Immune Response Towards HIV: Its Significance in Establishing the Diagnosis and the Stage of Infection

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ABSTRACT

Human Immunodeficiency Virus (HIV) causes damage to the human immune system and the disease known as Acquired Immune Deficiency Syndrome (AIDS). This virus is a member of the Lentivirus group of viruses of the Retrovirus subfamily, which has a reverse transcriptase enzyme. HIV infects cells which expres CD4, mediated by gp 120. HIV infection changes the lymphocyte migration pattern, the activity of cytotoxic T cells and CD4 T cell count. The T cell $CD4^+$ count is related to the progressivity of the disease.

Anti gp 120 is the antibody most abundantly produced during HIV infection. Spesific antibody concentration for the antigens vary among individuals and single individual at different stages of the infection. Expression of the HIV antigen and/or antibody can be used to establishing the diagnosis and determine the stage of the disease. $CD4^+$ cells count can be used to determine the stage of HIV infection, to predict the occurance of opportunistic infection and other complications, and to determine as well as to monitor therapy.

Keywords: HIV, AIDS, $CD4^+$T cells, $CD8^+$T cells, Anti-HIV

INTRODUCTION

The Human Immunodeficiency Virus (HIV) is a virus that damages the human immune system, thus allowing the body to be an easy target of other, possibly fatal, diseases. The illness caused by the virus is known as Acquired Immune Deficiency Syndrome (AIDS). Up to date, the illness is still incurable. The drugs we have now are only beneficial in reducing suffering, improving the quality of life, and extending the survival of AIDS patients.

Since it was first reported in the year 1981, the prevalence of this disease has continuously risen. According to reports from the Ministry of Health of the Republic of Indonesia, the General Directorate of Infectious Disease Control and Environmental Health (DITJEN PPM & PLP) in February 2001, there were 33 new cases of HIV infection. All patients were Indonesians, and the majority were males (69.69%). As many as 72.72% (24 cases) were infected through intravenous drug use, while the rest were infected through heterosexual intercourse. There were 18 new AIDS cases in Indonesian citizens reported. As many of 61.11% were intravenous drug users, while the remaining number were infected through heterosexual intercourse. As of February 28th, 2001, 1299 HIV positive cases and 479 AIDS cases have been reported.[1]

At Dr. Cipto Mangunkusumo General Central National Hospital, Jakarta, most HIV/AIDS patients were infected through intravenous drug use among drug abusers. Most of the patients ranged from 14 years of age to 20s. A study by Dr. Zubairi Djoerban in 2000 reported 82% of 146 HIV/AIDS cases were drug abusers infected through intravenous drug use.[2]

In this review article, we will discuss the structure of HIV, the way it enters the body, the immune response towards HIV, and its significant for establishing a laboratory diagnosis. We hope that this review article will be useful in increasing our knowledge.

THE STRUCTURE OF HIV

HIV is an enveloped virus that is relatively easy to inactivate outside of the body. HIV is a Lentivirus, a subfamily member of Retrovirus, which tend to cause chronic infection and a long latency phase. It possesses the unique enzyme reverse transcriptase, which can copy viral ribonucleic acid (RNA) into deoxyribonucleic acid (DNA).[3]

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There are 2 types of HIV, HIV-1 and HIV-2. These two viruses have very similar structure. HIV-2 has a nucleotide that is more similar to the ape immunodeficiency virus (75%) compared to the HIV-1 nucleotide. Clinical manifestation and the mode of transmission of the two viruses are the same, except that HIV-2 has a milder clinical manifestation, and is mostly transmitted sexually and perinatally. HIV-2 has a longer seroconversion compared tq HIV-1, thus taking a longer time to advance to the AIDS stage.[3]

Based on the "env" and "gag" sequence, HIV-1 is divided into 9 subtypes, subtypes A to H, and O. The A subtype is found in Central Africa and Thailand. Subtype B is found in Europe, North and South America, Asia, and Australia. Subtype C is found in South and Central Africa, and Europe. Subtype G is found in Central Africa, Taiwan, and Russia. Subtype H is found in Gabon, Zaire, Central Africa. Subtype O is found in West Africa and France.[3]

The nucleus of HIV-1/HIV-2 takes the form of a cone consisting of p24 proteins encircling the RNA virus genome, and the reverse transcriptase enzyme. The HIV genome is divided into 3 regions that code capsid and matrix protein (gag), reverse transcriptase, protease and integrase (pol), and envelope protein (env).[3]

The env gene is the gene that codes the formation of envelope potein gp41 and gp120. Gp41 is a transmembrane glycoprotein that binds gp120 to the virus. While gp120 is a glycoprotein at the surface of the virus, which binds with the cel surface receptor (CD4). These two proteins, especially gp120, has great variation. These variation determine the HIV strain.[3]

The gag gene is the gene that codes the synthesis of core proteins p24 and p18/p17.[3]

The pol gene is the gene that codes the formation of the enzymes reverse transcriptase, protease, and integrase. Reverse transcriptase is an enzyme that transcripts viral DNA from its RNA. The integrase enzyme facilitates the integration of viral DNA into host DNA. The protease enzyme acts to cut the viral core protein during viral budding from the cell. Inhibition of these enzymes can inhibit viral infectivity.[3]

The Long terminal repeat (LTR) is a gene promotor/enhancer that interacts with cell proteins to regulate viral replication.[3]

In addition to the gag, pol, and env genes, this virus has its own regulating gene consisting of the genes nef, rev, tat, vif, and vpr. The nef gene plays a role in determining HIV virulence. Patients infected with viral strains that underwent deletion of the nef gene, can life for years without suffering from immune deficiency. The rev gene is the gene that codes the rev protein, which changes the replication cycle to produce all viral particles. The tat gene is the gene that accelerates viral replication. The vif gene is the gene that determines viral infectivity outside of the host cell. The vpr gene facilitates DNA HIV transport into the cell nucleus and regulates the cell nucleus and regulates the cycle of the cell itself.[3]

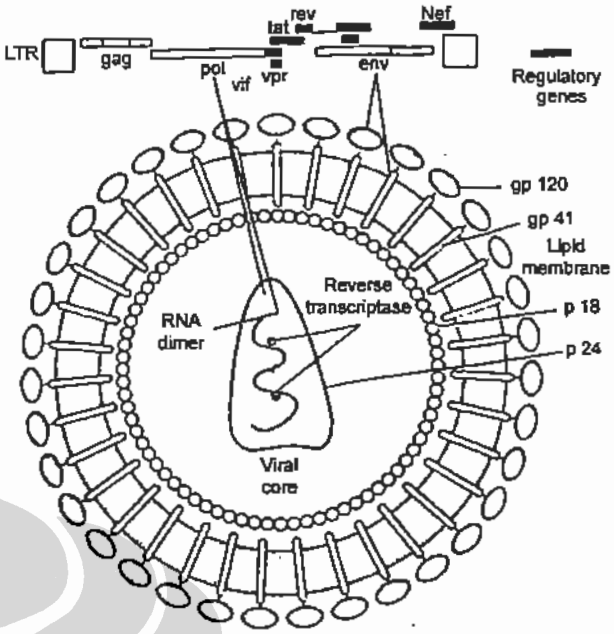

Figure 1. The Structure of the Human Immunodeficiency Virus.[3]

HIV's Mechanism of Entry Into the Host Cell

HIV can infect various cells that express CD4. CD4, as an HIV receptor, is found on 3 types of cells that function in immune response, the monocyte/macrophage, including the brain microglia and the placenta Hofbauer cell, dendritic cells (including the follicular dendritic cell found in lymph glands and skin Langerhans cells), and the CD4+ T helper-inducer lymphocyte.[4,5]

The virus enters the cell by adhering to the gp120 on CD4. The adherance causes a change in gp120 conformation. Then, viral gp41 fuses with the membrane of the host cell.[4,5]

After penetrating into the cell, the virus removes its envelope. Using the reverse transcriptase enzyme, it then transcribes DNA from viral RNA. The viral DNA then integrates with the host DNA, creating what is called a provirus. The HIV proviral DNA would generate more RNAs to be used to make new viral genomes or act as an RNA messenger to make the core, envelope, or other additional proteins. The core protein and RNA genome are then assembled into a viral core within the cytoplasm,

to be then wrapped in the envelope protein of the cell membrane, to create viral particle buds. Finally, the viral particles dettach from the cell and is ready to infect other cells.[4,5]

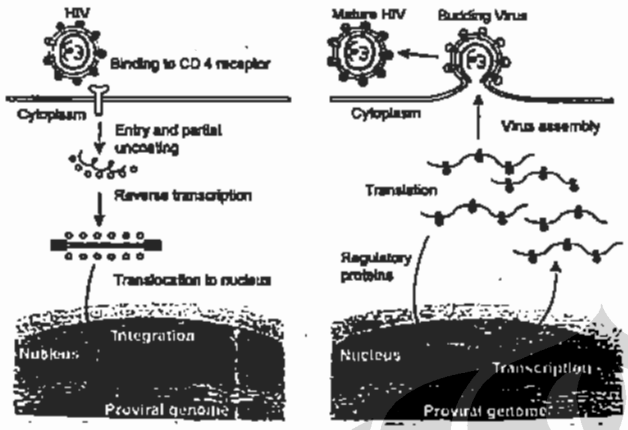

Figure 2. The Life Cycle of the HIV.[5]

In addition to requiring CD4 receptors to enter the cell, HIV also needs co-receptors such as CKR5, CKR2B, CKR3, and CXCR4. The CKR5 co-receptor is used by the variant non-syncytium-inducing (NSI) HIV. The NSI variant can live within the macrophage and primary T cell, and is thus also known as the Macrophage-tropic (M-tropic) HIV. While the CXCR4 co-receptors are needed by the syncytium-inducing (SI) strains of HIV. This latter strain can only enter T lymphocytes (and lymphoblastoid cell lines) and is thus also known as the T lymphocyte-tropic (T-tropic). The CKR2b and CKR3 co-receptors are only used by a small number of strains.[4,6]

Mutations in the CKR5 gene (CKR5?32) influence the interaction between the host and HIV. This mutation is common among people of Western European descent, with a heterozygote frequency of up to 20%. Approximately 1% of the homozygote population does not express CKR5 in the cell, thus increasing cell resistance towards HIV infection. Three large studies on 3000 HIV patients demonstrated that none of these patients were CKR5?32/ CKR5?32 homozygotes.[4,6]

A multi-center cohort analysis in the United States demonstrated that AIDS does not progress as rapidly in homosexual non-hemophiliac males with heterozygote CKR5?32 mutation. A heterozygote deficiency in CKR5?32 can increase bodily resistance towards HIV, even though not to the point of preventing infection, but only enough to slow down the progressiveness of the disease.[4]

THE IMMUNE SYSTEM IN GENERAL

Components of the Immune System

The immune system is an organization of cells and molecules that play an important role in the defense against infection. There are two types of known immune responses, the innate/natural immune response, and the acquired/adaptive immune response. The natural immune response is mediated by phagocytic cells (neutrophyles, moncytes and macrophages) and inflammatory mediators releasing cells (basophiles, mast cells, and eosinophyles, as well as natural killer (NK) cells. Molecular components that play a role in the natural immune response are complement, acute phase protein, and cytokines, such as interferon. On the other hand, the acquired immune response is mediated by B and T lymphocytes. Antigen-presenting cells (APC) introduce the antigen to the lymphocytes and cooperate with these cells in producing an antigen response. As a response towards antigen, the B cell secretes specific immunoglobulines that neutralizes antigens and destroy extracellular microorganism. T cells assist B cells in producing antibodies and destroying intracellular pathogens by activating macrophages and killing infected cells. The natural and acquired immune responses always cooperate in combating pathogenous microorganisms.[7]

The CD4+ T cell is mainly responsible for secretion of cytokines, which in turn is responsible for increasing the functions of other cells, such as B lymphocytes, while CD8+ T cells mainly function as cytotoxic killer cells. CD4+ T cells can be classified into two types, type 1 T helpers (Th1) that secrete interleukin-2 and gamma interferon, and type 2 helper T cells (Th2) that secrete interleukins 4,5,6, and 10. Cytokines produced by Th1 cells facilitate cell-mediated immunity, including activating macrophages and T cell-mediated cytotoxicity; while on the other hand Th2 cells assist B cells in the production of antibodies.[8]

Lymphocyte Migration Pattern

All cells involved in the immune system are formed from pluripotent stem cells in the fetal liver and bone marrow, which then circulates in the extracellular fluid. B cells mature within the bone marrow, but T cells must first enter the thymus to mature completely. Mature T cells then enter the bloodstream and remains in the bloodstream for approximately 30 minutes. It then enters secondary lymphoid organs such as lymph nodes, the tonsils, and Peyer's plaque through high endothelial venules (HEVs). Afterwards, the lymphocytes then migrate into the parenchyme, and in this tissue, they encounter spe-

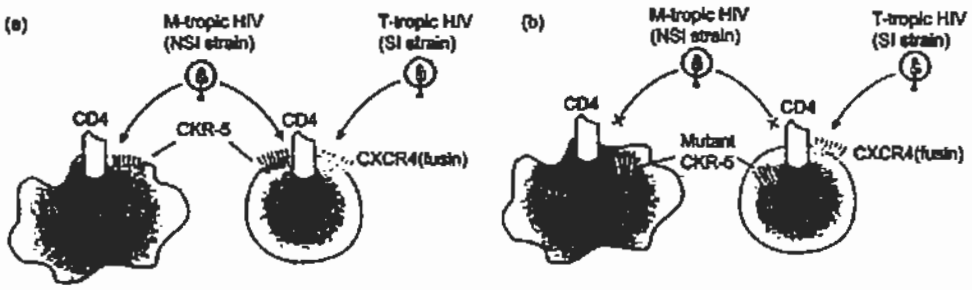

Figure 3. Co-receptors for HIV entry into the cell. (1) M-tropic HIV stran can infect monocytes/ macrophages and the T cell. The T-tropic cell can only infect T-cells. (b) Mutation in CKR5.[4]

cific antigens. Lymphocytes that do not encounter their specific antigen then return to the bloodstream through lymphatic vessels. This lymphocyte migration pattern is influenced by level of gamma-interferon (IFN) and alpha-Tumor Necrotizing Factor (TNF-α).[7,8,9]

In the parenchyme of secondary lymphoid organs, migrating lymphocytes may encounter interdigitating dendritic cells (IDCs) and macrophages that can stimulate lymphocytes to proliferate and increase in number. Without co-stimulators, the migrating lymphocytes may undergo apoptosis, thus reducing the number of lymphocytes. In addition, macrophages may play a role as HIV reservoirs.[9]

Immune Response in HIV Infection

Even though the infectious path of HIV varies from one person to another, the general pattern of the development of the disease is already known. Primary HIV infection is followed by a long latency phase (of an average of 10 years), which is usually asymptomatic. This latency phase is then followed by a symptomatic phase, which could end in death within 2 years.

Lymphocyte Migration Pattern in HIV Infection

HIV infection causes great changes in the lymphocyte migration pattern. Acute symptomatic HIV infection is characterized by unspecific lymphopenia cells only in CD4+ T cells, but non-selectively causes a reduction in the number of CD4+, CD8+, and CD20+ subsets within several days. The event is associated by increased levels of γ-IFN and α-TNF after infection. These two cytokines cause a reduction in the number of lymphocytes within the bloodstream by increasing the number of lymphocytes that migrate to secondary lymphoid tissues and reduces the number of lymphocytes that return to the bloodstream.[9]

During this initial phase, high levels of free viruses and viral proteins such as p24 can be detected in the blood, and the level of HIV infection in CD4+ proteins is also high. Within 2 to 4 weeks, the total number of lymphocytes continues to increase due to the increase in CD8+ T cells, as a part of immune response against the virus. However, the CD8+ cells that increase in number belong to an atypical subset of CD8 that is not commonly found in lymph nodes, the thymus, or the spleen, but is commonly found in the lungs. Rapid proliferation of these cells (over 50 times within 2 days) signifies a stream of cells migrating in the blood and mucous tissues (such as the lungs and intestines). After entering the blood circulation, these cells die, change phenotypes or return to their tissue of origin.[9]

HIV causes great changes in the composition of CD4+, CD8+, and B cells in the lymphoid organ. During the asymptomatic phase, the lymph nodes change and become follicular and hyperplastic due to accumulation of follicular dendritic cells (FDC) that bind viral particles in germinal centers. This event occurs continuously in germinal centers and paracortex. The number of CD4+ cells and CD4/CD8 ratio in lymph nodes remain stabile, even though the number of CD4+ cells in the bloodstream is reduced. The CD8+ phenotype that is initially dominated by $CD45RA^{hi}$ then changes into $CD45RA^{lo}$.[9]

CD4-gp120 adhesion create clusters of CD4 cells around FDCs. Gp120 that are fused with IDCs, macrophages, or other CD4 cells group around FDCs in the germinal center and paracortex, thus reducing the number of lymphocytes that return to the bloodstream.[9]

The Role of Cytotoxic T Cells in HIV Infection

During viral infections in general, the cytotoxic T-cells are a population of cells that play an important role in controlling acute infection by recognizing and destroying cells infected by the virus (even though this often increases damage of the host), thus preventing viruses from replicating and producing new virions.[8]

Cells infected by a virus signals itself as a target for cytotoxic T cells by showing a peptide from the viral protein bound to class I MHCs at the surface of the cell.

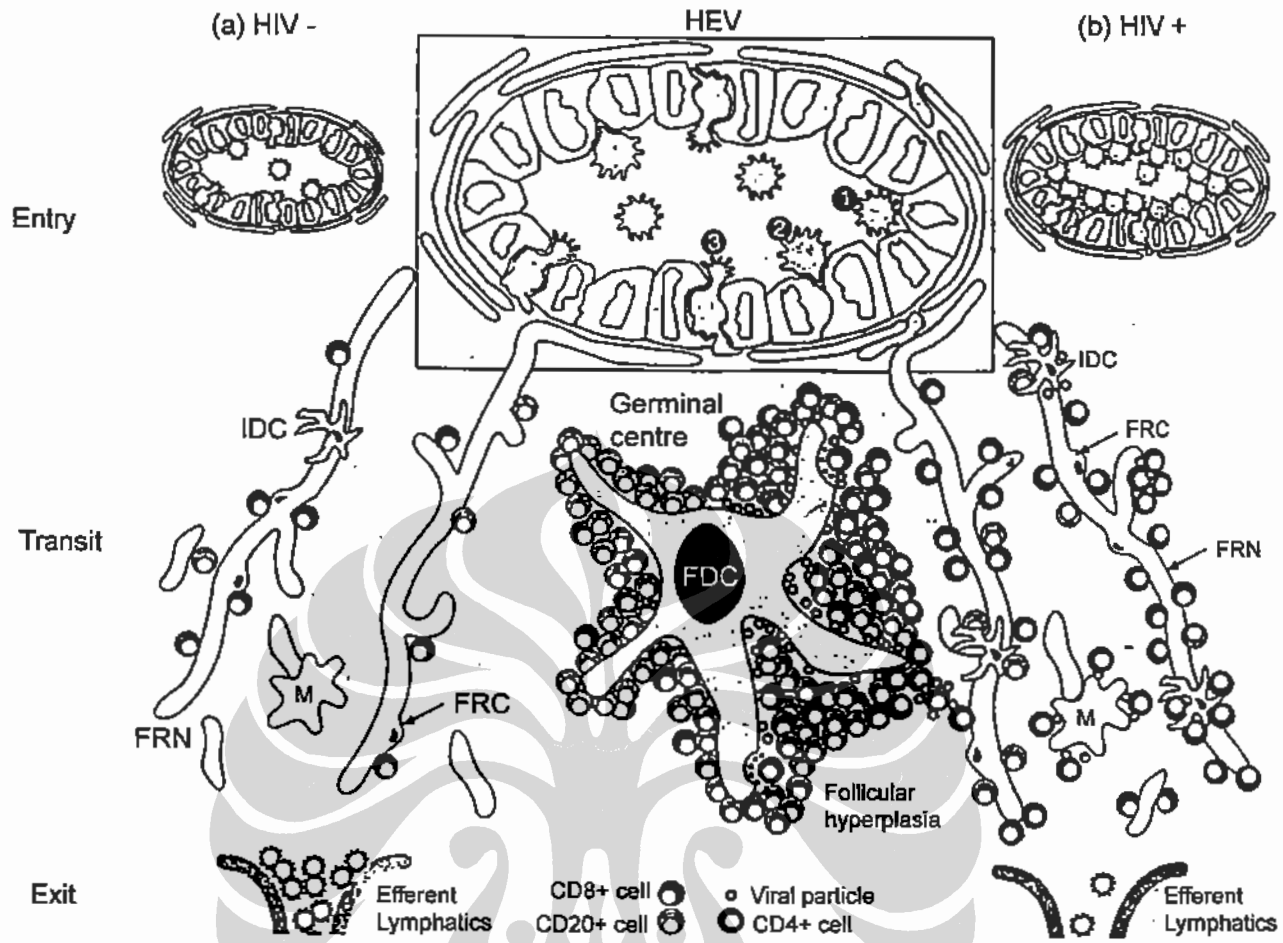

Figure 4. Lymphocyte trans-endothelial migration from the blood into lymph nodes in HIV–(a) and HIV + (b) individuals.9 HEV= High Endothelial Venules; IDC= interdigitating dendritic cells; FRN= Fibroblastic reticular cells conduit network; FRC= Fibroblastic reticular cells; FDC=Folicular dendritic cells; M=Macrophage; 1. Rolling phase; 2. Adhesion phase; 3. Endothelial crossing phase.[9]

Cytotoxic T cells recognize and bind with these MHC-peptide complex and then kill the cell by 2 means. The first way is by creating a perforation that destroys the membrane of the target cell, creating a hole to insert granzyme from cytotoxic T cells into the target cell. This enzyme activates the caspase enzyme, which mediates apoptosis of the target cell. The second method is where cytotoxic T cells bind to Fas molecules on the target cell using its Fas ligands, so that it is activated and undergoes apoptosis. The two ways prevent the virus from using its host to replicate and protect itself. The virus that is released is quickly neutralized by the antibody.[8]

CD8+ T cells can also directly kill infected cells by producing a number of cytokines, including alpha TNFs and lymphotoxins. Gamma IFNs that are also produced by CD8+ T cells, together with alpha IFNs and β IFNs secreted by the infected cell, could also increase the defense of the cells around the viral infection.[8]

Several authors found an increase in the activity of specific cytotoxic T cells for HIV protein in patients before and during seroconversion. Koup et al demonstrated that there is a correlation between a great number of HIV specific cytotoxic T cells precursors with the rate in reduction of free detectable HIV. The presence of cytotoxic T cells precedes neutralizing antibodies, sometimes up to several months. The study demonstrated that a reduction in free viruses and intracellular viruses are caused by lysis of the cell infected by HIV by CD8+ cytotoxic T cells. This also demonstrates that CD8+ cells activated from HIV infected individuals produce a number of soluble cytokines (including CAF/CD8+ T cell produced antiviral factors), a cytokine that can directly

inhibit HIV replication in CD4+ T cells, without causing lysis. Such response also occurs during acute infection prior to seroconversion, and may play a role in controlling virus production.[4]

HIV infected Th0/Th2 CD4+ cells express CD30. This increases the expression of CD30 Ligands (CD30L) on CD8+ T cells. The interaction between CD30 and CD30L increases viral replication, death of CD4+ T cells, and increases the release of soluble CD30s (sCD30). The level of serum sCD30 during the initial phase of HIV infection accelerates the progress of the disease into AIDS. After the number of CD4+ T cells is reduced during the advance stage of HIV infection, CD8+ T cells expressing CD30L increases the apoptosis of CD8+CD30+ T cells. This may be the cause in the reduction of CD8+ T cells in symptomatic AIDS.[10]

How HIV Reduces the Number of CD4+T Cells

The number of viruses demonstrates a correlation with a reduction in the number of CD4+ T cells and the progress of the disease. Intense virus replication greatly influences the turnover rate of CD4-T cells. From the studies by Ho et al[11] and Wei et al[10], we know that HIV replicates at a rate of 10^{10} per day, while its half-life is 6 hours.[11,12]

During asymptomatic HIV there is a slow and relatively constant reduction in CD4+ cells. From various studies, we found that this reduction in CD4+ T cells may be caused by various mechanisms.[13]

The reduction in the number of CD4+ T cells may be due to cell damage due to virus infection. Viruses replicating within the cells destroys the cell membrane during viral budding. In addition, the cell also no longer functions, due to viral RNA, DNA, and proteins.[4]

HIV infected CD4+ cells present viral antigen (gp 120). These cells become a target for immune responses through the antibody-mediated and cell-mediated immune response. This kills the CD4+ cell and thus reduces its number.[4]

HIV can infect CD34+ stem cells as a substitute for T cell precursors. Destruction of the stem cell causes failure to produce new T cells to replace T cells that are destroyed/killed due to HIV infection. Additionally, destruction of thymus epithelial cells may also disturb T cell maturation. Destroyed lymph nodes also inhibit the T cells after normal contact with the antigen, thus reducing/eliminating the ability for clonal distribution and T cell pool replacement (T cell anergy).[4,14]

HIV infected CD4+ T cells that lost its ability to produce cytokines, which is important in assisting its function. The first loss of function in CD4+ cells is its ability to bind with antigens that it had encountered. This is then followed by a loss of allogenic response, and finally, the loss of non-specific mytogenic response, such as phytohaemagglutinin.[4]

The number of CD4+ cells that rapidly decline initiates AIDS in most patients, often preceded by a level of CD4+ cells of over 300/ul. In a Dutch study, they found that 18 months prior to AIDS, there is a reduction of CD4+ cells up to 3-5 times the previous year. Subsequent studies correlated the change with changes towards a more virulent (syncytium-inducing) type of virus. The loss of lymphadenopathy indicates a bad prognosis. Loss of the immune system to combat viruses in the lymph glands causes rapid virus turnover, mutation towards more virulent types, and rapid reduction in CD4+ cells.[4,14]

CD8+ cells are also influenced by the reduction in the number and function of CD4+ cells. Even though CD8+ cells remain in adequate numbers, they still have difficulty facing HIVs due to reduced assistance due to the lack of production of various cytokines by CD4+ cells, such as IL-2.[4,14]

Even though only CD4+ T cells can be infected by HIV, when the number of CD4 cells falls below 200/ul, the CD8+ T cells (monocytes and dendritic cells) may also be infected. The mechanism of infection is still unclear. CD8+ cells may be infected in the thymus when they still have CD4 and CD8 antigens on their surface. HIV specific CD8+ cells may be infected during the process of destroying HIV infected CD4+ cells, or CD8+ cells may present another (still unknown) receptor for HIV. Whatever the mechanism, the possibility that HIV infected CD8+ cells play a role in increasing viral load and reducing the immune function during the final stage of infection needs further research.

Antibody Response in HIV Infection

As towards other infectious agents, the human body responds to HIV infection by producing antibodies. These antibodies are usually produced within 6 to 12 weeks after infection and throughout the infection. The period after infection before the appearance of antibodies is called the window period. Produced antibody function to eliminate viruses by binding directly with the virus or to the expression on virus-infected cells.[15,16]

Viral structural proteins (gag, env, pol) are strongly immunogenic. Antibodies against the gag protein (p24, p55) usually appear during the beginning of infection. As the disease progresses, the antibody against p24 is usually reduced, followed by an increased in p24 antigens. Antibody against env proteins (gp120, gp41) and

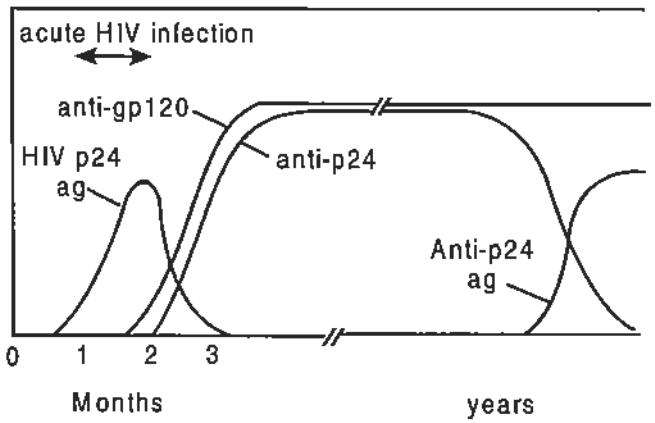

Figure 5. Antibody Response and Antigenemia in HIV Infection.[16]

pol appears simultaneously or a little afterwards. Antibody against env remains throughout the course of the infection.[15,16]

Even though virus regulation proteins (nef, vif, tat, and rev) are antigenic in nature, the level of antigenicity varies according to the characteristic of the antigen and the level of antigen expression. The antibody against HIV-1 regulated proteins cannot be persistently or transiently detected in 20-70% of infected individuals. There is no correlation between antibody response towards regulatory proteins and the progress of the disease.[15]

Antibodies against gp120 are most frequently produced. Several individuals have a stronger response against p24. However, most individuals respond to all virus components during the course of infection. The concentration of antibodies specific to all antigens also varies among individuals, and varies within an individual at different points of infection.

The antibody response shown in the figure above is immunoglobulin G (IgG) antibody. IgM response is inconsistent in HIV infection. A study demonstrated that the IgM response can be detected in 49% of patient serum 2 weeks prior to IgG response, and remains for approximately 3 months. However, since its appearance is inconsistent, IgM evaluation has not been widely used. In addition, more sensitive IgM testing needs to be developed.[15,16]

Detection of HIV specific IgM may be useful in detecting HIV in neonates, since maternal IgM does not pass through the placental blood barrier. However, presently available IgM evaluation does not demonstrate consistent results, and is thus not routinely used. In many individuals with seroconversion and in neonates, no IgM antibody was found. Thus, the absence in specific IgM antibody cannot be considered to be an absence of infection. This may be due to a low sensitivity and specificity of the test for IgM detection. It is unclear when IgM antibodies are produced in the neonate, but it is estimated to be produced at an age of approximately 6 months. A positive IgM should be viewed with conscious, since perturbing substances such as the rheumatoid factor may create a false positive. RF is an IgM antibody that reacts with IgG. If IgM is found in infant serum, it would react with anti-HIV specific IgG class from the mother, thus causing a reaction in the test. This is also disturbing, since if an anti-IgM conjugate is used, it also produces a reactive result.[16]

Such antibody reactivity pattern may also be found in normal individuals who have not been infected by HIV. How this occurs is still unclear. It may be due to an unknown cross reaction against retrovirus or as a result of another illness, such as an autoimmune disease.[15,16]

The Significance in the Mechanism of Infection and the Pattern in HIV Antigen Expression Pattern in Establishing Laboratory Diagnosis of HIV Infection

Through the production of cytokines that regulate the activity of B lymphocytes, macrophages, and CD8+ T cells, CD4+ T helper cells play the chief role in most immune responses. In reality, CD4+ T cells are selectively infected by HIV cells, then the analysis of CD4+ T cell response towards HIV infection becomes very complex.[16]

CD4+ T cell count is utilized to determine the stage of HIV disease and predict the presence of opportunistic infection and other complications. When initiating antiviral treatment, evaluation of CD4+ T cell count and viral load is used as initial findings to monitor treatment.[17]

There is a correlation between clinical symptoms and the immunopathogenesis of the reduction in CD4+ cells. During the primary phase of infection there is an initial reduction, followed by an increase, in the number of CD4 cells. During this phase, symptoms such as fever, myalgia, arthralgia, adenopathy, malaise, rash, and menigoencephalitis may be found. Anti-HIV antibodies have not been form, and thus only the p24 antigen can be detected. During the initial asymptomatic phase, there is an immune reduction (CD4 cell count > 500/ul), but the immune system is still able to control infection and malignancy. The strength of the immune stimulation can develop into autoimmune diseases, and lymph cells often develop into persistent generalized lymphadenopathy. Lymphadenopathy is one of the first detected symptoms as a clinical finding of HIV infection. During this phase, anti-HIVs are formed, and p24 antigens disappear. An intermediate immune reduction (CD4 cell count

200-500/ul) causes small infections in the skin and mucous tissues. Oral candidiasis, as well as sarcoma caposi, occur at a CD4 cell count of approximately 250/ul. At this stage, the immune system has great difficulty in conducting its function. Generalized persistent lymphadenopathy can disappear due to destroyed lymph nodes, which is the beginning of the AIDS phase. Anti-p24 antibodies are reduced, accompanied by an increase in p24 antigens. Severe immune deficiency (CD4 cell < 200/ul) indicates the collapse of the immune system, increasing opportunistic infection and malignancy. During this phase, there is an increase in p24 antigen, accompanied by loss of anti-p24 antibodies.[4]

Evaluation of the absolute CD4 count is greater compared to the percentage CD4 (the percentage of lymphocytes that express CD4) or CD4:CD8 ratio. This increase in the physiology of CD8 population due to HIV infection may obscure the results of CD4:CD8 ratio.[17]

Diurnal variation may also influence the evaluation in CD4 count up to 50%. Thus, the evaluation should be conducted at the same time of day, and evaluation during the acute phase of the disease (such as influenza, urinary tract infection) should be avoided and cannot be used for the diagnosis of HIV infection. During the first weeks after the diagnosis, 3 values are needed for the base point value. After that, evaluation is performed every 6 months in asymptomatic patients or every 3 months after the appearance of symptoms.[17]

Antigen expression or anti-HIV antibodies may be used to determine the diagnosis and stage of disease. The presence of p24 antigen signifies initial infection and advance stage of HIV infection. During the window period, when anti-HIV antibodies are still undetected, a method of evaluation is needed to be able detect p24 antigens for the diagnosis of HIV.[18,19]

After 6-12 weeks of infection, anti-HIV antibodies are produced. During this phase, detection of anti-HIV antibodies can be used to diagnose HIV. However, anti-p24 could suddenly disappear. A reduction in serum anti-p24 titer is a bad prognosis for HIV-infected patients, since it demonstrates a high viral replication.[16]

HIV-infected patients with negative HIV antibodies can pass the initial HIV screening test. This can occur during the window period phase. They have now developed test to simultaneously detect p24 Ag and anti-HIV to increase the sensivity during the window period.[18,19]

A study by Binsbergen18 and Weber19 proved that HIV evaluation that is able to detect p24 and anti-HIV is able to detect 65% seroconversion during the window period. Using the p24 antigen HIV evaluation, 100% seroconversion during the window period can be detected. However, anti-HIV evaluation is unable to detect seroconversion during the window period.

SUMMARY

HIV is a retrovirus that causes chronic infection with a long latency phase. This virus has an envelope and reverse transcriptase enzyme. HIV can infect cells that express CD4 and enter the cell through gp120 adhesion to CD4. In addition to requiring CD4, HIV also requires co-receptor to enter the cell.

In HIV infection, the immune system undergoes changes in lymphocyte migration pattern, the number of CD8+ and CD4+ T cells, as well as the formation of anti-HIV antibodies.

CD4+ T cell count can be used to determine the stage of HIV, to predict opportunistic infection and other complications, as well as evaluate and monitor treatment. Expression of antigens/antibodies against HIV can be used to determined the diagnosis and stage of disease.

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