PREDICTORS OF CD4 COUNT IN HIV INFECTED PATIENTS

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CERTIFICATE

This is to certify that this dissertation titled "**PREDICTORS OF CD4 COUNT IN HIV INFECTED PATIENTS"** submitted by **DR.BHARATH KUMAR.G** to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

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CONTENTS

ABBREVATIONS

HIV-Human Immuno deficiency Virus

ART-Anti Retroviral Therapy

ELISA-Enzyme Linked Immuno Sorbent Assay

TLC-Total Lymphocyte Count

BMI-Body Mass Index

HB-Haemoglobin

PLT-Platelet Count

ESR- Erythrocyte Sedimentation Rate

WHO-World Health Organisation

AIDS-Acquired Immuno Deficiency Syndrome

IDU-Injectable Drug Usage

INTRODUCTION

HIV infection/AIDS is a global pandemic[1], with cases reported from virtually every country. At the end of 2007, 33.2 million individuals were living with HIV infection (range: 30.6–36.1 million) according to the Joint United Nations Programme on HIV/AIDS (UNAIDS)[2]. More than 95% of people living with HIV/AIDS reside in low and middle-income countries[3] of which 50% are female, and 2.5 million are children <15 years.

In 2007, there were an estimated 2.5 million new cases of HIV infection worldwide, including 420,000 in children <15 years. In 2007, global AIDS deaths totalled 2.1 million (including 330,000 children <15 years). UNAIDS estimate that global HIV prevalence has been level since 2001. HIV incidence likely peaked in the late 1990s at >3 million new infections per year. Recent reductions in global HIV incidence likely reflect natural trends in the pandemic as well as the results of prevention programs resulting in behaviour change.

Although the AIDS epidemic was first recognized in the United States and shortly thereafter in Western Europe, it very likely began in sub-Saharan Africa , which has been particularly devastated by the epidemic. More than two-thirds of all people with HIV infection (about 22.5 million) live in that region, even though sub-Saharan Africa is home to just 10–11% of the world's population .Within the region, southern Africa is worst-affected. In eight southern African countries, available sero prevalence data indicate that >15% of the adult population aged 15–49 is HIV-infected.

In Asia, an estimated 4.9 million people were living with HIV at the end of 2007, of which 3.6 million people are in south east Asia. In 2007 there were 2.4 million people live with HIV/AIDS in India with an estimated adult HIV prevalence of 0.34%.

The cost of combination ART has dropped in recent years as a result of generic medicines and differential pricing based on country need and ability to pay. The cost of diagnostic services to determine eligibility for treatment and to monitor treatment response has kept ART inaccessible to many, however. The US Department of Health and Human Services (DHHS) and the World Health Organization (WHO) recommend initiating ART therapy based on consideration of a patient's CD4 T-cell count when available. A CD4 cell count requires expensive laboratory equipment and trained technicians, which are absent in many areas of high HIV prevalence.

The cost of monitoring HIV therapy may become more prohibitive than the cost of the medications themselves[4,5]. In December 2003, the WHO broadened the recommendations for initiation of ART when CD4 testing is unavailable to include WHO stage III or IV or WHO stage II in combination with a TLC 1200 cells/mm^3 [6,7]. Many studies have evaluated the use of TLC as a surrogate marker for CD4+ cell count with mixed results[8,9]. Some studies[10,11,12] have found a good correlation but others have not. In addition

to low Lymphocyte count, Anaemia[13],. Thrombocytopenia[14], and Body Mass Index (BMI)[15,16] have been associated with advanced HIV infection.

In considering the above facts ,a cross sectional study was conducted in Govt Rajaji Hospital using various clinical and inexpensive laboratory measures such as WHO clinical Staging , Anthropometry(BMI),Total Lymphocyte Count (TLC),Haemoglobin ,Platelet count, ESR, S. Albumin were done and compared with CD4 count. It is analysed that these parameters can be used as a surrogate marker for CD4 count to initiate ART and to monitor the therapy.

REVIEW OF LITERATURE

AIDS is a retroviral disease caused by the human immunodeficiency virus (HIV). It is characterized by infection and depletion of CD4+ T lymphocytes, and by profound immune suppression leading to opportunistic infections, secondary neoplasm, and neurologic manifestations. Although AIDS was first described in the United States, it has now been reported in virtually every country in the world. Worldwide, more than 22 million people have died of AIDS since the epidemic was recognized in 1981; about 42 million people are living with the disease, and there are an estimated 5 million infections each year. Worldwide, 95% of HIV infections are in developing countries, with Africa alone carrying more than 50% of the HIV burden. Although the largest number of infections is in Africa, the most rapid increases in HIV infection in the past decade are in Southeast Asian countries, including Thailand, India, and Indonesia.

AIDS is caused by HIV, a human retrovirus belonging to the lenti virus family (which also includes feline immunodeficiency virus, simian immunodeficiency virus, Visna virus of sheep, and the Equine infectious anaemia virus). Two genetically different but antigenically related forms of HIV, called *HIV-1* and *HIV-2,* have been isolated from patients with AIDS. HIV-1 is the more common type associated with AIDS in the United States, Europe, and Central Africa, whereas HIV-2 causes a similar disease principally in West Africa. Specific tests for HIV-2 are now available, and

blood collected for transfusion is also routinely screened for HIV-2 sero positivity.

GLOBAL PREVALENCE OF HIV

STRUCTURE AND GENOME OF HIV[17]

Like most retroviruses, the HIV-1 virion is spherical and contains an electron-dense, cone-shaped core surrounded by a lipid envelope derived from the host cell membrane . The virus core contains: (1) major capsid protein p24, (2) nucleocapsid protein p7/p9, (3) two copies of genomic RNA, and (4) three viral enzymes (protease, reverse transcriptase, and integrase). p24 is the most readily detected viral antigen and is therefore the target for the antibodies used to diagnose HIV infection in blood screening. The viral core is surrounded by a matrix protein called *p17,* lying beneath the virion envelope.

STRUCTURE OF HIV

The viral envelope itself is studded by two viral glycoproteins (gp120 and gp41), critical for HIV infection of cells. The HIV-1 proviral genome contains the *gag, pol,* and *env* genes, which code for various viral proteins. The products of the *gag* and *pol* genes are translated initially into large precursor proteins that must be cleaved by the viral protease to yield

the mature proteins. The highly effective anti-HIV-1 protease inhibitor drugs thus prevent viral assembly by inhibiting the formation of mature virions. *In addition to these three standard retroviral genes, HIV contains several other genes* (given three-letter names such as *tat, rev, vif, nef, vpr,* and *vpu*) that regulate the synthesis and assembly of infectious viral particles[18].

MODES OF TRANSMISSION

Sexual Transmission

HIV infection is predominantly a sexually transmitted disease (STD) worldwide the most common mode of infection, particularly in developing countries, is clearly heterosexual transmission.

Transmission by Blood and Blood Products

HIV can be transmitted to individuals who receive HIV-tainted blood transfusions, blood products, or transplanted tissue as well as to IDUs who are exposed to HIV while sharing injection paraphernalia such as needles, syringes, the water in which drugs are mixed, or the cotton through which drugs are filtered.

Occupational Transmission of HIV: Health Care Workers, Laboratory Workers, and the Health Care Setting

There is a small, but definite, occupational risk of HIV transmission to health care workers and laboratory personnel and potentially others who work with HIV-containing materials, particularly when sharp objects are used.

Maternal-Foetal/Infant Transmission

HIV infection can be transmitted from an infected mother to her fetus during pregnancy, during delivery, or by breast-feeding. This is an extremely important form of transmission of HIV infection in

certain developing countries, where the proportion of infected women to infected men is ~1:1.

Transmission by Other Body Fluids

The following fluids are considered potentially infectious: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid .

Faeces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious unless they are visibly bloody.

Life Cycle of HIV

The entry of HIV in to cells requires the CD4 molecule, which acts as a high-affinity receptor for the virus. This explains the tropism of the virus for CD4+ T cells and its ability to infect other CD4+ cells, particularly macrophages and DCs. However, binding to CD4 is not sufficient for infection; the HIV envelope gp120 must also bind to other cell surface molecules (*coreceptors*) to facilitate cell entry. Two cell surface chemokine receptors, CCR5 and CXCR4, serve this role[19,20] .

HIV envelope gp120 (non covalently attached to transmembrane gp41) binds initially to CD4 molecules .This binding leads to a conformational change that exposes a new recognition site on gp120 for the CXCR4 (mostly on T cells) or CCR5 (mostly on macrophages) coreceptors. The gp41 then undergoes a conformational change that allows it to insert

into the target membrane, and this process facilitates fusion of the virus with the cell[21].

The coreceptors are critical components of the HIV infection process. HIV strains could be classified according to their relative ability to infect macrophages and/or CD4+ T cells. Macrophage-tropic (R5 virus) strains infect both monocytes/macrophages and freshly isolated peripheral blood T cells, whereas T-cell tropic (X4 virus) strains infect only activated T cell lines.

R5 strains use CCR5 as their coreceptor, and, because CCR5 is expressed on both monocytes and T cells, these cells succumb to infection by R5 strains. Conversely, X4 strains bind to CXCR4, which is expressed on T cell lines (and not on monocytes/macrophages), so that only activated T cells are susceptible.

LIFE CYCLE OF HIV

Interestingly, approximately 90% of HIV infections are initially transmitted by R5 strains. However, over the course of infection, X4 viruses gradually accumulate; these are especially virulent and are responsible for T-cell depletion in the final rapid phase of disease progression[22,23].

It is thought that during the course of HIV infection, R5 strains evolve into X4 strains, as a result of mutations in genes that encode gp120. The resultant transition in the ability of the virus to bind CXCR4 but not CCR5 is probably important in the pathogenesis of AIDS because T tropic (CXCR4)viruses are capable of infecting naive T cells and even thymic T cell precursors and cause greater T Cell depletion and impairment.

Once internalized, the viral genome undergoes reverse transcription, leading to formation of complementary DNA (cDNA). In quiescent T cells, HIV proviral cDNA may remain in the cytoplasm in a linear episomal form. However, in dividing T cells, the cDNA enters the nucleus and becomes integrated into the host genome. After integration, the provirus may remain non transcribed for months or years, and the infection becomes *latent;* Alternatively, proviral DNA may be transcribed to form complete viral particles that bud from the cell membrane. Such productive infections, associated with extensive viral budding, lead to cell death.

MECHANISM OF CD4+ T CELL DYSFUNCTION AND DEPLETION[24,25,26]

DIRECT MECHANISMS

INDIRECT MECHANISMS

1.Loss of plasma membrane integrity due to viral budding

1. Aberrant intracellular signalling events

2.Autoimmunity

2. Accumulation of unintegrated viral DNA

3. Innocent bystander killing of viral antigen–coated cells

3.Interference with cellular RNA processing

4. Apoptosis

4. Intracellular gp120-CD4 autofusion events

5. Inhibition of lymphopoiesis

5. Syncytia formation

6. Activation-induced cell death

7.Elimination of HIV-infected cells by virus-specific immune responses

MAJOR ABNORMALITIES OF IMMUNE FUNCTION IN AIDS

Lymphopenia
Predominantly caused by selective loss of the CD4 helper T-cell subset;

inversion of CD4:CD8 ratio.

Decreased T-Cell Function in Vivo

Preferential loss of activated and memory T cells.

Decreased delayed-type hypersensitivity.

Susceptibility to opportunistic infections.

Susceptibility to neoplasm.

Altered T-Cell Function in Vitro

Decreased proliferative response to mitogens, alloantigens, and soluble antigens

Decreased cytotoxicity.

Decreased helper function for B-cell antibody production.

Decreased IL-2 AND IFN- γ production.

Altered Monocyte or Macrophage Functions

Decreased chemotaxis and phagocytosis.

Decreased HLA class II antigen expression.

Diminished capacity to present antigen to T cells.

Increased spontaneous secretion of IL-1, TNF, IL-6.

Polyclonal B-Cell Activation

Hypergammaglobulinemia and circulating immune complexes.

Inability to mount de novo antibody response to a new antigen.

Poor responses to normal signals for B-cell activation in vitro.

Diagnosis and laboratory monitoring of HIV infection

The establishment of HIV as the causative agent of AIDS and related syndromes early in 1984 was followed by the rapid development of sensitive screening tests for HIV infection. By March 1985, blood donors in the United States were routinely screened for antibodies to HIV. In June 1996, blood banks in the United States added the p24 antigen capture assay to the screening process to help identify the rare infected individuals who were donating blood in the time (up to 3 months) between infection and the development of antibodies.

DIAGNOSIS OF HIV INFECTION

The CDC has recommended that screening for HIV infection be performed as a matter of routine health care. The diagnosis of HIV infection depends upon the demonstration of antibodies to HIV and/or the direct detection of HIV or one of its components. As noted above, antibodies to HIV generally appear in the circulation 2–12 weeks following infection.

ANTIBODY DETECTION BY ELISA/EIA :

This is the most widely used screening method. It has a sensitivity of more than 99.5 %. Hence the false positivity is also present with conditions such as influenza vaccination, hepatic disease auto antibodies. Direct solid phase anti globulin ELISA is the most commonly used method.

WESTERN BLOT

The most commonly used confirmatory test is the Western blot . This assay takes advantage of the fact that multiple HIV antigens of different, well-characterized molecular weights elicit the production of specific antibodies. These antigens can be separated on the basis of molecular weight, and antibodies to each component can be detected as discrete bands on the Western blot.

LABORATORY MONITORING OF PATIENTS WITH HIV INFECTION[27]

The epidemic of HIV infection and AIDS has provided the clinician with new challenges for integrating clinical and laboratory

data to effect optimal patient management. The close relationship between clinical manifestations of HIV infection and CD4+ T cell count has made measurement of the latter a routine part of the evaluation of HIV-infected individuals. Determinations of CD4+ T cell counts and measurements of the levels of HIV RNA in serum or plasma provide a powerful set of tools for determining prognosis and monitoring response to therapy.

CD4+ T CELL COUNTS

The CD4+ T cell count is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection. This measurement, which can be made directly or calculated as the product of the percent of CD4+ T cells (determined by flow cytometry) and the total lymphocyte count [determined by the white blood cell count (WBC) and the differential percent], has been shown to correlate very well with the level of immunologic competence.

Patients with CD4+ T cell counts <200/μL are at high risk of disease from *P. jiroveci*, while patients with CD4+ T cell counts <50/μL are at high risk of disease from CMV, mycobacteria of the *M. avium* complex (MAC) and/or *T. gondii* .

Patients with HIV infection should have CD4+ T cell measurements performed at the time of diagnosis and every 3–6 months thereafter. More frequent measurements should be made if a declining trend is noted.

According to most guidelines, a CD4 T cell count <350/μL is an indication for consideration of initiating ARV therapy, and a decline in CD4+ T cell count of >25% is an indication for considering a change in therapy.

Once the CD4+ T cell count is <200/μL, patients should be placed on a regimen for *P.jiroveci* prophylaxis, and once the count is <50/μL, primary prophylaxis for MAC infection is indicated. As with any laboratory measurement, one may wish to obtain two determinations prior to any significant changes in patient management based upon CD4+ T cell count alone. In patients with

hypersplenism or who have undergone splenectomy the CD4+ T cell percentage may be a more reliable indication of immune function than the CD4+ T cell count. A CD4+ T cell percent of 15 is comparable to a CD4+ T cell count of 200/μL.

CD4 LEVELS IN RELATION TO SEVERITY OF IMMUNO SUPPRESSION

Not significant immunosuppression

>500 cells/μL
Mild immunosuppression
350 – 499 cells/μL
Advanced immunosuppression
200 −349 cells/μL
Severe immunosuppression
<200 cells/μL

HIV RNA DETERMINATIONS

Facilitated by highly sensitive techniques for the precise quantification of small amounts of nucleic acids, the measurement of serum or plasma levels of HIV RNA has become an essential component in the monitoring of patients with HIV infection. The two most commonly used techniques are the RT-PCR assay and the bDNA assay. HIV RNA measurements are greatly influenced by the state of activation of the immune system and may fluctuate greatly in the setting of secondary infections or immunization. For these reasons, decisions based upon HIV RNA levels should never be made on a single determination. Measurements of plasma HIV RNA levels should be made at the time of HIV diagnosis and every 3–6 months thereafter in the untreated patient. In general, most guidelines suggest that therapy be considered in patients with >100,000 copies of HIV RNA per milliliter.

HIV RNA measurements are to be done frequently to monitor therapy, which has great economic burden to many people in developing countries. Hence the need other simple clinical or laboratory parameter to monitor therapy is essential in developing countries.

OTHER TESTS

A variety of other laboratory tests have been studied as potential markers of HIV disease activity. Among these are quantitative culture of replication-competent HIV from plasma, peripheral blood mononuclear cells, or resting CD4+ T cells; circulating levels of $\beta_2$microglobulin, soluble IL-2 receptor, IgA, acid-labile endogenous interferon, or TNFα; and the presence or absence of activation markers such as CD38, HLA-DR, or PD-1 on CD8+ T cells. While these measurements have value as markers of disease activity and help to increase our understanding of the pathogenesis of HIV disease, they do not currently play a major role in the monitoring of patients with HIV infection.

Hence in our study various clinical and inexpensive laboratory measures such as clinical Staging WHO, Anthropometry (BMI),Total Lymphocyte Count (TLC),haemoglobin ,platelet count, ESR, S. Albumin were done to assess HIV disease activity and compared with CD4 count. Then ,it was analysed that these parameters may be used as a surrogate marker for CD4 count to initiate ART and to monitor the therapy.

CLINICAL MANIFESTATIONS:

The clinical consequences of HIV encompasses a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease.

THE ACUTE HIV SYNDROME:

The *acute phase* represents the initial response of an immunocompetent adult to HIV infection. Clinically, this is typically a self-limited illness that develops in 50% to 70% of adults 3 to 6 weeks after infection; it is characterized by nonspecific symptoms including sore throat, myalgia, fever, rash, and sometimes aseptic meningitis.

The Asymptomatic Stage—Clinical Latency

Although the length of time from initial infection to the development of clinical disease varies greatly, the median time for untreated patients is approximately 10 years. HIV disease with active virus replication is ongoing and progressive during this asymptomatic period.

The middle, *chronic phase* represents a stage of relative containment of the virus. The immune system is largely intact at this point, but there is *continued HIV replication that may last for several years.* Patients either are asymptomatic or develop persistent lymphadenopathy, and many patients have "minor" opportunistic infections such as thrush (*Candida*) or herpes zoster. During this phase, viral replication in the lymphoid tissues continues unabated. The extensive viral turnover is associated with continued loss of CD4+ cells, but a large proportion of the CD4+ cells is replenished and the decline of CD4+ cells in the peripheral blood is modest.

Symptomatic Disease

The final, *crisis phase* is characterized by a catastrophic breakdown of host defenses, a marked increase in viremia, and clinical disease. Typically, patients present with fever of more than 1 month's duration, fatigue, weight loss, and diarrhoea; the CD4+ cell count is reduced below 500 cells/μL. After a variable interval, patients develop serious opportunistic infections, secondary neoplasm, and/or neurologic manifestations (so-called *AIDS-defining conditions*), and the patient is said to have full-blown AIDS.

A diagnosis of AIDS is made in anyone with HIV infection and a CD4+ T cell count <200/μL and in anyone with HIV infection who develops one of the HIV-associated diseases considered to be indicative of a severe defect in cell-mediated immunity .

Revised World Health Organization (WHO) Clinical Staging of HIV/AIDS For Adults and Adolescents (2005)[28]

Primary HIV infection

- Asymptomatic
- Acute retroviral syndrome

Clinical stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical stage 2

- Moderate and unexplained weight loss (<10percent; of presumed or measured body weight)
- Recurrent respiratory tract infections (such as sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster

- Recurrent oral ulcerations
- Papular pruritic eruptions
- Angular cheilitis
- Seborrhoeic dermatitis
- Fungal finger nail infections

Clinical stage 3

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (intermittent or constant for longer than one month)
- Severe weight loss (>10percent; of presumed or measured body weight)
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years
- Severe presumed bacterial infections (e.g. pneumonia, empyema, meningitis, bacteraemia, pyomyositis, bone or joint infection)

- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Conditions where confirmatory diagnostic testing is necessary

- Unexplained anaemia (< 80 g/l), and or neutropenia (<500/µl) and or thrombocytopenia (<50 000/ µl) for more than one month

Clinical stage 4

Conditions where a presumptive diagnosis can be made on the basis of clinical signs or simple investigations

- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)
- Oesophageal candidiasis
- Extrapulmonary Tuberculosis
- Kaposi's sarcoma
- Central nervous system toxoplasmosis
- HIV encephalopathy

Conditions where confirmatory diagnostic testing is necessary

- Extrapulmonary cryptococcosis including meningitis

- Disseminated non-tuberculous mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Candida of trachea, bronchi or lungs
- Cryptosporidiosis
- Isosporiasis
- Visceral herpes simplex infection
- Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)
- Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)
- Recurrent non-typhoidal salmonella septicaemia
- Lymphoma (cerebral or B cell non-Hodgkin)
- Invasive cervical carcinoma
- Visceral leishmaniasis

The aim of proposed revisions of WHO staging were to:

◗ facilitate the use of the clinical staging system and HIV/AIDS case definitions by non-specialist and at the basic level and in peripheral health care facilities;

- assist with clinical decision-making, including decisions on starting, substituting, switching and stopping ART, and with routine follow up of patients on treatment;

ANTHROPOMETRY

HIV wasting, or an unintentional weight loss of more than10% of normal weight, is a common AIDS-defining condition[29].

HIV-associated weight loss is an independent predictor of opportunistic infections, hospitalisation and mortality .It was postulated that HIV wasting is a cachectic process in which weight loss is disproportionately loss of lean body mass, with relative conservation of fat. Loss of fat was deemed a poor marker of AIDS wasting. Proposed mechanisms for muscle wasting include altered cytokine levels[30] and alterations in circulating levels of anabolic sex hormones.

Anthropometry especially BMI is useful to asses the disease progression.

JE Forrester1, D Spiegelman, M Woods [49] conducted a study on "Weight and body composition in a cohort of HIV-positive men and women".516 persons were enrolled in the study. According to this study there was a significant trend towards lower weight and BMI with lower CD4 counts.

TOTAL LYMPHOCYTE COUNT (ABSOLUTE LYMPHOCYTE COUNT)

TLC is easily obtained from the routine complete blood count (CBC)

with differential through multiplication of lymphocyte percentage by white blood cell count.

TLC= % of lymphocyte x total WBC count

TLC has been suggested as a measure of when to initiate both HAART and prophylaxis against opportunistic illness in resource-limited settings.

In December 2003, the WHO issued the recommendations for initiation of ART when CD4 testing is unavailable to include WHO stage III or IV or WHO stage II in combination with a TLC <1200 cells/mm≥ [31,32,33].

Caroline Costello, MPH, Kenrad E. Nelson, MD[43], conducted a study in thai population on "Predictors ofLowCD4Count in Resource-Limited Settings". In this study TLC<1200 cells/mm≥ has good correlation with CD4<200 Cells/µL.A Total Lymphocyte Count (TLC) cut off at <1200 cells/mm≥ improved the sensitivity above that of meeting the WHO guidelines for onset of antiretroviral therapy while maintaining a specificity above 99%.

S.M. Alavi , F. Ahmadi et al conducted a study on "Correlation between Total Lymphocyte Count, Haemoglobin, Haematocrit and CD4 Count in HIV/AIDS Patients". In this study a strong correlation was observed between CD4 count and TLC.

ANAEMIA

Disorders of the hematopoietic system including lymphadenopathy, anaemia[34], leukopenia, and/or thrombocytopenia are common throughout the course of HIV infection and may be the

direct result of HIV, manifestations of secondary infections and neoplasm, or side effects of therapy .

Anaemia[27] is the most common hematologic abnormality in HIV-infected patients and in the absence of a specific treatable cause is independently associated with a poor prognosis. Among the specific reversible causes of anaemia in the setting of HIV infection are drug toxicity, systemic fungal and mycobacterial infections, nutritional deficiencies, and parvovirus B19 infections. Folate levels are usually normal in HIV-infected individuals; however, vitamin B_{12} levels may be depressed as a consequence of achlorhydria or malabsorption.

True autoimmune haemolytic anaemia is rare, although ~20% of patients with HIV infection may have a positive direct antiglobulin test as a consequence of polyclonal B cell activation. Erythropoietin levels in patients with HIV infection and anaemia are generally less than expected given the degree of anaemia. Treatment with erythropoietin at doses of 100 μg/kg three times a week may result in an increase in haemoglobin levels.

During the course of HIV infection, neutropenia may be seen in approximately half of patients. In most instances it is mild; however, it can be severe and can put patients at risk of spontaneous bacterial infections. This is most frequently seen in patients with severely advanced HIV disease and in patients receiving any of a number of potentially myelosuppressive therapies[34].

Many studies are conducted worldwide.[47] **Belperio PS, Rhew DC**. Prevalence and outcomes of anaemia in individuals with human immunodeficiency virus. In this study it was found that anaemia was more commonly associated with disease progression with progressive decrease in

CD4 count . **Mocroft A, Kirk O, Barton SE, et al**. Conducted a study on "Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients" from across Europe. In this study it was found that anaemia was a independent predictor of mortality in HIV infected patients[48].

PLATELET COUNT

Thrombocytopenia[14] may be an early consequence of HIV infection. Approximately 3% of patients with untreated HIV infection and CD4+ T cell counts ≥400/μL have platelet counts <150,000/μL. For untreated patients with CD4+ T cell counts <400/μL, this incidence increases to 10%. Thrombocytopenia is rarely a serious clinical problem in patients with HIV infection and generally responds well to ARV therapy. Clinically, it resembles the thrombocytopenia seen in patients with idiopathic thrombocytopenic purpura.

Immune complexes containing anti-gp120 antibodies and anti-anti-gp120 antibodies have been noted in the circulation and on the surface of platelets in patients with HIV infection. Patients with HIV infection have also been noted to have a platelet-specific antibody directed toward a 25-kDa component of the surface of the platelet. Other data suggest that the thrombocytopenia in patients with HIV infection may be due to a direct effect of HIV on megakaryocytes.

Sullivan and colleagues[45] evaluated the 1-year incidence of thrombocytopenia(<50,000/mm^3) in a group of 30,214 HIV infected patients.

The incidence of thrombocytopenia during 1 year was 8.7% in patients with clinical AIDS,3.1% in patients with immunologic AIDS(CD4 count <200 cells/μL).Over time, development of thrombocytopenia was associated with clinical or immunologic AIDS, history of injection use, anaemia, lymphoma and African race. After controlling for multiple factors (AIDS,CD4 count, anaemia, neutropenia, ART therapy, prophylaxis against p.carnii) thrombocytopenia was significantly associated with shorter survival (risk ratio,1.7:95% confidence interval = 1.6-1.8)

SERUM ALBUMIN

S.albumin levels decreases progressively with progression of disease to AIDS. It correlate well with low CD4 count. Even though serum albumin is not a specific marker for HIV-1 infection, it was one of the strongest independent predictors of mortality.

Because HIV infection is known to be associated with systemic inflammation and elevations in the levels of proinflammatory cytokines, a strong association of albumin and mortality would be expected in HIV patients.

The mechanism of reduced albumin in HIV are

1.proinflammatory cytokines suppress albumin[35] synthesis.

2. the HIV-1 Tat-1 protein may disrupt the barrier function of the endothelium, resulting in both an increase in trans capillary escape of albumin and the dissemination of HIV-infected cells into tissue and, consequently, disease progression[36].

3. HIV-related anorexia may depress albumin synthesis, although albumin is not regarded as a sensitive marker of nutrition, especially in the short term[37].

4. the onset of HIV-associated nephropathy will increase renal losses of albumin

Joseph G. Feldman[46], Stephen J. Gange , conducted a study on "Serum Albumin Is a Powerful Predictor of Survival among HIV-1–Infected Women". This was a multicenter prospective study of the natural history of HIV-1 infection in women conducted in five United States cities. According to this study Albumin fell 0.44 g/L/y in 1627 women who survived and at a faster rate in 397 who died (1.54 g/L/y; $p < .01$). In a time-dependent model adjusting for disease markers, the relative hazard (RH) was fivefold higher in patients with serum albumin <35 g/L compared with patients with serum albumin >42 g/L.

AIM OF THE STUDY

1.To find out the best predictor of CD4 count in HIV infected patients, among the selected clinical parameters (WHO staging, anthropometry) and laboratory parameters(Total Lymphocyte Count, Haemoglobin, platelet count, ESR, Serum Albumin).

2. To study the correlation between these parameters and CD4 count to suggest that these can be used as a surrogate for CD4 count to initiate ART in resource limited settings.

MATERIALS AND METHODS

SETTING:

About 100 documented HIV positive patients attending ART centre and admitted in various medical wards in Govt. Rajaji Hospital were studied.

COLLABORATIVE DEPARTMENTS:

Department of STD , Anti Retroviral Therapy centre,

Department of pathology and Biochemistry,

Madurai medical college,

Madurai.

STUDY DESIGN:

Analytical Study

PERIOD OF STUDY:

June 2008- June 2009

SAMPLE SIZE:

About 100 Patients with documented HIV+ using ELISA.

ETHICAL CLEARANCE:

Necessary ethical clearance was obtained from Ethical committee , GRH, Madurai

CONSENT: informed consent was obtained

FINANCIAL SUPPORT: NIL

CONFLICT OF INTEREST: NIL

INCLUSION CRITERIA:

patients with documented HIV + were included in this study.

EXCLUSION CRITERIA:

Patient on ART therapy

Patients on Anti Tubercular Therapy (ATT)

Patients on steroid, iron or vitamin therapy

Patient with bleeding disorder

Pregnancy

Diabetes and other metabolic disorders

Chronic renal failure patients

METHODS

After obtaining the verbal consent either from the patient or the relatives, all patients were evaluated by complete medical history and standardized baseline investigations such as blood sugar, blood urea ,serum creatinine and liver function tests were done.

All patients underwent through a list of questionnaire and detailed clinical examination to stage (I ,II, III,IV) according to WHO CLINICAL STAGING REVISED CRITERIA 2005[28] as per proforma. Anthropometric measurements such as BMI was calculated.

The following specific investigation was done in patients

1. CD4 count
2. Total Lymphocyte Count(TLC)
3. Haemoglobin(HB)
4. Platelet count(PLT)
5. Erythrocyte Sedimentation Rate (ESR)

6. Serum Albumin.

CD4 COUNT:

CD4 count was done using Flow Cytometry. Flow cytometers use lasers to excite fluorescent antibody probes specific for various cell surface markers, such as CD3, CD4, and CD8.It is calculated in cells/μL.

AUTOMATED CELL COUNTER:

Total WBC count, Differential count, Haemoglobin, Platelet count were obtained using automated cell counter.

Automated cell counters sample the blood, and quantify classify and describe the cell populations using both electrical and optical techniques.

Total lymphocyte count was easily obtained from total WBC count and differential percentage of lymphocyte using the following formula.

TLC = % of lymphocyte x total WBC count

Normal TLC is usually > 1800 cells/mm≥.

ESR:

ESR was obtained using westergren tube. Anticoagulated blood is placed in a upright westergren tube and rate at which the RBC's sedimented is measured and reported in mm/hr .

The normal values are

MEN <50 years - <13 mm/hr and

> 50 years - <20 mm/hr

WOMEN < 50 years - < 20mm/hr

>50 years- < 30 mm/hr

LIMITATIONS OF OUR STUDY:

WHO clinical staging in our cases were done on presumed clinical basis and some basic laboratatory investigations,so some of the patients may be wrongly staged.

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2008).**

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

Sensitivity, specificity, accuracy, positive predictive value and negative predictive values were calculated using the following formulae

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive + False negative}} \times 100$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{False positive + True negative}} \times 100$$

$$\text{Accuracy} = \frac{\text{True Positive + True Negative}}{\text{Total cases}} \times 100$$

$$\text{Positive predictive value} = \frac{\text{True positive}}{\text{True positive + False positive}} \times 100$$

$$\text{Negative predictive value} = \frac{\text{True negative}}{\text{True negative + False negative}} \times 100$$

RESULTS

Figure 1: AGE DISTRIBUTION

TABLE 1: AGE DISTRIBUTION

AGE GROUP(in years)	CASES

	No.	%
13 -20	3	3
21-30	20	20
31-40	54	54
41-50	17	17
>50	6	6
Total	100	100
Range	18-60 years	
Mean	35.9 years	
SD	8.5 years	

In our study about 54% of people were in age group between 31-40 years.91% of patients are age group between 21-50 yrs. so majority of patients in our study were in reproductive age group.

Figure 2: GENDER DISTRIBUTION

TABLE 2: GENDER DISTRIBUTION

SEX	CASES	
	No.	**%**
Male	66	66
Female	34	34
Total	100	100

In our study about 66% of patients were males and 34% were females.

TABLE 3:MARITAL STATUS

MARITAL STATUS	CASES		CD4 COUNT	
	No.	**%**	**mean**	**SD**
Married	66	66	265.8	212.6
Unmarried	21	21	299.4	233.7
Separated	13	13	234.8	215.3
Total	100	100	**p** 0.5441	
			Not significant	

As shown in above table ,most of the patients about 79% were married of which 13% of patients were separated after marriage and living alone.21% of patients were unmarried. Marital status when correlated with CD4 count ,**p** value was not statistically significant.

TABLE 4 : PREMARITAL SEX

PREMARITAL SEX	CASES	
	No.	**%**
Yes	42	42
No	58	58
Total	100	100

In the above table about 58% of the patients denies history of premarital sex and 42% gives positive history of premarital sex.

TABLE 5: EXTRA MARITAL PATNERS

EXTRAMARITAL PATNERS	CASES		CD4 COUNT	
	No.	%	MEAN	SD
None	22	22	258.4	201.5
single	24	24	92.5	53.0
Multiple >1	54	54	603.5	327.6
Total	100	100	p value 0.0185 significant	

As shown in above table , 54% of the patients were having more than one extra marital patners.22% of the patients had no extramarital exposure. Extra marital sex when correlated with CD4 count, p value 0.0185 was significant.

Figure 3 : OCCUPATION

TABLE 6: EDUCATION

EDUCATION	CASES		CD4 COUNT	
	No.	%	MEAN	SD
<10 TH Std	54	54	230.1	189.1
10-12 th Std	36	36	291.1	212.2
Higher Education	10	10	394.6	314.9
TOTAL	100	100	p value 0.0778	
			Not significant	

As shown in above table Majority of the patients in our study i e. about 54% were less educated (below tenth standard) whereas only 10% of the patients studied higher education. Education when correlated with CD4 count p value 0.0778 was not significant.

TABLE 7: OCCUPATION

OCCUPATION	CASES	
	No.	%
Labourer	58	58
Drivers	11	11
House Wife	20	20
Business Men	6	6
Service Men	3	3

Police Men	1	1
Student	1	1

Most of the patients 58% in the study group were labourers as shown in Table-7 and Fig 3. Housewives constitutes 20% of study population. Drivers accounted for 11% and Business men constitutes 6%.

TABLE 8: ECONOMIC STATUS

ECONOMIC STATUS	CASES		CD4	
	No.	%	MEAN	SD
Upper	7	7	687.1	330.5
Middle	21	21	336.9	194.2
Lower	72	72	208.3	151.3
Total	100	100	p value 0.0001 significant	

In our study about 72% of the patients were in lower socio economic status,21% of patients belong to middle class, only 7% of the patients were in upper economic status. Economic status has significant p value 0.0001 when correlated with CD4 count.

TABLE 9: EXPOSURE TYPE

EXPOSURE	CASES	
	No.	%

Heterosexual	94	94
Homosexual	2	2
Blood Products	4	4
Iv Drug Abuser	-	-
Needle Stick	-	-
Materno Foetal	-	-

The above table shows that the heterosexual mode of transmission was the commonest mode of transmission, accounting for 94% of the cases. only 2% of cases transmission was through homosexual route and 4% of cases showed transmission through blood products such as blood transfusion.

Figure 4 : STAGING AND CD4 COUNT

TABLE10: STAGING AND CD4 COUNT

STAGING	**cases**		**CD4**	
	No .	**%**	**MEAN**	**SD**
I	17	17	571.2	228

II	9	9	434.4	291.2
III	43	43	210.1	100.3
IV	31	31	136.4	80.7
	100	100	**p value 0.0001**	
			significant	

As shown in the above table, about 74% of the patients were came under stage III & IV of WHO staging. When staging was correlated with CD4 count the p value was statistically significant. patients with Stage IV had average CD4 count of 136.4 cells/µL and Stage III had 210 cells/µL. whereas stage I and II had average count of 571.2 and 434.4 cells/µL respectively as shown in Figure 4.

TABLE 11: OTHER LABORATORY PARAMETERS

	RANGE	**MEAN**	**SD**
CD4 cells/µL	31-1050	269	216
TLC cells/mm≥	184-3020	1316	696
TC cells/mm≥	1840-9400	6199	1537
HB g/dl	3.2-14.4	8.41	2.68
HT cm	140-178	162	9.4
WT kg	38-70	47.9	7.2
BMI kg/m²	14.2-25.4	18.2	2.2
PLATELET	40000-420000	180910	91177

ESR mm/hr	4-112	41.4	29.1
S.albumin g/dl	2.3-4.5	3.28	0.61

Figure 5: TOTAL LYMPHOCYTE COUNT AND CD4 COUNT

TABLE 12 : TOTAL LYMPHOCYTE COUNT AND CD4 COUNT

TLC	**CASES**		**CD4**	
	No.	**%**	**MEAN**	**SD**
<1200	48	48	121.9	52.8
1200-1800	10	10	266.3	51.7
>1800	42	42	565.8	234.5
Total	100	100	**p value 0.0001**	
			Significant	

Total Lymphocyte count was <1200 cells/mm≥ in about 48% of patients and it shows very good correlation with CD4 count and p Value was statistically significant.

The patients with TLC <1200 cells/ mm^3 had average CD4 count of 121.9 cells/ µL. Whereas patients with TLC of 1200 to 1800 and > 1800 cells/mm^3 had average CD4 count of 266.3 and 565.8 cells/ µL respectively.

As shown in Figure 5 ,Of patients with CD4 count <200 cells/µL all of them 100% (n=45) are having TLC <1200 cells/mm≥.patients with CD4 count between 200 and 350 were having TLC <1200 cells/mm≥ in 9% (n=3)of cases and 71% were having TLC >1800/ mm^3.Most of the patients with CD4 count >350 cells/ µL were having TLC >1200 cells/mm≥, none were having TLC <1200 cells/mm≥.

Figure 6: BMI AND CD4 COUNT

Figure 7: HAEMOGLOBIN AND CD4 COUNT

TABLE 13: Body Mass Index and CD4 count

BMI	CASES		CD4	
	No.	%	MEAN	SD
<18.5	63	63	203.3	167.1
18.5-24.99	26	26	383.5	249.6
25-29.99	11	11	325.5	181.7
>30	-	-	-	-
Total	100	100	p value 0.0001	

significant

As shown in the above table and Fig 6, Body mass index was < 18.5 kg/m² in 63% and had good correlation with CD4 Count and p value was significant. Average CD4 count with BMI <18.5kg/m² was 203.3 cells/ µL.

TABLE 14: Haemoglobin and CD4 count

HB	CASES				CD4	
	M	F	T	%	MEAN	SD
<5	4	6	10	10	136	91
5-8	25	16	41	41	209.7	174.9
8-11	20	11	31	31	282.5	203.4
>11	15	3	18	18	461.8	254.6
Total	64	36	100	100	p value 0.0001	
					significant	

In our study Haemoglobin was < 11g% in about 92% (n=33)of females and 77% of males (n=49).when correlated with CD4 count showed a statistically significant p value. patients with HB < 5 g% were having mean CD4 count of 136 cells/ µL as shown in Figure 7.

Figure 8: PLATELETS AND CD4 COUNT

Figure 9 : ESR AND CD4 COUNT

TABLE 15:

PLATELET COUNT AND CD4 COUNT

PLATELET COUNT	CASES		CD4	
	No.	%	mean	SD

<150000	54	54	175.1	109.6
>150000	46	46	383.4	256.7
Total	100	100	**p value 0.0001**	
			Significant	

As shown in above table platelet count was less than 150000 in about 54% of cases and it also showed a good correlation with CD4 statistically significant p value. The mean CD4 count with PLT <150000 cells was only175.1cells/ µL when compared to CD4 count of 383.4 cells/ µL with PLT>150000 cells/ mm^3 as shown in Figure 8.

TABLE 16: ESR AND CD4 COUNT

ESR	**CASES**		**CD4**	
	No.	**%**	**MEAN**	**SD**
0-30	35	35	425.7	271
31-60	38	38	206.5	112.3
61-90	21	21	158.9	107.2
>90	6	6	125.2	98.2
Total	100	100	**p value 0.0001**	
			significant	

In the above table, ESR was > 30mm/hr in about 65% of the cases and shows a significant p value with CD4 count. The average CD4 count with ESR > 90mm/hr was only 125.2 cells/ µL. Patients with ESR <30mm/hr were having mean CD4 count of 425.7 cells/ µL as shown in Figure 9.

Figure 10: SERUM ALBUMIN AND CD4 COUNT

TABLE 17: SERUM ALBUMIN AND CD4 COUNT

SERUM ALBUMIN	cases		CD4	
	No.	%	MEAN	SD
<2.8	30	30	150.2	124.9
2.8-3.5	39	39	242	182.2
>3.5	31	31	414.4	244.6
Total	100	100	**p value 0.0001**	
			significant	

As shown in above table, serum albumin was less than 3.5g/dl in 69% of cases and in 30% of cases it was less than 2.8 g/dl. It has good correlation with CD4 and p value was significant.

As shown in Figure 10 ,patients with serum albumin <2.8 g/dl and between 2.8-3.5 g/dl were having mean CD4 count of 150.2 cells/ µL and 242 cells/ µL respectively. The mean CD4 count of patients with s.albumin >3.5 g/dl was 414.4 cells/ µL.

TABLE 18:EFFICACY OF VARIOUS INVESTIGATIONS

IN VESTIGATIONS	CD4 COUNT <200 cells/µL No.	%	>200 cells/µL No.	%
Staging				
III, IV	42	56.8	32	43.2
I,II	3	11.5	23	88.5
TLC Count				
<1200 cells /mm≥	45	73.8	3	6.5
>1200 cells /mm≥	-	-	52	100
Staging + TLC count				
Positive	42	93.3	3	6.7
Negative	3	5.5	52	94.5
BMI				
<18.50 kg / m²	36	57.1	27	42.9
>18.50 kg / m²	9	24.3	28	75.7
HB				
<11 g/dl	41	50	41	50
>11g/dl	4	22.2	14	77.8
Platelet				
<150000 cells/mm≥	32	58.2	23	41.8
>150000 cells/mm≥	13	28.9	32	71.1
Serum Albumin				
<3.5 g/dl	38	55.1	31	44.9
>3.5 g/dl	7	22.6	24	77.4
ESR				
>30 mm/hr	35	53.8	30	46.2
<30 mm/hr	10	28.6	25	71.4

Figure 11: EFFICACY OF VARIOUS INVESTIGATIONS

TABLE 19: SENSITIVITY ,SPECIFICITY ,PREDICTIVE VALUE OF VARIOUS INVESTIGATIONS

INVESTIGATIONS	True + ve	False + ve	True - ve	False - ve	Efficacy. Sensi -tivity	Speci- -ficity	Accu- -racy	PPV	NPV
Staging	42	32	23	3	93	42	65	57	92
TLC Count	45	3	52	-	100	95	97	94	100
Staging + TLC count	42	3	52	3	93	95	94	93	95
BMI	36	27	28	9	80	51	64	57	76
HB g%	41	41	14	4	91	25	55	50	78
TLC+ HBg%	41	3	52	4	91	95	93	93	93
Staging+ HBg%	39	29	26	6	87	47	65	57	81
Platelet	32	23	32	13	71	58	64	58	71
Serum Albumin	38	31	24	7	84	44	62	55	78
ESR	35	30	25	10	78	45	60	54	71

As shown in the Table-19, WHO clinical staging had sensitivity 93%,specificity 42% in predicting CD4 count < 200 cells/μL and it had good negative predictive of 92%.Its accuracy was 65%.

Total Lymphocyte Count had sensitivity 100% , specificity 95%,positive predictive value 94%,negative predictive value 100% and accuracy 97%. When compared with WHO staging TLC had very good sensitivity, specificity, positive and negative predictive value.TLC was more accurate than WHO staging in predicting CD4 count < 200 cells/μL.

On combining both WHO staging and TLC, we got sensitivity 93%, specificity95%,PPV 93%,NPV 95% and accuracy was 94%.

BMI had sensitivity and specificity of 80% and 51% respectively. Haemoglobin had sensitivity and specificity of 91% and 25% respectively.

Platelet count had sensitivity 71% and specificity 58%.serum albumin had sensitivity 84% and specificity 44%. ESR had sensitivity and specificity of 78% and 45% respectively.

DISCUSSION

If CD4 lymphocyte counts are available and HIV infected patient's CD4 lymphocyte count is less than200 cells/mm^3, it would be universally agreed that ART should be initiated regardless of the fact that CD4 counts have biologic variability by sex, age, and ethnicity as well as some variability in measurement in the laboratory.

Although the CD4 count has become the ''gold standard,'' in resource-limited settings where the CD4 count is not routinely available, other clinical and laboratory factors can be predictive of severe immune compromise. Routine hematologic testing is inexpensive and widely accessible and can provide measurements of the TLC and haemoglobin level.

In our study about 100 patients are randomly enrolled, of which 66% are males and 34% are females. Most of the patients are in reproductive age group.71% of the patients are in age group between 21 -40 years. This shows that HIV is more in reproductive age group .This indicates a trend of young and productive generation being affected ;a reflection of the

devastating effects India will face as the younger generation work force is affected.

In this study age ,number of extra marital partners, type of exposure and economic status of the patients are very well correlated with CD4 count with a statistically significant P value.

In our study 54% of patients are having more than one extra marital partners and the most common mode of transmission is heterosexual route (94%). This is in consistent with **Uzgare R et al**[50] found that the percentage of various modes of transmission as sexual route (93.02%)commonly heterosexual, Blood (2.32%) , Perinatal(2.32%),surgery and IV needles(3.72%).

In our study Sex of the patient, Marital status, Premarital sex, Education and Occupation are not correlated with CD4 count .

STAGING:

WHO in 2005 Proposed a revised clinical staging to initiate ART in resource limited settings especially in Africa and Asia.[28]

Clinical events are categorized as those where a presumptive clinical diagnosis may be made (conditions that can be diagnosed clinically or with basic laboratory tests) and those where a definitive diagnosis may be

made (for conditions requiring more complex and sophisticated laboratory investigations).

CLINICAL AND IMMUNOLOGICAL CRITERIA FOR INITIATING ART IN ADULTS AND ADOLESCENTS

Clinical stage	**ART**
IV	Treat.
III	Consider treatment: CD4, if available, can guide the urgency with which ART should be started.
I ,II	Only if CD4 <200/mm3.

Many studies were conducted to assess the WHO recommendation for clinical criteria to initiate ART in resource limited settings.

In our study using WHO clinical staging III and IV when correlated with CD4 count <200 cells/μL we get a significant statistical P value 0.0001. It has sensitivity 93%, specificity 42% in predicting CD4 count < 200 cells/μL and it has good NPV of 92%.Its accuracy is 65% and PPV is 57%.

Caroline Costello, MPH, Kenrad E. Nelson, MD,Denise J. Jamieson, MD, Lisa Spacek, MD, PhD, Supaluk Sennun, MS did a study on "Predictors of

LowCD4Count in Resource-Limited Settings" . This study was based on an Antiretroviral-Naive Heterosexual Thai Population. Totally 519 people were included in the study. In this study WHO clinical staging III has specificity of 90.2% and 91.7% and sensitivity of 27.4% and 20.4% in men and women. respectively. WHO clinical staging IV has specificity of 100% and 100% and sensitivity of 2.2% and 1.2% in men and women respectively

When compared with above study , our study is having good sensitivity of 93%, though it is not specific but the negative predictive value is 92% is good. Majority of the patients (74%) in our study belongs to clinical staging III and IV .So we are getting low specificity when compared with above study.

Patients are categorised in to stage III or IV when they acquire the opportunistic infections and other AIDS defining illness as listed in WHO staging. Opportunistic infections are more common when CD4 count is less than 200 cells/µL.In our study,patients with Stage IV has average CD4 count of 136.4 cells/µL and of patients with CD4 count < 200 cells/µL(n=45), 93% (n=42) were in stage III or IV.

So clinical staging III and IV is a good predictor of CD4count <200 cells/ µL.

TOTAL LYMPHOCYTE COUNT:

In December 2003, the WHO broadened the recommendations for initiation of ART when CD4 testing is unavailable to include WHO stage III or IV or WHO stage II in combination with a TLC 1200 cells/mm3[6,7]. Many studies have evaluated the use of TLC as a surrogate marker for CD4+ cell count with mixed results[8,9]. In our study, as shown in TABLE 21,We get a sensitivity of 100% specificity of 95% ,accuracy is 95% ,PPV is 94% and NPV is 100% for TLC in predicting CD4 count <200 cells/ μL.

Caroline Costello, MPH, Kenrad E. Nelson, MD[43], conducted a study on "Predictors ofLowCD4Count in Resource-Limited Settings". In this study TLC <1200 cells/mm3 has specificity of 99.2% in men and 99.5% in women. It has sensitivity of 23.4% in men and 13% in women in predicting the CD count <200 cells/μL. The TLC was highly correlated with the CD4 count in this Thai cohort, consistent with studies of HIV-infected patients in South , the United kingdom [39], and the United States[31.40,41].Similar to above study, in our study TLC has very good specificity of 95%.

Ray Y. Chen, MD, Andrew O. Westfall, MS,J. Michael Hardin[44] : Complete Blood Cell Count as a Surrogate CD4 Cell Marker for HIV Monitoring in Resource-Limited Settings; This study was conducted in The University of Alabama at Birmingham (UAB) Outpatient HIV Clinic. According to this study TLC < 1200 cells/mm^{3}has specificity of 90% and

sensitivity of 71% in predicting CD4 count< 200 cells/µL. It has PPV OF 78% and NPV of 87%.

In comparing with above study, Our study is having very good sensitivity(100%),specificity(95%), PPV (94%) and NPV (100%).

In our study compared to other parameters TLC < 1200 cells/mm^3 is very specific in predicting CD4 count < 200 cells/mm^3. This is because marked reduction in the CD4+ T cells is the immunologic hallmark if AIDS. Productive infection of T cell and viral replication in infected cells is the major mechanism of lysis of CD4 T cells. The other mechanism of lysis of CD4 T lymphocytes are Elimination of HIV-infected cells by virus-specific immune responses, Activation-induced cell death, Aberrant intracellular signaling events, Apoptosis and Syncytia formation.

This decrease in CD4 T cells is directly reflected in total lymphocyte count. So, Total Lymphocyte Count is exact measure of CD4 T cell count .Measurement of peripheral blood CD4 T lymphocytes is probably the most important laboratory assay for evaluation and monitoring of patients with HIV.The most common technique for measuring CD4 counts in developed country settings is Flow cytometry which use lasers to excite fluorescent antibody probes specific for various cell surface markers, such as CD3, CD4, and CD8, which distinguish one type of lymphocyte from

another. But it is no not widely available in developing countries especially in peripheral set up where the HIV prevalence is high.

In our study, the patients with TLC <1200 cells/ mm^3 has average CD4 count of 121.9 cells/ µL .So instead of CD4 count, TLC<1200 cells/mm^3 which is more specific marker of CD4 count can be used as a surrogate for CD4 count < 200 cell/µL in resource limited settings.

STAGING + TLC :

On combining both the staging and TLC we are getting a sensitivity 93%, specificity 95% , accuracy 94%, PPV 93%and NPV 95% in predicting CD4 count < 200 cells/µL.

Schechter M, Leite DM, Zajdenverg R [42] has conducted a study on predictors of CD4 count in HIV infected Brazilian individuals based upon WHO clinical staging .171 patients were included in the study. WHO clinical staging and absolute lymphocyte count (TLC) was significantly correlated with CD4 count and has specificity of 89% and PPV OF 85.3%.

But in our study on using staging alone has specificity of 42% and PPV 57% in predicting CD4 count <200 cells/µL. When using both staging and TLC the specificity increased from 42 to 95% and PPV increased from57% to 93%.

Thus when combining both staging and TLC, the specificity, accuracy, PPV and NPV are all increased rather than using staging alone.

BODY MASS INDEX;

In our BMI has sensitivity 80%, specificity 54% ,accuracy 64%, PPV 57%and NPV 76% in predicting CD4 count < 200 cells/μL.

Caroline Costello, MPH, Kenrad E. Nelson, MD, Predictors ofLowCD4Count in Resource-Limited Settings .In this study BMI< 18.5 kg/ m² has specificity of 95.6% and sensitivity of 13.4% in predicting CD4 count < 200 cells/μL.

In our study BMI is more sensitive but less specific when comparing with above study in predicting CD4 count < 200 cells/μL. This is because low BMI is more prevalent(63%) in our study which decrease the specificity. The BMI is low in our study because most of our patients are in WHO staging III and IV ,they are having more opportunistic infections and succumb to cachectic process and muscle wasting due to inflammatory cytokines[30].

BMI <18.5kg/m^2 is more common in stage III and IV when CD4 count is <200 cells/ μL .Thus it is useful in predicting CD4 count <200 cells/μL.

ANAEMIA;

Anaemia is more common in our country. In our study about 82% of the patient are anaemic.92% (n=33)of females and 77% of males (n=49) were anaemic in our study. patients with HB < 5 g% were having mean CD4 count of 136 cells/ µL. Anaemia very well correlated with CD4 count with a statistically significant P value of 0.0001.

Anaemia has sensitivity 91%, specificity 25% , accuracy 55%, PPV 50%and NPV 78% in predicting CD4 count < 200 cells/µL.

[47]**Belperio PS, Rhew DC**. Prevalence and outcomes of anaemia in individuals with human immunodeficiency virus. In this study it was anaemia more commonly associated with disease progression with progressive decrease in CD4 count and anaemia was more common in females when compared to females. **Caroline Costello, MPH, Kenrad E. Nelson, MD,** Predictors of Low CD4Count in Resource-Limited Settings. In this study also anaemia more common in females (15.6%) compared to males(9%) and the specificity of anaemia in predicting CD4 count <200 cells/µL was 96.4% and 85.5% in males and females respectively. Among men in this study , anaemia was highly predictive of CD4 count <200 cells/µL .

Compared to above study, our present study has good sensitivity of 91% and specificity is only 25% . This is mainly due to, as anaemia is more prevalent in our country the specificity in predicting CD4 count < 200 cells/µL is very low.

Anaemia in the setting of HIV is due to multifactorial causes and it is the most common hematologic abnormality in HIV-infected patients. As most of our patients are in WHO staging III and IV the most important causes are systemic fungal and mycobacterial infections, nutritional deficiencies, and vitamin B_{12} levels may be depressed as a consequence of achlorhydria or malabsorption.

Anaemia when combined with TLC count, we are getting a sensitivity 91%, specificity 95% ,accuracy 93%, PPV 93%and NPV 93% in predicting CD4 count < 200 cells/µL.

When combining anaemia with TLC specificity, accuracy of the test, PPV and NPV are all increased rather than using anaemia alone.

Thus anaemia combined with TLC count can be used as a more sensitive and specific test in predicting CD4 count <200 cells/µL in resource limited settings in primary health care centres in our country.

PLATELET COUNT:

The prevalence of thrombocytopenia in our study is 55% of which 58% of patients are having CD4 count <200 cells/µL. The platelet count decreases progressively with decrease in CD4 count and more common in AIDS.

In present study platelet count has sensitivity 71%, specificity 58% ,accuracy 64%, PPV 58% and NPV 71% in predicting CD4 count < 200 cells/μL. It shows a significant correlation with CD4 count with a significant P value of 0.0001.

In HIV positive patients ,according to Sullivan PS,Hanson DL et al[45] isolated thrombocytopenia may be early consequences of HIV infection. **Fauci et al Harrison's principles of internal medicine[27]** AIDS and related disorders mentioned approximately 3% of patients with untreated HIV infection and CD4+ T cell counts ≥400/μL have platelet counts <150,000/μL. For untreated patients with CD4+ T cell counts <400/μL, this incidence increases to 10%.In our study the prevalence of thrombocytopenia is 58% with CD4 count <200 cells/μL.

The low platelet count in our study is explained by

1.Anti gp 120 and gp 41antibody are removed from circulation by macrophages in the Spleen, similar to mechanism seen in ITP.

2. due to a direct effect of HIV on megakaryocytes.

In our study, in patients with PLT <150000 cells the mean CD4 count was only 175.1cells/ μL .Though the platelet count has low specificity and sensitivity when compared to TLC ,as it is more prevalent when CD4 count

< 200 cells/µL, it may be used in addition to TLC in predicting CD4 count < 200 cells/µL.

ERYTHROCYTE SEDIMENTATION RATE:

ESR is a marker of ongoing inflammation. In the setting of HIV, ESR is very much increased in various opportunistic infections especially tuberculosis when CD4 count is <200 cells/µL. ESR in our study is more than 30mm/hr in about 65% of the cases and shows a significant P value with CD4 count. Of the whole 65% of cases with ESR >30mm/hr about 70% of the patients are having CD4 count < 200 cells/µL.

Most of the patients (74%)in our study come under WHO clinical staging III and IV who are having opportunistic infections. so ESR is naturally raised with progressive decrease in CD4 count and the average CD4 count with ESR > 90mm/hr was only 125.2 cells/ µL. Thus ESR may be used as an additional test along with TLC, in predicting CD4 count < 200 cells/µL.

SERUM ALBUMIN:

In present study Sr.Albumin levels decreases progressively with progression of disease to AIDS. It correlate well with low CD4 count. About 69% of the patients are having serum albumin <3.5 g% and most of them (55%) are having CD4 count < 200 cells/µL.

Serum albumin has sensitivity 84%, specificity 44% ,accuracy 62%, PPV 55% and NPV 78% in predicting CD4 count < 200 cells/µL in our study.

Joseph G. Feldman[46], Stephen J. Gange , conducted a study on “Serum Albumin Is a Powerful Predictor of Survival among HIV-1–Infected Women”. According to this study Albumin fell progressively with decrease in CD4 count at a rate of 0.44 g/L/y in 1627 women who survived and at a faster rate in 397 who died (1.54 g/L/y; p < .01). In a time-dependent model adjusting for disease markers, the relative hazard (RH) was fivefold higher in patients with serum albumin <35 g/L compared with patients with serum albumin >42g/L. Even though serum albumin is not a specific marker for HIV-1 infection, it was one of the strongest independent predictors of mortality[46].

In our study , patients with serum albumin <2.8 g/dl are having mean CD4 count of 150.2 cells/ μL .Progressive decrease in Sr. Albumin with decline in CD4 count is explained in our study by the following:

1.Because HIV infection is known to be associated with systemic inflammation and elevations in the levels of pro inflammatory cytokines, which can suppress albumin[35] synthesis.

2. The HIV-1 Tat-1 protein may disrupt the barrier function of the endothelium, resulting in both an increase in trans capillary escape of albumin and the dissemination of HIV-infected cells into tissue and, consequently, disease progression[36].

3. HIV-related anorexia may depress albumin synthesis.

Thus serum albumin is a very good marker associated with disease progression. It may be used as a predictor of CD4 count < 200 cells/μL in addition to TLC.

CONCLUSION

1.TLC<1200 cells/mm^3 is the most sensitive and specific test and best predictor of CD4 count < 200 cells/µL, whereas WHO staging is a good sensitive test.

2. TLC along with WHO staging or Anaemia, is more specific in predicting CD4 count <200 cells/µL , rather than using staging or anaemia alone.

3. Though BMI, Anaemia ,platelet count, ESR and serum albumin are good predictors of CD4 count < 200 cells/µL, these tests are less sensitive and specific when compared to TLC or staging.

4. Platelet count and Serum Albumin level decreases with progressive decrease in CD4 count. Platelet count <150000/mm≥ and s.albumin <2.8 g/dl are also good predictors of CD4 count <200/µL.

Although the CD4 count is used as "gold standard" test, TLC < 1200 cells/mm≥ or TLC along with WHO staging or anaemia can be used as a surrogate marker for CD4 count <200 cells/µL to initiate ART in resource limited settings.

SUMMARY

This study **"PREDICTORS OF CD4 COUNT IN HIV INFECTED PATIENTS"** , was conducted in 100 HIV positive patients who were attended the ART medical centre in Govt. Rajaji Hospital ,Madurai from June 08 to June 2009.

In our study 100 patients were randomly selected of which 66% were males and 34% were females. About 74% were in age group between 21- 40 years showed the prevalence of disease in reproductive age group.

In all the patients various clinical and inexpensive laboratory measures such as WHO clinical Staging ,BMI ,Total Lymphocyte Count (TLC),haemoglobin ,platelet count, ESR, S. Albumin were done and correlated with CD4 count .It was analysed that these parameters may be used as a surrogate marker for CD4 count to initiate ART and to monitor therapy.

WHO staging III and IV had sensitivity of 93% and specificity of 25% in predicting CD4 count < 200 cells/µL and it showed a significant correlation with CD4 count.

TLC <1200 cells/mm3 had sensitivity of 100% and specificity of 95% in predicting CD4 count <200 cells/µL and it showed a statistically significant correlation with CD4 count.

BMI<18.5kg/m^2,Haemoglobin<11g%,Platelets<150000cells/mm3, ESR >30mm/hr and s.albumin<3.5g/dl showed a statistically significant correlation with CD4 count but they were less sensitive and less specific when compared to TLC or WHO staging.

Therefore TLC is most sensitive and specific best predictor of CD4 count <200 cells/µL.

WHO clinical staging is a good sensitive test in predicting CD4 count less than 200 cells/µL.

TLC when combined with WHO staging or Anaemia, specificity in predicting CD4 count <200 cells/µL increases, than using staging or anaemia alone.

Although the CD4 count has become the "gold standard", TLC < 1200 cells/mm≥ or TLC along with WHO staging or anaemia may be used as a surrogate marker for CD4 count <200 cells/µL to initiate ART in resource limited settings.

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PROFORMA

Name

Age

Sex

ART No.

Address

Occupation

Education - < 10 th /10-12 th/higher education

Economic status-upper/middle/lower

Marital status- single /married /separated

Premarital sex-yes/no

Extra Marital Patners

Exposure- heterosexual/homosexual/IV drug abuser/blood transfusion

CLINICAL WHO STAGING HISTORY AND EXAMINATION

- Persistent generalized lymphadenopathy
- Moderate and unexplained weight loss
- Recurrent respiratory tract infections (such as sinusitis, bronchitis, otitis media, pharyngitis)
- Herpes zoster
- Recurrent oral ulcerations
- Papular pruritic eruptions
- Angular cheilitis
- Seborrhoeic dermatitis
- Fungal finger nail infections
- Unexplained persistent fever
- Unexplained chronic diarrhoea for longer than one month
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (TB) diagnosed in last two years

- Severe presumed bacterial infections (e.g. pneumonia, empyema, meningitis, bacteraemia, pyomyositis, bone or joint infection)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia
- Oesophageal candidiasis
- Extrapulmonary Tuberculosis

WHO STAGING : I ,II, III, IV

PAST HISTORY DM , HT , BA , PT (CAT I II III), STD, HEPB

FAMILY HISTORY

GYNAECOLOGICAL HISTORY for females

PERSONAL HISTORY- Smoking Alcohol Tobacco Drug Abuse

ANTHROPOMETRY

HT cm

WT Kg

BMI kg/m2

INVESTIGATIONS

Hb

Tc

Dc

Platelet Count

ESR

Serum Albumin

Blood Sugar

Blood Urea

Serum Creatinine

Lipid Profile

Total Bilirubin

Direct/Indirect

HIV ELISA

CD4 Count

Chest Xray

Sptum For AFB

VDRL

OGD Scopy