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Review Article

A Review on Human Immunity System and HIV Infection

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ABSTRACT
The human immune system comprises of a network of cells, organs and molecules responsible for maintaining the body's homeostasis. Innate immunity system operates in conjunction with adaptive immunity for first line defence.The mechanism includes chemical,physical,biological barriers, cellular components as well as soluble molecules. The progression of HIV infection is dependent on the interaction between the viral factors and host factors as well as depends upon genetic factors.HIV infects the CD4 lymphocytes in the body and destroys it through multiple mechanisms. Innate immune mechanism is linked with disease progression and adaptive immune system controls HIV infection. This present review outlines the idea about human immune system, life cycle of HIV and pathogenesis of HIV.

Keywords: Innate immunity, Adaptive immunity, CD4, HIV.

INTRODUCTION

AIDS is considered one of the most dangerous and a pandemic[1] disease which is present over a large demographic area of the world. The disease may cause Kaposi's sarcoma, pneumocytis carini pneumonia[2] and serious opportunistic infections. AIDS is the most serious infectious disease and actively spreading worldwide among society. Young women are susceptible to HIV at early stage in some areas the prevalence of infection among women between 15-24 years than twice that of young men. Women living in lower income countries are particularly at risk as extreme poverty and other structural factors such as gender inequities[3], lack of education and violence violence reduce their ability to control health outcomes or access HIV related information and services. Human immunodeficiency virus infection/acquired immune deficiency syndrome[4] (HIV/AIDS) is a disease of human immune system caused by infection with human immune deficiency virus. AIDS is called when a person infected with HIV has a CD4 count of less than 200cells/mm^3 or has an AIDS defining condition. During HIV infection[5,6] the virus attacks and destroys the infection fighting CD4 cells of the body's immune system. It is difficult for immune system to fight infections due to loss CD4 cells.HIV gradually destroys the immune system by attacking and killing CD4 cells.HIV [7,8] uses the machinery of the CD4 cells to multiply (make copies of it) and spread throughout the body. HIV pathogenesis is characterized by faster disease progression and shorter time to AIDS and death. The innate and adaptive immune systems is tolerogenic after birth and fail to control viral replication. Persistent viremia[9,10] reactivation of co infections and microbial translocation during chronic infection drive HIV pathogenesis through increased immune activation resulting in immune dysregulation and functional immune exhaustion.HIV is transmitted primarily via unprotected sexual intercourse[11] (including anal and even oral sex), contaminated blood transfusions, hypodermic needles and from mother to child during pregnancy, delivery or breastfeeding[12]. Prevention of HIV infection primarily through safe sex[13] and needle exchange programs is a key strategy to control the spread of disease and may lead to a near normal life expectancy. While antiretroviral treatment reduces the risk of death and complications from the disease these medications are expensive and may be associated with side effects. The wide range of microorganisms infects humans and can cause disease. The human body has evolved an immune system to combat these pathogens. The main function of human immune system is to recognize antigens within the body and arrange for its elimination. To achieve defense immune system is developed. This present review gives idea about human immunity system, HIV structure,HIV life cycle and progression of HIV infection.

Immunity

Immunity is the balanced state of having adequate biological defenses to fight infection, disease or other unwanted biological invasion while having adequate tolerance to avoid inflammation, allergy and autoimmune diseases. It is the capability of the body to resist harmful microorganisms or viruses from entering it. Immunity involves both specific and non-specific components. The non-specific components act either as barriers or as eliminators of wide range of pathogens irrespective of the antigenic specificity.

Innate immunity/non-specific immunity

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It is the natural resistances with which a person is born. It provides resistances through several physical, chemical and cellular approaches. Innate immunity[14] includes the external barriers of the body like the skin and mucous membranes (like those that line the nose, throat and gastrointestinal tract) which are the first line of defense in preventing diseases from entering the body. If this outer defensive wall is broken the skin attempts to heal the break quickly and special immune cells on the skin attack invading germs.

Adaptive immunity

Adaptive immunity is classified into two types depending on how the immunity was introduced. Naturally acquired immunity occurs through contact with a disease causing agent. Artificially acquired immunity develops through vaccination. Both naturally and artificially acquired can be divided depending on whether immunity is induced in the host or passively transferred from an immune host. Passive immunity is acquired through transfer of antibodies or activated T cells from an immune host. Active immunity is induced in the host itself by antigen and lasts much longer sometimes lifelong. Adaptive[15] immunity can be characterized by the cells involved. Humoral immunity is the immunity that is mediated by secreted antibodies. But cell mediated immunity provides protection which is involved by T lymphocytes.

Passive immunity

It transfers active immunity in the form of readymade antibodies from one individual to another. It can occur naturally when maternal antibodies are transferred to fetus through the placenta and can be induced artificially when high levels of human antibodies specific for a pathogen or toxins are transferred to non-immune individuals.

Naturally acquired passive immunity

Maternal passive immunity is a type of naturally acquired passive immunity and refers to antibody mediated immunity conveyed to a fetus by its mother during pregnancy. IgG is the antibody can pass through the placenta and IgA antibodies pass through breast milk to infants protecting from bacterial infection.

Artificially acquired passive immunity

Artificially acquired passive immunity is a short term immunization induced by the transfer of antibodies which can be administered in several forms as human or animal blood plasma as pooled human immunoglobulin for intravenous or intramuscular use and in the form of monoclonal antibodies.

Active immunity

Active immunity often involves both the cell mediated and humoral aspects of immunity as well as input from the innate immune system. The innate system is present from birth protects an individual from pathogens regardless of experiences whereas adaptive immunity arises only after infection or immunization.

Naturally acquired active immunity

It occurs when a person is exposed to a live pathogen and develops a primary immune response which leads to immunological memory. Many disorders of immune system can affect the formation of active immunity such as immunodeficiency and immunosuppression.

Artificially acquired active immunity

Artificially acquired immunity can by a vaccine a substrate that contains antigen. A vaccine stimulates a primary response against the antigen without causing symptoms of the disease.

The Healthy Immune System

The immune system protects the body by recognizing antigens on invading bacteria and viruses and reacting to them. An antigen is any substance that induces a state of sensitivity and immune responsiveness. These antigens interact with antibodies and immune cells initiating an immune response. This process destroys the antigen allowing the body to be free of infections. Types of antigens include bacteria, viruses, fungi and parasites. When immune system is weakened or destroyed by a virus such as HIV, the body is left vulnerable to infections. The immune system consists of lymphoid organs and tissues including the bone marrow, lymph gland, lymph nodes, spleen, tonsils, adenoids, appendix, blood and lymphatic vessels. All components of the immune system are vital in the production and development of lymphocytes or white blood cells lymphocytes and T lymphocytes are produced from stem cells in the bone marrow cells stay in the bone marrow to complete the maturation process, but T lymphocytes travel to the thymus gland to complete their maturation. There T lymphocytes become immune competent, multiply and become more differentiated.

B lymphocytes (B Cell)

The main function of B lymphocytes is humoral (antibody) immunity. Each B cell can recognize specific antigen targets and can secrete specific antibodies. Antibodies function by coating antigens which makes the antigens more vulnerable to phagocytosis (engulfing and ingestion of invading organisms by leukocytes or macrophages) or by triggering the complement system, leading to an inflammatory response. Antibodies are highly specialized serum protein molecules. They are grouped into five classes each having a specialized function, immunoglobulin G (IgG),IgA, IgM, IgE and IgD.

T lymphocytes (T Cell)

T lymphocytes have two major functions regulation of the immune system and killing of cells that bear specific target antigens. Each T cell has a surface marker such as CD4+,CD8+ and CD3+, that distinguishes it from other cells.CD4+ cells are helper cells that activate B cells, killer cells and macrophages when a specific target antigen is present. There are two main types of CD8+ cells. The first type cytotoxic CD8+ cells kills cells infected by viruses or bacteria as well as cancer cells. The second type of CD8+ cells,T suppressor cells inhibits or suppresses immune responses. Normal CD8+ cell count is between 300 and 1000 cells in adults and children. The normal CD4+: CD8+ ratio is between 1.0 and 2.0.T cells can secrete cytokines (chemical that kill cells) such as interferon. Cytokines can bind to target cells and activate the inflammatory process. They also promote cell growth activate phagocytes and destroy target cells. Interleukins are cytokines that serve as messengers between white blood cells.

Phagocytes

Phagocytes include monocytes and macrophages[16] large white blood cells that engulf and digest cells carrying antigenic particles. Found throughout the body, phagocytes rid the body of worn out cells, initiate the immune response by presenting antigens to lymphocytes are important in immune response regulation and inflammation and carry receptors for cytokines. Dendritic cells another type of phagocyte also are antigen presenting cells. They have long thread like extensions that help trap lymphocytes and antigens and are found in the spleen and lymphnodes. Neutrophils are granulocytic phagocytes that are important in the inflammatory response.

Complement

The complement system consists of 25 proteins. It can include an inflammatory response when it functions with antibodies to facilitate phagocytosis or weaken the bacterial cell membrane. The complement proteins interact with one another in a sequential activation cascade promoting the inflammatory process.

HIV's Structure

The human immunodeficiency virus(HIV) is a retrovirus belonging to the family of lentiviruses.Retroviruses can use their RNA and host DNA to make viral DNA and are known for their long incubation periods. Like other retroviruses HIV infects the body has a long incubation period (clinical latency) and ultimately causes the signs and symptoms of disease here AIDS.HIV causes severe damage to immune system and eventually destroys it by using the DNA of CD4+cells to replicateitself.In that process the virus eventually destroys CD4+ cells. HIV consists of a cylindrical center surrounded by a sphere shaped lipid bilayer envelope. There are two major viral[17] glycoproteins (Fig.1) in this lipid bilayer gp120 and gp41.The major function of these proteins is to mediate recognition of CD4+ cells and chemokine receptors thereby enabling the virus to attach to and invade CD4+ cells.The inner sphere contains two single stranded copies of the genomic material RNA as well as multiple proteins and enzymes necessary for HIV replication and maturation p24,p17 reverse transcriptase integrase and protease. Unlike other retroviruses HIV uses nine genes to code for the necessary proteins and enzymes. The three principal genes are gag,pol and env.The gag gene encodes core proteins. The pol gene encodes the enzymes reverse transcriptase, protease and integrase.The env gene encodes the HIV structural components known as glycoproteins. The rest of the genes rev,nef,vif,vpu,vpr and tat are important for viral replication and enhancing HIV's infectivity rate[18].

HIV's life cycle

Host cells infected with HIV have a shortened life span as a result of the virus's using them as factories to produce multiple copies of new HIV.Thus HIV continuously uses new host cells to replicate itself. As many as 10 million to 10 billion virions (individual viruses) are produced daily. In the first 24h after exposure HIV attacks or is captured by dendrite cells in the mucous membranes and skin. Within 5 days after exposure these infected cells make their way to the lymph nodes and eventually to the peripheral blood where viral replication becomes

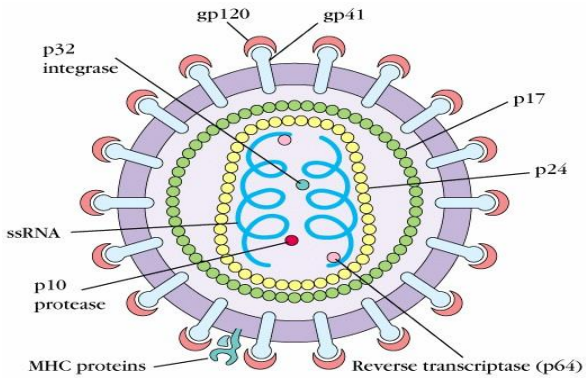

Figure 1: Structure of HIV.

rapid.CD4+ lymphocytes that are recruited to respond to viral antigen migrate to the lymph nodes. These become activated and then proliferate via complex interaction of cytokines released in the microenvironment of the lymph nodes. This sequence of events makes the CD4+ cells more susceptible to HIV interaction[19] and it explains the generalized lymphadenopathy characteristic of the acute retroviral syndrome seen in adults and adolescents. In contrast HIV infected HIV infected monocytes allow viral replication but resist killing. Thus monocytes act as reservoirs of HIV and as effectors of tissue damage in organs such as the brain. The HIV life cycle includes six phases binding and entry, reverse transcription, integration, replication, budding and maturation[20].

Binding and entry

The envelope proteins gp120 and gp41 bind to CD4+ cell receptors and co receptors on the outside of CD4+ cells and macrophages. The chemokine receptors CCR5 and CXCR4 facilitate viral entry.T cell tropic viruses require CXCR5 to bind and macrotropic strains of the virus require CCR5.R5 is the most common virus transmitted during acute infection and later during infection X4 is the virus that is most common. The presence of a homozygous inactive mutation of the CCR5 allele has caused resistance to infection by the R5 virus. The joining of the proteins and the receptors and co receptors fuses the HIV membrane with the CD4+ cell membrane and the virus enters the CD4+ cell and macrophage. The HIV membrane and the envelope proteins[21] remain outside of the CD4+ cell whereas the core of the virus enters the CD4+ cell.CD4+ cell enzymes interact with the viral core and stimulate the release of viral RNA and the viral enzymes reverse transcriptase and protease.

Reverse transcription

The HIV RNA must be converted to DNA before it can be incorporated into the DNA of the CD4+ cell. This incorporation must occur for the virus to multiply. The conversion of HIV from RNA to DNA is known as reverse transcription and is mediated by the HIV enzymes reverse transcriptase. The result is the production of a single strand of DNA from the viral RNA. The single strand of this new DNA then undergoes replication into double stranded HIV DNA.

Integration

Once reverse transcription has occurred the viral DNA can enter the nucleus of the CD4+ cell. The viral enzyme

integrase then inserts the viral DNA into the CD4+ cell's DNA. This process is known as integration. The CD4+ cell has now been changed into a factory used to produce more HIV.

Replication

The new DNA which has been formed by the integration of the viral DNA into the CD4+ cell causes the production of messenger DNA that initiates the synthesis of HIV proteins.

Budding

The HIV proteins and viral RNA all the components needed to make a new virus gather at the CD4+ cell membrane to form new viruses. These new viruses push through the different parts of the cell wall by budding[22]. Many viruses can push through the wall of one CD4+ cell. These new viruses leave the CD4+ cell and contain all the components necessary to infect other CD4+ cells.

Maturation

The new virus has all the components necessary to infect other CD4+ cells but cannot do so until it has matured. During this process the HIV protease enzyme cuts the long HIV proteins of the virus into smaller functional units then resemble to form a mature virus. The virus is now ready to infect other cells[23].

Progression of HIV Infection

Loss of CD4 + cells

The principal effect of HIV infection on the immune system is by destroying the CD+ T lymphocytes. The half life of HIV infected T cells is 12-36hr.HIV may destroy the infected and uninfected CD4 T lymphocytes[24] by using multiple mechanism.

Apoptosis

Apoptosis is a mechanism that destroys T cells due to HIV infection. In this mechanism normally body is used to eliminate redundant cell populations and defective cells and is utilized thus by HIV to destroy both infected and uninfected cells. The disease progression[25] is directly correlated with elevated levels of apoptosis and inversely related to T helper cells count. The levels of CD95 and FasL may up regulate by HIV proteins Nef,Env and Tat, thus increasing the susceptibility to fasmediated killing.HIV proteins such as gp120,Tat,Nef and Vpu may cause cell death in uninfected cells. Cross linking[26] of CD4 molecules is a mechanism of gp120 induced apoptosis in HIV infected T cells. The Nef protein[27] of HIV in the extracellular matrix can induce cell death in uninfected T cells. The Tat protein of HIV induces apoptosis through both fas mediated and fas independent mechanisms.

Other mechanisms of CD4 T cell destruction

CXCR4 tropic HIV isolates generally found in the late stage of HIV infection preferentially infect T cells and induce membrane fusion between adjacent cells to form a giant multinucleate cell called syncytium. Both HIV infected and uninfected cells participate in syncytium[28] formation thus accelerating the cell destruction during advanced disease. Due to continuous budding of the viruses from infected cells may cause membrane disruption and increased permeability resulting in ultimate death of cell. The HIV protein Vpu increases membrane permeability causing to cell death. The growth of unintegrated linear viral DNA in the cell increase cellular cytotoxicity. HIV specific cytolytic T lymphocytes recognize HIV infected cells through T cell receptor in HLA restricted manner. The cell to cell contact causes to the activation of mechanisms for the lysis of target cell. The host factors such as genetic factors, innate immunity and most importantly HIV specific immune responses impact greatly the progression of HIV infection.

Influence of Genetic Factors on HIV Disease Progression

Human leucocyte antigen (HLA) and HIV infection

The alleles B57,B14 and B 27 are linked with long term non progressor[29] status. Homozygosity[30] for HLA BW-4 was found to be linked with long term non progression to AIDS. Heterozygosity at all HLA loci is more likely to be associated with better control of viraemia and slower disease progression.

Chemokine receptors

Chemokine receptors and chemo attractant substances were secreted at the sites of infection or injury which acts as second receptor for HIV. The association of genetic polymorphism, HIV susceptibility and disease progression shown that a mutation of 32 base pair deletion in the CCR5 receptor gene. Persons homozygous[31] for this mutation decrease susceptibility to HIV infection and heterozygous individuals for CCR5 gene receptor are not less susceptible to HIV infection. The mutation in coreceptors CCR2, CCR2V641 may influence HIV disease progression[32]. The progression of AIDS is slow by co receptor mutation. The mutation in stromal derived factor 1(SDF-1), ligand for CXCR4 delay progression to AIDS.

Other genetic mechanisms

The central MHC region contains immunoregulatory genes which are linked disequilibrium with MHC alleles. These genes are cytokines, chaperon proteins etc. These genes may destroy the pathogens. The adaptive immune response is influenced by polymorphism in killer inhibitory receptor gene cluster. The host genetic factors may influence the disease progression.

Innate immunity and HIV infection

The innate response plays a major role in initial containment of infection and hence may be crucial in acute primary HIV infection.

Anti viral non cytotoxic responses

The CD8+ T cells are able to block active HIV replication through non cytolytic virus suppressive mechanisms. The activity is attributed to soluble factors that are capable of suppressing primary HIV isolates[33] that are both CCR5 tropic and CXCR4 tropic. These soluble factors are collectively called as CD8 antiviral factor or CAF.It is reported that ligands for chemokine receptors RANTES, macrophage inflammatory proteins α and β are involved in suppressor activity when released by activated CD8 cells[34]. It is shown that HIV suppression by non cytolytic mechanisms use multiple mechanisms of suppression such as CD4 cross linking, inhibition of pro viral integration, down regulation of receptors and inhibition of viral entry.The suppressor activity is based on various factors such as the cell types producing the factor, the stimulus for activation of the cells and time kinetics in culture system.

Innate cellular responses

Plasmacytoid dendritic cells (PDC) and natural killer(NK) cells have important role in innate cellular immune response. Plasmacytoid dendritic cells produce type 1 interferons. Depletion[35] of these cells reflected by decreased interferon alpha production is linked with higher HIV RNA levels and progression to AIDS.HIV infected patients may observe normal or high PDCs who remain healthy without receiving any therapy or their low CD4+ cell count. PDCs involve in the innate immune response through interferon production and also involve in the adaptive immune response. PDC operate innate immune mechanisms when adaptive immune response is lost. Mature dendritic cells(DC) induce adaptive immune response and transmit HIV. The DC specific lectin DC-SIGN (Dendritic cell specific ICAM-3 non integrin) bind to HIV virions is expressed by DCs located in mucosal sub epithelia and shuttle viruses to susceptible T cells. NK cells are large granular lymphoid cells. It lacks surface markers characteristic of T or B cells. It forms a critical component of host innate immune response against viruses, fungi, parasites and bacteria. It has natural capacity to kill virus infected cells in the absence of prior sensitization and without MHC restriction. It kills target cells either by direct contact in the absence of antibody or by antibody dependent cellular cytotoxicity.NK cell decreases lytic activity in HIV-1 infected patients as compared to uninfected controls. It suppresses viraemia through CC chemokine production.

Adaptive immune response

The adaptive immune response can control viraemia. It uses multiple effector mechanisms to control the virus multiplication. The major things in HIV specific adaptive immune responses are HIV specific neutralizing antibodies, CTL responses and T helper response.

Neutralizing antibodies

The initial HIV-1 specific immune response[36] is observed by appearance of non-neutralizing antibodies detected by ELISA 2 to 4 weeks after infection. These antibodies act as the basis for the diagnosis for HIV infection. Neutralizing antibodies can be detected 8 week or more after infection. These antibodies appear after initial containment of HIV replication in newly infected individual. The neutralizing antibody[37] response results in complete replacement of neutralization sensitive virus by successive population of resistant virus. Escape virus contains mutation in Env protein that changes the conformation of gp120 protein which diminishes antibody binding and modify glycosylation pattern of envelope[38] protein. The neutralizing antibody response in individuals having infection in LTNPs reported that broad and high tittered neutralizing activity compared to individuals that show rapid disease progression. The infected lymphocytes of individuals produce HIV-1 neutralizing monoclonal antibodies (Table-I).

Table-1.Neutralizing monoclonal antibodies and epitopes recognized by them

Human monoclonal antibodies showing broad HIV-1 neutralizing activity	Recognized epitope
IgG1b12	CD4 binding domain of gp 120
2F5	Transmembrane proximal region of gp41
17b,48D	CD4 induced epitope of gp 120
2G12	Mannose residues of gp 120

Helper T cell response

HIV infects CD4+ T lymphocytes causing to the death of infected CD4 cells but also uninfected bystander cells. The depletion in CD4 cell count affects the CD4 T cell responses, HIV specific response, response to recall antigens as well as response to T cell mitogens. T cell help is useful for generation of antibody response as well as cytotoxic T cell responses. The CD4 T cells generate cytokines[39] which activates and maintains effector cells. The dysfunction of lymphocyte proliferative response to HIV-1 antigens is a functional defect of cell mediated immunity found in HIV-1 infected patients. The magnitude[40] of CD4 T lymphocyte proliferation, quantity and pattern of cytokine production is correlated with the clinical status. Patients having controlled viraemia show strong response to HIV antigens and production of Th1 type of cytokines and the response are inversely correlated with plasma virus load. Depletion of HIV-1 specific CD8+ T cell function correlates with progressive infection. It is restored in chronic infection by augmentation of HIV-1 specific T helper cell function either by vaccine induction or infusion of autologous CD4 helper cells.CD4+ T cell secrets cytokines which activates the effector cells of immune system and fight against infection. Cytokines activate the cells of immune system and influence the expression of various critical molecules on the cell surface and may up regulate or down regulate HIV multiplication in infected cells. The proregulatory cytokines are IL2,IL12,IFN$^{\gamma}$ and the proinflammatory cytokines(Th2) are IL4,IL10,IL5,IL13 etc.

HIV-1 specific cytotoxic T lymphocyte(CTL) response

Cytolytic T lymphocytes detect HIV infected cells through HIV antigens expressed on the surface of the infected cells in association with HLA class I peptides. This activity requires cell to cell contact. The cytotoxic T cells initiate biochemical pathways in the target cell that ultimately cause to destruction of cells. After destruction of infected cells the CTLs puts halt to multiplication of HIV.HIV-1 specific[41] CTL is present in seropositive individuals.CTLs can control HIV infection by studies in animal model,cytolytic T cell responses in early HIV infection and CTL responses in person who are exposed to HIV infection but not infected[42].

Mucosal antibody response

HIV first contacts with mucosal surfaces. The immunopathogenesis of HIV at mucosal surfaces linked with innate and acquired immunity. The defense mechanisms by innate at the mucosa primarily include the antimicrobial products derived from the epithelial cells and neutrophils such as lysozyme, lactoferrin and defensins, the bacterial flora and p^{H} of the mucosal microenvironment. Adaptive mucosal immunity plays a

vital role for mucosal antigen presenting cells (APCs) and DCs in HIV infection. Epithelial surface contains DCs which is in infected by HIV after mucosal exposure to virus. The virus bound to DC-SIGN on DCs may remain infectious for several days and virus pulsed DCs transmit virus when they contact with CD4+ and co receptor positive cell types[43].The CD8+ cell mediated immune response is obtained from the vaginal epithelium of SIV infected macaques.CD4 and CD8 CTLs obtained from cervix of HIV infected women.HIV-1 specific MHC prevents CD8+ and CD4+ CTL which may be capable of both destroying HIV-1 infected cells and releasing anti-viral cytokines.

CONCLUSION

AIDS has a major source of morbidity and mortality in the world. AIDS is life threatening, dangerous and as of present there is no cure for disease but it can be controlled. HIV infection leads to decrease of the CD4+ T cell. The progression of AIDS can be known by the immune system. The immune system is characterized by innate and adaptive immunity that restricts potentially harmful autoimmunity and inflammatory responses and is geared toward preferential protection against extracellular pathogens. AIDS can be well controlled by taking preventive measure, awareness among people regarding AIDS

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