflammation associated with spillage of cellular contents that occurs in nonphysiologic necrotic cell death. Perhaps the most compelling evidence that apoptosis may play a role in HIV pathogenesis is that an increased frequency of apoptosis in $CD4^+$ T cells is seen in HIV infected humans[52].

3. **Autoimmune phenomena** : may contribute to $CD4^+$ T cells depletion in HIV infected individuals.

4. **Bystander Phenomena :** HIV-uninfected cells as a contributory mechanism to the loss of $CD4^+$ T cells during the course of infection.

b. Decreased Production

Decreased production of $CD4^+$ T cells could occur by disruption of the thymic microenvironment[53] and by HIV induced depletion of thymocytes.

c. Redistribution

Data from HIV infections indicate that there is significant trafficking of $CD4^+$ T cells from the peripheral blood to lymphoid tissue in acute and chronic infection[54].

$CD8^+$ T Cells

Dysregulation of $CD8^+$ T cell numbers and function is evident through out the course of HIV disease. After acute primary infection, $CD8^+$ T cell counts usually rebound to supranormal levels and may remain elevated for prolonged periods. Increases in $CD8^+$ T cells during all but the late stages of disease may in part reflect the expansion of HIV - specific $CD8^+$ cytotoxic T lymphocytes. In addition to cytotoxic T lymphocyte activity, other $CD8^+$ T cell functions are impaired during HIV disease progression, including loss of noncytolytic non-MHC restricted $CD8^+$ T cell derived HIV suppression.

B - lymphocytes :

Dysregulation of B - cell activation and the decreased ability of these cells to respond to antigen are likely responsible in part for the increase in certain bacterial infections seen in advanced HIV disease in adults. The number of circulating B cells may be decreased in primary HIV infection, However this is usually a transient phenomenon and likely reflects, at least in part, a redistribution of cells into lymphoid tissues. Soon after the resolution of acute HIV infection, hypergammaglobulinemia and B - lymphocyte hyperactivation are noted. The increase in immunoglobulins occurs for all classes of antibody.

NATURAL KILLER CELLS

Abnormalities of NK cells are observed throughout the course of HIV disease and these abnormalities increase with disease progression. Most studies report that NK cells are normal in numbers and phenotype in HIV-infected individuals. However, decreases in numbers of the $CD16^+/CD56^+$ subpopulation of NK cells with an associated increases in activation markers have been reported[55]. NK cells from HIV-infected individuals are defective in their ability to kill typical NK target cells as well as gp 160-expressing cells. In addition, it has recently been demonstrated that HIV viremia is inversely correlated with the ability of NK cells and NK-derived cell supernatants to suppress virus replication. Thus, NK cells, like $CD8^+$ T cells, may inhibit HIV replication by cell-mediated killing, as well as by secretion of soluble HIV inhibitory factors.

NEUTROPHILS

Dysregulation of neutrophil function occurs at all stages of HIV-infection. The oxidative capacity of neutrophils after priming with granulocyte macrophage colony-stimulating factor is also increased in HIV-infected individuals. The opsonizing activity of neutrophils is significantly impaired in HIV infection and the degree of impairment correlates with disease progression.

MONOCYTE - MACROPHAGES

Cells of the monocyte-macrophage lineage play key roles in the immunopathogenesis of HIV disease. These cells serve as reservoirs of viral infection and are responsible for a variety of tissue-specific pathologic processes. Dysfunction of these cells contributes to $CD4^+$ T cell dysfunction and to impaired host defense against intracellular pathogens[33]. These cells are central to the pathogenesis of HIV-induced central nervous system disease. As a consequence of these HIV-induced functional abnormalities, monocyte-macrophages exhibit poor intracellular killing of Histoplasma capsulatum[56] and others.

DENDRITIC CELLS

Dendritic Cells are among the first cells to encounter HIV after mucosal exposure and are probably responsible for transporting the virus to lymphoid organs thus facilitating infection of $CD4^+$ T cells and viral dissemination.

HIGHLY ACTIVE ANTIRETROVIRAL TREATMENT:

Studies of HIV kinetics showed rapid replication of HIV throughout the course of the illness, and 99% of viral production is from recently infected cells. And the average patient, in the absence of treatment, progresses to AIDS defining diagnosis during 9-10 years after viral transmission and has an average viral burden of 10^4 to 10^5 copies / mL. The increasing availability of

superior combination of drugs reduces viral burden, $CD4^+$ Cell slope (the rate of decline of the number of $CD4^+$ cells) and rates of progression.

The commonly used combinations are usually among Nucleoside Analogs like Zidovudine, Didanosine, Zalcitabine, Stavudine, lamivudine, Abacavir, Tenofovir and among Nonnucleoside reverse transcriptase inhibitors like Nevirapine, Delavirdine, Efavirenz and among protease inhibitors like Indinavir, Ritonavir, Saquinavir, Nelfinavir, Amprenavir, Lopinavir.

The HAART treatment required atleast 3 drugs to achieve maximum viral suppression but adherence was challenging and critical[57,58]. Despite hundreds of studies with thousand of patients, there was no evidence of long-term benefit with therapy started before the CD4 count was 200 / mm^3. There were large cohort studies that showed that treatment initiated with a CD4 count of less than 200 / mm^3 was beneficial and possibly too late. The result of these observations is the recommendation to start therapy when the CD4 count is 350 / mm3 but the current NACO guidelines recommend the threshold of 200 / mm^3.

WHAT TO START:

Once the decision is made to initiate treatment, the regimen used should provide maximum viral suppression. This is best achieved with one of the following[59,60]. Generally recommended combination are Two nucleosides and a Protease Inhibitors, Two nucleosides and an NNRTI, Two nucleosides and two Protease Inhibitors.

WHEN TO CHANGE:

The goal is maximal viral suppression, which is generally defined as a viral load of less than 20 to 50 copies / mL after at least 6 months of treatment. The rationale for this goal is that maximal viral suppression means minimal viral replication with evolution of resistance mutations. Nevertheless, it should be acknowledged that (a) opportunistic infections are infrequent with viral loads less than 5,000 copies / mL[61], (b) the threshold for risk of resistance is unclear[62,63], (c) there is benefit to treatment even in the absence of a demonstrable antiviral effect attributed to viral fitness[64], (d) for many patients the goal of a viral load of less than 20 to 50 copies / mL is unrealistic, so changes based on this threshold could result in the rapid loss of therapeutic options[65]. The conclusion is that the goal of therapy should ideally be "no detectable virus" using an assay with a threshold of 20 to 50 copies / mL, but that several additional considerations include the need to preserve therapeutic options and the benefit of partial suppression[66].

MONITORING:

The major method to determine response to therapy is sequential viral load measurements. Expectations with HAART for treatment-naive patients is a viral load decrease of 1 to 2 $\log_{10}$ copies / mL at 1 to 2 months, viral load less than 400 copies / mL at 12 weeks, and less than 50 copies / mL at 16 to 24 weeks[66]. The CD4 count is another method to monitor response to therapy and is the most critical measurement for determining vulnerability to HIV-associated complications. In general the average increase in CD4 count with complete viral suppression is 80 to 100 cells / mm3 per year. Discordance in

the CD4 cell response and the viral load response is seen in up to 30% of patients, about 15% showing a CD4 response with minimal viral response, and 15% showing a good virologic response with no CD4 response[67].

THE IMPACT OF HAART ON THE CLINICAL MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS :

Changes in plasma viral and $CD4^+$ cell counts resulting from antiretroviral drug treatment have been shown to be strong predictors of clinical progression (or regression) of HIV disease[68,69]. A study from Switzerland indicates that patients receiving effective antiretroviral treatment have a risk of death that is similar to that in patients with cured cancer[70].

Effective therapy has not only decreased the incidence of new opportunistic infections but also led to resolution of preexisting conditions; HAART represent atleast a partial immune reconstitution, although the recovery of antigen-specific immunity appears to lag behind $CD4^+$ cell count increases[71,72,73,74]. The incidence of new opportunistic infections in patients who have had satisfactory virologic and immunologic responses to HAART is extremely low, even when primary prophylaxis has been discontinued[75,76]. The clinical course of HIV disease in individuals receiving combination antiretroviral therapy is likely to evolve further in the coming years.

PATIENTS AND METHODS

Patients who are confirmed to have HIV/AIDS and attending the ART CLINIC were taken up for the study in the period between December 2005 to September 2006. Only adults above the age of 12 years among both males and females were selected. Total of 58 number of patients were analysed.

INCLUSION CRITERIA:

- All confirmed HIV/AIDS patients whose CD4 cell count was less than 200/μl were only taken up for highly active antiretroviral therapy.
- Patient above the age of 12 years.

EXCLUSION CRITERIA:

- Patients who were confirmed as HIV/AIDS positive patients whose CD4 cell count was more than 200 / μl were excluded from the study.
- Pt who were in the pediatric age group of less than 12 years were also excluded.

In this study, patients irrespective of the clinical stage, whose CD4 count was less than 200 / μl were started on HAART.

CONFIRMATION OF HIV/AIDS

Screening:

All patients who had high risk behaviour were screened. High risk behaviour was defined as premarital sex / Extramarital sex / Multiple partners / Tuberculosis / Intravenous Drug Abuse / Men having Sex with Men / Commercial Sex Workers were screened and confirmed in a three stage process.

Stage I: (HIV 1+2 Immunodot Test Kit) Dot immunoassay employs the same principle as Enzyme immunoassay whereby the immobilised antigen antibody complex is visualized by means of colour producing (chromogenic) reaction.

PROCEDURE:

All kit components and samples to be tested should be brought to room temperature before starting the test. Add 2 drops (o.1ml) into micro test wells and diluted.

Antigen coated comb is labeled and incubated in diluted samples for 10 min.

Wash solution concentrate is diluted

Comb is washed to remove unbound proteins.

Comb is incubated for 10 min at room temperature.

Then comb is washed with wash buffers.

Results are read visually and a magenta red spot is a positive indication of HIV 1/ and or 2 antibodies in the sample.

STAGE 2/3:

If stage 1 is positive, than a colloidal gold enhanced rapid immuno chromotographic assay for the qualitative detection of antibodies was done.

PROCEDURE :

Bring all reagent and specimens to room temperature.

Dispense 3 drops (100 μl) of the specimen or control into the sample well on the card.

Interpret in 15 mts.

The appearing of T1 test line indicates HIV 1 positive result.

The appearing of T2 test line indicates HIV 2 positive result.

The appearance of Both test lines indicates both HIV 1 and 2 as positive.

And another spot test to detect HIV 1 & 2 antibodies in plasma / serum is done to detect the bound antibodies. They are visualised by reacting with protein A Gold conjugate which binds to the HIV antibodies giving a distinct red spot. If two red spot appears, the specimen was taken as positive.

If both the 2nd and 3rd test were positive, the case was confirmed as HIV positive.

CD4 COUNT ASSAY:

Blood was collected in heparinized bottles for flow cytometry analysis. Blood was drawn in the morning and heparinized and was sent to Madras Medical College for analysis of CD3, CD4 and CD8 counts by flow cytometry. Flow cytometry is used in the phenotyping of T cell subsets for monitoring of HIV pts[77].

PROCEDURE:

The Heparinized blood of about 100 μl of whole blood is simultaneously stained and analysed for CD3, CD4 and CD8[78] by FACS Count Cytometry using LASER.

RESULTS

Total number of 58 patients were analysed. Both the initial CD4 count and CD4 count after 6 months of highly active antiretroviral therapy were obtained as follows:

TABLE - 1: AGE DISTRIBUTION - ANALYSIS

Age Group	No of Cases	Percentage
< 30 y	9	15.52
31-40 y	36	62.07
41-50 y	9	15.52
51-60 y	4	06.90

Mean ± SD

37.03448 ± 6.965996

Interpretation:

Among the 58 patients studied the age incidence was highest in the 31-40 year age group (62-07%). This was followed by 15.52% in both under 30 and between 41-50 years age group.

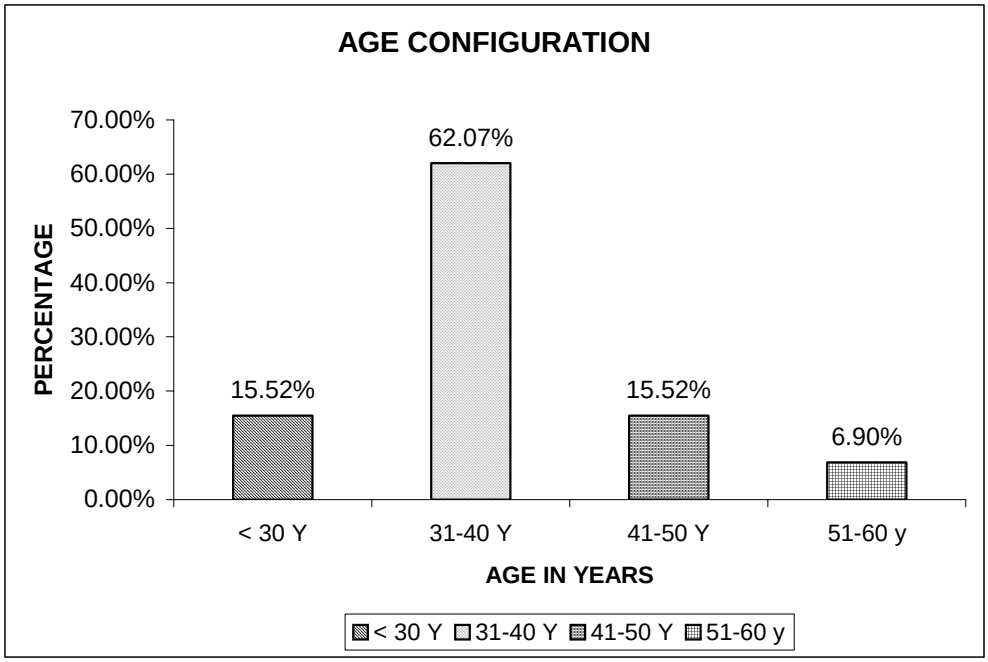


TABLE - 2: SEX DISTRIBUTION – ANALYSIS

Sex	No of Cases	%
Male	39	67.24
Female	18	31.03
Transgender	1	1.72
Total	58	100

Interpretation:

Among the 58 patients studied the males where more commonly affected (67.24%) when compared to females 31.03% and transgender of (1.72%).

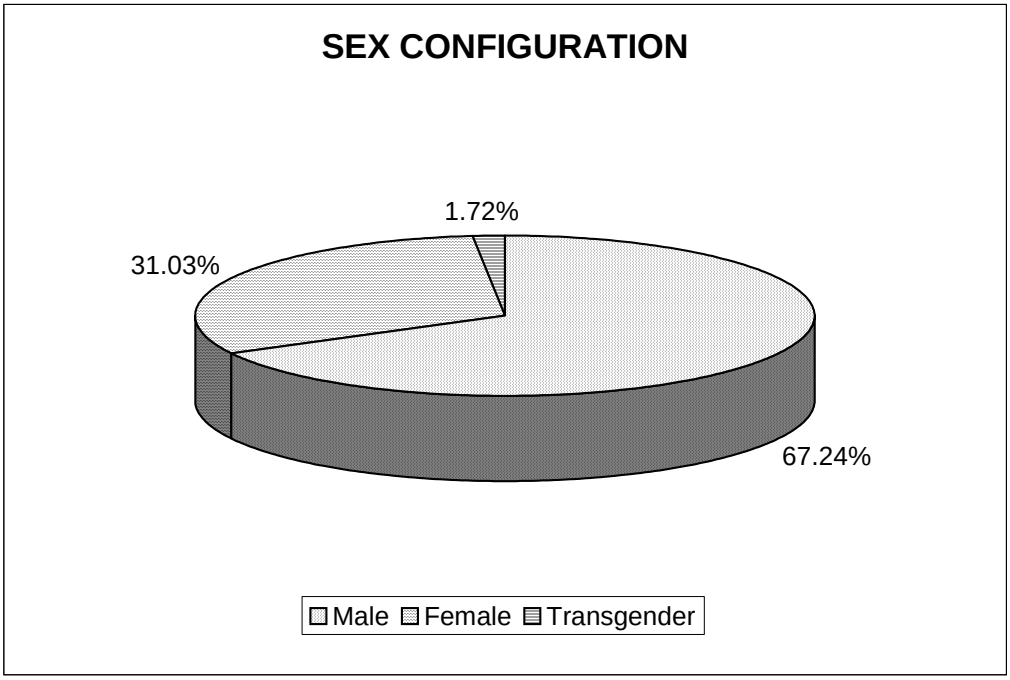


TABLE - 3: MODE OF SPREAD

Mode	No of Cases	%
Heterosexual (1)	53	91.38
Intravenous Drug abuse (2)	2	3.45
Commercial sex workers (3)	1	1.72
Men having sex with men (4)	2	3.45
Total	58	100

Interpretation:

Among the 58 patients analysed it is the heterosexual transmission that is most common mode of transmission (91.38%), With men having sex with men constituting 3.45% and intravenous drug abuse constituting 3.45% and commercial sex workers constituting 1.72%.

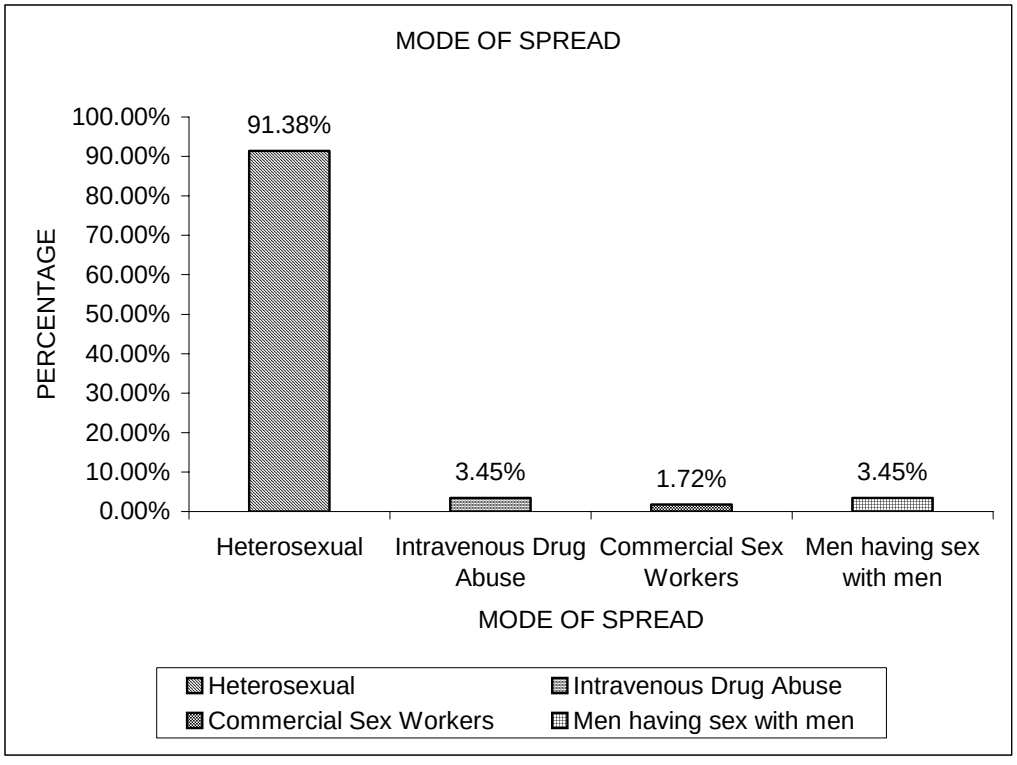


TABLE - 4: ALCOHOLISM - CORRELATION

TO SEXUAL BEHAVIOUR

History of Alcohol Intake	No of Cases	%
Yes	32	55.17
No	26	44.83

TABLE - 5: SMOKING - CORRELATION TO SEXUAL BEHAVIOUR

History of Smoking	No of Cases	%
Yes	26	44.83
No	32	55.17

Interpretation:

Among the 58 patients studied 32 cases (55.17%) have history of Alcohol intake and 26 cases have history of smoking. Overall 18 patients out of 58 patients were both alcoholic and smoker. So it seems that smoking and alcohol influence sexual behaviour.

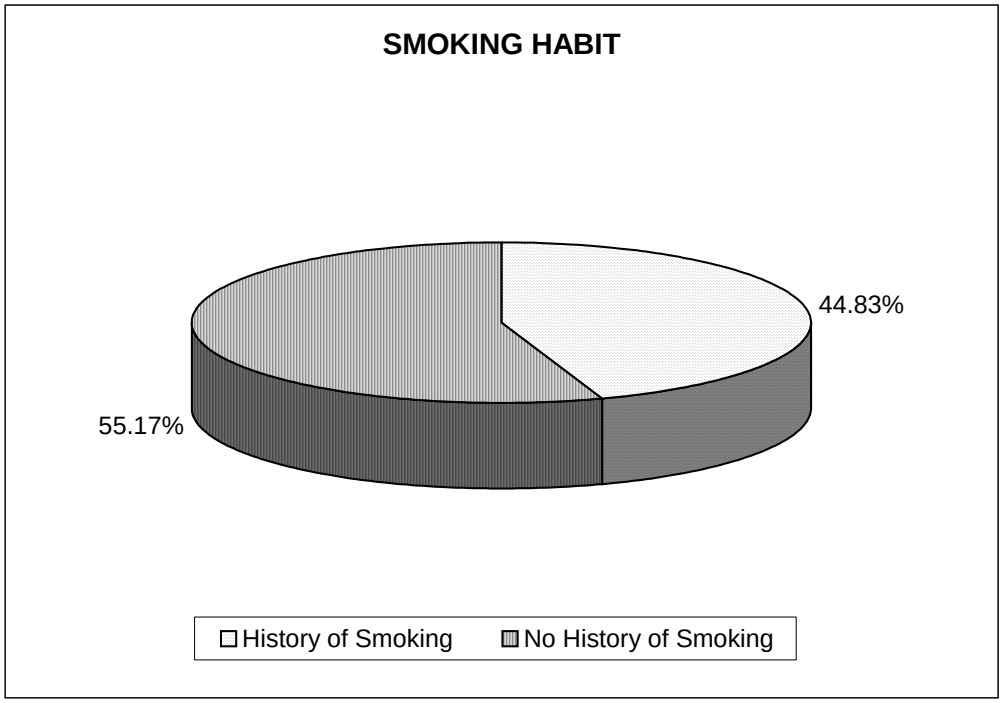


TABLE: 6 - INCOME ANALYSIS

Group	No of Cases	%
Group I (<1500 Rs.)	28	48.28
Group II (1500 – 2500 Rs.)	27	46.55
Group III (>2500 Rs.)	3	5.17
Total	58	100

Interpretation

Among the 58 patients studied 94.83% of the patients were earning lessthan Rs.2500 per month. So its seems that lower socio economic status is playing a role in altering sexual behaviour patterns. But this could also be because of a sampling bias, as most people who come to Government Hospital are poor patients.

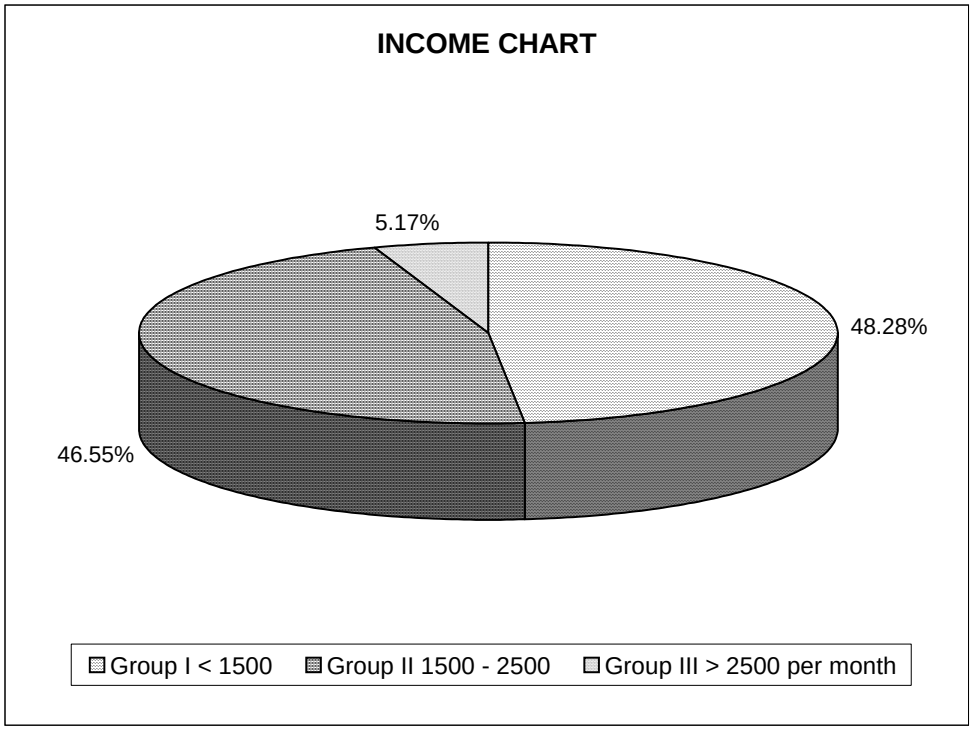


TABLE - 7: ASSOCIATED ILLNESS / DISEASE

Group	Associated Illness	No of Cases	%
1.	Yes	6	10.34 %
2.	No	52	89.66 %

TABLE - 8: DISEASE CONFIGURATION [N = 6]

Disease	No of Cases	%
Pul.TB	4	66.67
Extrapul.TB	1	16.67
Jaundice	1	16.67
Total	6	100

Interpretation:

Among the 58 patients studied, 6 patients had co-existing illness. Pulmonary tuberculosis was present in 4 patients, extra pulmonary tuberculosis in one patient and jaundice in one patient. So tuberculosis was the most common opportunistic infection in the study population. The associated illness was diagnosed at the time of the initial diagnosis of HIV and no patient developed any opportunistic infection during HAART so its seems HAART decreases the incidence of opportunistic infections.

TABLE - 9: BMI COMPARISON [N = 58]

BMI	Mean ± SD
Pre HAART BMI	18.84483 ± 2.867248
During HAART BMI (after 6 months ART)	20.77586 ± 3.068191

Interpretation

Among the 58 patients when the initial BMI was analysed it showed a mean BMI of 18.84483 ± 2.867248, which showed the high incidence of wasting in the HIV/AIDS patients. The follow up BMI showed a mean BMI of 20.77586 ± 3.068191%. When analysed for the statistical significance using paired 't' test its showed 'p' value of 0.000660, which seems to show that BMI also improved by HAART.

TABLE - 10: CD4 COUNT ANALYSIS [N = 58]

	Pre HAART CD4 Count	**No of Patients**	**Percentage**
Group I	0 - 99	17	29.31
Group II	100 - 149	16	27.59
Group III	150 - 199	25	43.10
Total		58	100

Interpretation

Among the 58 patients, the maximum no. of patients who were started on HAART had a CD4 count between 150-199 (43.10%) followed by 17 patients in Group I having CD4 count between 0-99 (29.31%) followed by 16 patients in Group II having CD4 count between 100-149 (27.59%).

TABLE - 11: CD4 CELL COUNT COMPARISON [N = 27]

CD4 Cell Count	Mean ± SD
Pre HAART CD4	127.4444 ± 53.08218
During HAART CD4 (after 6 months follow up)	332.1482 ± 158.08

Interpretation

Among the 27 patients analysed for the impact of HAART on CD4, the mean increase of 205 cells / mm^3 was noted after six months of HAART, which was also statistically significant when analysed by paired 't' test which showed the 'P' value of 0.0000.

DISCUSSION

HIV/AIDS is an evolving health problem world wide, with more than 40 million people already infected[3].

It is important to view untreated HIV infection as a chronic ultimately fatal process that is punctuated by various manifestations, which are influenced by multiple factors like route of HIV infection, size of inoculum, gender, medical intervention etc. In India it is commonly acquired through Heterosexual contact. In the study the most common mode of transmission was found to be heterosexual with 91.38% acquiring the disease through this route.

Once acquiring the infection, one to 6 weeks later patients experience a nonspecific illness called as "acute retroviral syndrome"[26]. During this episode, counts of total lymphocyte (both CD4 and CD8) characteristically fall, followed by an increase of CD8[79]. CD4 count have been reported to be between 244 - 1055 cell / mm^3 in one review within the first 4 weeks after acquisition of HIV[80]. CD4 count may recover for some patients but most patients demonstrate a decrease of 100 to 200 cells in the first 6 months after seroconversion and a decline of an additional 100 cells in the next 6 months.

In one review of 318 seroconverters mean $CD4^+$ cell count in the initial 12 month after seroconversion fell from 999 to 673/ mm[81]. In this study the mean initial CD4 count of all 58 patients who were started on HAART was 130 cells / mm3 ± 53.95.

Studies suggest that early intervention with HAART can slow the decline of CD4 and reduce the no of clinical events during the initial several years of infection[79,82]. Barring one patient who died during the study no patient developed any clinical illness during the study period. And the natural history of illness have been dramatically altered by HAART. The likelihood of an initial AIDS defining condition developing in an untreated person who is HIV positive average about 4 to 10 percent per year after acquisition of HIV infection[83].

In terms of laboratory parameters the absolute peripheral CD4 lymphocyte count and percentage of peripheral cells that are $CD4^+$, both correlate with the likelihood of development of AIDS. And also retrospective and prospective studies show that lower the absolute CD4 count more likely is the patient to develop opportunistic infections like Cytomegalovirus, Pneumocystis Carinii pneumonia. Hence the relationship of the CD4 count to the development of opportunistic infectious complications of HIV is important in approaching the management of HIV infection.

First, HIV infection implies that unless an effective therapeutic intervention is administered the immune function inexonerably declines and infectious complication occur. Second, the monitoring of the immunologic decline primes the clinician to do the measures in anticipation of the complication. Third the immunologic state as measured by CD4 cell count provides guidance regarding the benefit of HAART. When the CD4 count falls below 200 cells /μl, effective HAART can clearly improve survival. At higher levels, HAART may improve survival. Fourth, a rise of CD4 in response to HAART predicts clinical benefit of therapeutic intervention.

During potent antiretroviral therapy, immune recovery is characterized by suppression of HIV - 1 replication and increasing $CD4^+$ T Cell count[84]. In our study group, the CD4 cell count improved by a mean of 205 cells / mm^3.

Control of HIV - 1 replication reduces CD4 T cell loss resulting from direct cytolysis[85,86] and may partially restore T cell homeostasis by promoting decreased T cell proliferation[87.88]. Redistribution of T cells into peripheral circulation[73,89] and improved thymic output[90]. Although many patients continue to have CD4 T cell recovery for several years after receiving HAART[91], the degree of immune recovery achieved during viral suppression is highly variable. In some individuals increases in the CD4 cell count appears to plateau after the first few months of HAART[92,93,94,95,96]. This suboptimal CD4 T cell response during therapy otherwise known as 'immunologic discordance' can have detrimental clinical consequences[67]. At present there is no validated or accepted, definition of immune discordance during HAART.

In general, reconstitution of CD4 T cells during viral suppression follows a biphasic pattern[97]. During the first three months of HAART the number of CD4 T cells typically increase by 50 to 120 cells per mm^3[3, 92,98,99]. This burst is followed by a, second slower phase of T cell repopulation with an average rate of increase of 2 to 7 cells mm^3 per month[92,98,99,100].

In our study population, the CD4 count seems to have risen to a greater degree of about 205 cells / mm^3, which could be both due to the smaller sample size but also could be because of the nutritional counselling that is given to our patients at the ART centre and also because of the supplementation of micro and macro nutrients and monthly monitoring of body weight and height.

The extent of early immune recovery may be a function of prior T cell destruction, because lower CD4 T cell nadirs have been associated with limited immune recovery during therapy[101]. Furthermore because viral replication is incompletely suppressed by HAART[102]. In our study the patient on Group I and Group II showed a lesser increase when compared to Group III which showed the most statistically significant increase. This increase in Group III patients during HAART follow up showed a mean increase of 194 cell / mm3, which when analysed for statistical significance by using paired 't' test showed a 'p' value of 0.000506, which is highly significant, in concordance with the previous studies. The intent of the present study was to investigate the impact of HAART on CD4 count in a small prospective study.

In this study there were 58 patients with CD4 cell count of less than 200 / µl, who were started on highly active antiretroviral therapy and followed up for 6 months. Of these 58 patients 17 patients had a CD4 count between 0-99, who were classified a Group I, 16 patients had a CD4 cell count between 100-150, who were classified as Group II and, 25 patients had a CD4 cell count between 150-199, who were classified as Group III. But, of these 58 patients only 27 patients could be followed up for 6 months and a repeat CD4 count could be done. These 27 patients' 6 month follow up CD4 count was analysed and it showed an improvement by a mean of 205 cells / mm^3, which was also statistically significant when analysed by paired 't' test, that showed 'p' value of 0.0000. When the groups were analyzed individually, the 3 groups of group I, group II, group III showed a 'p' value of 0.006, 0.008 and 0.0005 respectively. But it is Group III, with the higher initial CD4 count of 150 – 199 that showed the most statistically significant improvement when compared to the other two groups. When the improvement in BMI was assessed after 6 months by using paired 't' test it also showed a statistically significant improvement, with a 'P' value of 0.000660. From the study it is clear, when HAART is started, with the CD4 count at a higher level (Group III), the improvement in CD4 count as well as the general condition improvement is better.

CONCLUSION

1. In this study there were 58 patients with CD4 cell count of less than 200 / µl who were started on highly active antiretroviral therapy and followed up for six months. But only 27 patients came back after 6 months of HAART, whose follow up CD4 count was done and analysed to evaluate the impact of HAART on CD4 cell count.

2. It is important to do CD4 cell count in all the patients who are confirmed as HIV/AIDS, irrespective of the clinical stage, since the clinical stage and the CD4 count do not correlate.

3. Patients were classified into three groups as per the initial CD4 cell count. (N = 27)

	Initial CD4 Cell Count	No of Patients followed up for 6 months
Group I	0-99	8
Group II	100-149	8
Group III	150-199	11
	Total	27

4. These 27 patients 6 month follow up CD4 count was analysed and it showed an improvement by a mean of 205 cells / mm^3 which was also statistically significant when analysed by using the paired 't' test, that showed a 'p' value of 0.0000. When the groups were analysed individually, the three groups of Group I, Group II, Group III, showed

a 'P' value of 0.006, 0.008, and 0.0005 respectively. Among these 3 groups, it is group III, that showed the most statistically significant improvement. So HAART has a significant improvement on CD4 cell count when HAART is started with the CD4 count at a higher level as in Group III.

5. HAART has improved the BMI and thereby improving the general condition and well being of the patients. This could also be attributed to the micronutrients and the macronutrients that were provided to the patients at the ART centre, KMCH.

6. HAART decreases the incidence of opportunistic infections.

7. Tuberculosis was the most common opportunistic infection.

8. CD4 cell count monitoring is very important and could be done every 3 months, but for resource constraints it is being done every 6 months.

9. Limitation of the study:

   (a) small sample size,

   (b) four combinations of HAART regimens where used in these 27 patients and the individual effect of each combination on CD4 count was not evaluated.

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PROFORMA

Name : **Age** : **Sex** :

Name of the Treatment Unit :

Confirmed HIV Test Date :

Risk factor for HIV :

1. **Heterosexual** ☐
2. **IVDU** ☐
3. **Sex Work** ☐
4. **Men having sex with men** ☐
5. **Blood transfusion** ☐
6. **Mother to Child** ☐
7. **Unknown** ☐

Smoker : Yes / No

Alcohol : Yes / No

	Height	**Weight**	**CD4 Count**	**Clinical Stage**
Ist visit				
After 6 months during HAART				

HAART Regimen :

1. **$d4T_{30}$ + 3TC + NVP** ☐
2. **$d4T_{40}$ + 3TC + NVP** ☐
3. **$d4T_{30}$ + 3TC + EFV** ☐
4. **$d4T_{40}$ + 3TC + EFV** ☐
5. **ZDV + 3TC + NVP** ☐
6. **ZDV + 3TC + EFV** ☐

Associated Diseases / Illness

1. Tuberculosis — Pulmonary / Extra Pulmonary
2. Jaundice
3. Other Illness

ABBREVIATIONS

AIDS	-	Acquired Immuno Deficiency Syndrome
HIV	-	Human Immuno Deficiency Virus
RNA	-	Ribo Nucleic Acid
PGL	-	Persistent Generalised Lymphadenopathy
HAART	-	Highly Active Anti retro Viral Therapy
DC	-	Dentritic Cell
SIV	-	Simian Immuno Deficiency Virus
CTL	-	Cytotoxic T Lymphocyte
MHC	-	Major Histocompatiblity Complex
NK	-	Natural Killer
NACO	-	National Aids Control Organisation
NNRTI	-	Non Nucleoside Reverse transcriptase Inhibitor
CD	-	Cluster of Differentiation
ART	-	Anti retroviral Therapy
USA	-	United States of America