

Immune Response and Possible Causes of CD4⁺T-cell Depletion in Human Immunodeficiency Virus (HIV) - 1 Infection

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Abstract: In this review, immune response and possible causes of depletion of CD4⁺ T-cell counts in patients with human immunodeficiency (HIV)-1 infection, have been documented. HIV has been recognized as a global problem; however, the developing countries are the most affected by epidemic diseases. Countries in the sub-Saharan Africa seem to bear the bulk of the HIV burden among the developing countries with about 24.7 million (\approx 63%) of all people living with HIV globally in 2006. The major factor obstructing progress towards an effective vaccine to prevent or modulate HIV - 1 infection is that the critical features needed for a protective immune response are not fully understood. Although, it has been found that potent neutralizing antibodies can protect against experimentally acquired HIV infection in animal models, they are scarcely generated *in vivo* in the infected person and neutralization resistant viral variants have been monitored to develop rapidly in chronic infection. It is generally believed that cellular immune responses, particularly specific cytotoxic T lymphocytes (CTL), are significant in the host response to HIV - 1 infection. Scientists have observed that CTL develop very early in acute HIV - 1 infection, coincident with a rapid fall in plasma viremia, whereas in chronic infection their levels are inversely related to viral load. However the potent HIV-specific CTL response ultimately fails to control HIV replication. This could be as a consequence of the emergence of viral variants that escape CTL recognition or impairment of CTL function.

Key Words: Immune system, immune suppression, virus-mediated cell destruction, chronic infection, AIDS, Computational model, Cybernetics.

INTRODUCTION

Untreated HIV disease is characterized by a gradual deterioration of immune function. Most prominently, the CD4⁺ T-cells are disrupted and destroyed during the typical course of HIV infection. It is known that the CD4⁺ T-cells (T-helper cells) play a major role in the immune response, signaling other cells in the immune system to perform their specific functions.

Basically, a healthy, HIV-negative person usually has 800 to 1, 200 CD4⁺ T-cells per mm³ of blood. During untreated HIV infection, the number of these cells in a person's blood progressively declines. When the CD4⁺ T-cell count falls below 200/mm³, a person becomes particularly vulnerable to the opportunistic infections that are commonly associated with AIDS (the end stage of HIV disease). Most scientists believe that HIV causes AIDS by inducing the death of CD4⁺ T-cells or interfering with their normal function and by triggering other events that weakens a person's immune system. For example, the network of signaling molecules that normally regulates a person's immune response is interrupted during HIV disease, impairing a person's ability to fight against other infections. The HIV-mediated destruction

of the lymph nodes and related immunological organs also play a major role in causing the immuno-suppression seen in people with HIV infection.

CD4⁺ T-CELL AND ITS IMPORTANCE

CD4⁺ is a molecule found primarily on the surface of helper T-lymphocytes. The designated CD stands for "Cluster of Differentiation" and refers to a nomenclature applied by immunologists who are all involved in the business of generating monoclonal antibodies against surface proteins of blood cells as a means of identifying the surface proteins and studying them. When a "cluster" of monoclonal antibodies (antibodies produced *in-vitro* by single clones of B-lymphocytes) is found to react with the same protein, it represents a group of reagents defining a specific marker and that marker is given a CD number [1].

FUNCTION OF CD4⁺ T-CELL

The CD4⁺ molecule is also the main receptor involved in combating HIV-1 infection and docks with the 120 glycoprotein found on the envelope of the HIV-1 viral particle. The CD4⁺ T-cell performs a central role in the immune response [2]. These cells also known as T4 or helper/inducer T lymphocytes, recognize antigens presented by cells bearing HLA class II molecules such as monocytes and macrophages. The CD4⁺ molecule helps to stabilize the binding of these T-lymphocytes to HLA II molecule on the antigen-presenting

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cell [3]. Once an antigen is recognized, CD4⁺ T lymphocytes orchestrate the body's antigen-specific immune response and specific functions of CD4⁺ T lymphocytes include the: coordinating B-lymphocyte production of antibodies to these antigens; producing cytokins; induction of cytotoxic lymphocytes.

These crucial functions make CD4⁺ T lymphocytes critical elements of the immune system, and their dysfunction and destruction in HIV-1 infection seriously impairs the ability to respond to diverse pathogens [4, 1].

PROGRESSIVE DESTRUCTION OF THE IMMUNE SYSTEM IN ADVANCED HIV INFECTION

In the absence of suppressive antiviral therapy, HIV infection advances and progressively infect more cells in the follicular dendritic cell (FDC) network, leading to the destruction of lymph node architecture. This promotes the release of more viral particles into the circulation [1]. The release of HIV into circulation causes CD4⁺ T-cells to be infected and destroyed at a faster rate than can be replaced, thereby shifting the dynamic equilibrium in favour of the virus [5-7]. Studies have been shown that an important cause of declining CD4⁺ T-cell counts in the failure of the regenerative capacity of the immune system to produce immune cells [6, 8, 9] This is a result of HIV infection of precursor stem cells and is also due to failure of "Programming" of CD4⁺ T-cells in the HIV-infected thymus gland. This culminates in the destruction of the immune system and consequent failure of mount immune responses that are adequate to prevent opportunistic infection and/or neoplastic disease [5, 6, 10].

DYNAMIC EQUILIBRIUM BETWEEN CD4⁺ T-CELL PRODUCTION AND CLEARANCE

The initial process in the life cycle of HIV infection in the binding of a specific HIV glycoprotein that is present on the surface of the virus to CD4⁺ molecule [11, 12]. Once the virus gains entry into the cell, it begins the process of virus replication following binding to CD4⁺ T-cell and fusion with the cell membrane. A direct cytopathic effect of HIV on CD4⁺ T-cells may occur *via* the destruction of the cell membrane that is subsequent to massive viral budding [13, 14], the presence of large amounts of nan-integrated viral DNA, heterodisperse RNAs and viral core proteins in the cytoplasm of the infected cell that interferes with proper cell function, and the complexing of HIV gp120 with intracellular CD4⁺ T molecules [2, 15].

The depletion of CD4⁺ T-cells may also be due to the destruction of precursor cells that give rise to CD4⁺ T-cells *in vivo* or cells which produce factors essential for CD4⁺ T-cell growth [16]. An alternative mechanism for CD4⁺ T-cell depletion involves the formation of short-lived multinucleated giant cells or syncytia between an HIV-infected CD4⁺ T-cell and a cluster of uninfected CD4⁺ T-cells. It has been estimated that between 100 million and 10 billion virus particles are produced and cleared every 24 hours. Thus, virus production occurs not only during the primary and advanced stages of the disease (typically symptomatic) but also during the intermediate stage of the infection (the virus is not truly latent) [17]. At the intermediate

stage of HIV infection, levels of the virus in the plasma are the result of a dynamic equilibrium between the production of HIV and its clearance by the immune system. In this continuous turnover of the virus population, about 50% of the circulating virus is suggested to be replaced with newly produced virions daily [18]. The extensive production of HIV is closely related to the destruction and replacement of CD4⁺ T-cells. Scientists have estimated that the half-life of HIV-producing CD4⁺ T-cells is about 1.2 days and between 1 to 2 billion new CD4⁺ T-cells are produced every day [19]. There appears to be a difference between the half-lives of various populations of HIV-infected cells. It is said that productively infected CD4⁺ T-cells constitute a short lived population (about 1.2 days), while other HIV-infected cells, for instance macrophages, constitute a long-lived population with an average half life of 14 days [18, 19].

HIV ATTACKS THE IMMUNE SYSTEM VIA THE CD4+ T-CELL

HIV attacks the immune system by targeting the heart of the immune system, the CD4⁺ T-cells, which are the conductors of the immune system. When a pathogen is introduced into the body as either a virus or a bacterium, it is first recognized by CD4⁺ T-cells. The CD4⁺ T-cells are responsible for coordinating each of the host immune defenses, namely, the killer cells, the antibodies and the phagocytes that will eliminate the pathogens [20]. However, if the CD4⁺ T-cells are destroyed, the immune defenses that remain become less functional and are unable to eliminate the pathogens and the latter can proliferate to cause disease [20]. In the body, HIV is replicating in its niche, which is the memory CD4⁺ T-cells, the cells that are very actively mobilized against the most current infections. Each time a memory CD4⁺ T-cell is infected by HIV and each time HIV is replicating memory CD4⁺ T-cell, which dies and ultimately undergoes the process of elimination. In the healthy young adult or at the beginning of the HIV infection, these dying memory CD4⁺ T-cells are replaced by a constant source or a reservoir of native CD4⁺ T-cells originating from the thymus. It is reported that during the course of HIV infection, about 1 billion HIV particles are produced per day, resulting in increasing numbers of infected CD4⁺ T-cells. The infection spreads in the memory cells, in the native CD4⁺ T-cells in thymus, the source is therefore progressively exhausted surpassing the capacity to produce new CD4⁺ T-cells [20].

It has been shown that progressive loss of CD4⁺ T-cells is the cardinal manifestation of the effects of HIV infection. The CD4⁺ T-cells count can therefore serve as a useful indicator of severity of the infection, providing both a convenient measure of immunological status and giving some indication of the risk of opportunistic infection and neoplasia, particularly in individuals who have already begun to show a substantial CD4⁺ T-cell decline. The CD4⁺ T-cell count indeed has considerable importance in some systems used to stage HIV infection and by implication the guidance of treatment decisions. It is particularly important in determining whether it is appropriate to initiate prophylactic therapy for opportunistic infections [2, 21]. The significance of the destruction of CD4⁺ T-cells in an HIV infected person becomes evident when there functions are considered.

CD4⁺ T-CELL DEPLETION IN HIV DISEASE

In many parts of the world, infection with the HIV leads to AIDS and then to death if not treated. In time, it became clear that the virus could replicate within human CD4⁺ T-cells *in vitro*, that the viral envelope protein could bind to CD4⁺ T-cell and circulating CD4⁺ T-cells decreased in number as the disease progressed [22]. It was also apparent that CD4⁺ T-cells were crucial in coordinating cellular and humoral immune responses against exogenous antigens. As a result of these observations, it was not difficult to imagine that HIV-associated immunodeficiency was due to virally mediated destruction of CD4⁺ T-cells [23].

EVIDENCE FOR CD4⁺ T-CELL DEPLETION

There is a growing realization that the T-lymphocyte compartment is comprised of multiple subpopulations and that there are inadequate means by which to monitor the relative growth, death and movement of these subpopulations in an individual patient over time. The definition of CD4⁺ T-cell loss in HIV disease thus remains unclear [23]. Most researchers agreed that HIV infection leads to the progressive loss of CD4⁺ T-cells from circulation as well as the depletion of CD4⁺ T-cells from total body stores [22, 24]. Quantitative assessments using a variety of assumptions, indicate that the normal young adult (<30 year old) harbours about 2×10^{11} mature CD4⁺ T-cells [24]. In the HIV infected patients, this total number is halved by the time the peripheral blood CD4⁺ T-cell count falls to 200 cells/ml. As the HIV infection progresses to a more advanced stage, destruction of parenchymal lymphoid spaces is so extensive that enumeration of the total body CD4⁺ T-cell count has not been attempted. With further disease progression, there is also a decrease in the proportion of resting native (CD45RA⁺CD62L⁺) T-cells and an increase in the proportion of activated memory/effector (CD45RO⁺) T-cells; concomitantly the T-cell receptor (TCR) repertoire is both perturbed and restricted. Among those cells that persist, many may be dysfunctional. On the whole HIV induces both quantitative and qualitative defects in the CD4⁺ T-cell compartment and the circulating CD4⁺ T-cell count continues to be one of the best surrogate markers by which to gauge prognosis in the late infection and to trigger treatment interventions. [23, 24].

POSSIBLE CAUSES OF CD4⁺ T-CELL DEPLETION

Several mechanisms have been proposed to explain HIV mediated depletion of CD4⁺ T-cells. All are based on experimental observations [22, 23]. The total body CD4⁺ T-cells may be depleted in absolute number because they are destroyed or because their production is impaired. In addition, the fraction of circulating cells may decrease if viral infection results in their redistribution out of the intravascular space and into the confines of lymphoid organs [1, 23].

The balance of destruction and production is one important factor that can be explained by multiple mechanisms. It is possible, for example, that CD4⁺ T-cell depletion is related directly to the virally mediated destruction of infected cells. On the other hand, physiological responses to HIV infection might initiate events that result in the destruction of uninfected cells. In either case, loss of mature cells should be

compensated for by increased production of new cells and mature CD4⁺ T-cell depletion should occur only if cells lost in the periphery, cannot be replaced. The devastating feature of HIV infection is that the virus can have direct and indirect pathogenic effects on both mature CD4⁺ T-cells and on the progenitor cells from which they arise [23].

ACCELERATED DESTRUCTION OF MATURE CD4⁺ T-CELLS

Preliminary experiments performed with laboratory-adapted HIV isolates in tissue culture revealed a cytopathic virus with exquisite tropism for CD4⁺ T-cells. The provision of potent (Protease inhibitor containing) antiretroviral medications to patients with advanced HIV disease caused the viral load to drop and the CD4⁺ T-cell count to rise. By making reasonable and widely accepted assumptions about T-cell distribution and by assuming that antiretroviral therapy does not alter the production rate of T-cells, the statement was interpreted to reflect that, before therapy, continuous rounds of infection sustained the viral load and that as many as 2×10^9 infected CD4⁺ T-cells were destroyed per day. By extension, HIV disease is a high state, accelerated destruction of mature CD4⁺ T-cells and leads to eventual exhaustion of the immune system [5, 6]. In HIV infected human subjects, quantitative image analysis revealed decreased numbers of CD4⁺ T-cells and increased levels of cellular proliferation and apoptosis in lymphoid tissue [6, 23].

CHRONIC ACTIVATION AND CD4⁺ T-CELL DEATH

It is agreed that CD4⁺ T-cell death may occur in uninfected cell as a by-product of HIV infection of other cells. HIV disease is typified by a state of chronic activation driven in part by the antigenic stimulus of HIV and in part by an antigen-independent mechanism [25]. For instance, cytokines are released by apoptotic cells and activated T-cells. Multiple bursts of activated cells spread throughout the body and would be characterized by apoptotic cell-mediated activation of resting lymphocytes, cytokine-driven expansion of responding cells and contraction of the responding population by activated-induced cell death. It is believed that if apoptotic cells are infected by or otherwise carry HIV, antigen-specific cell activation could support virus dissemination to responding CD4⁺ T-cells, irrespective of their TCR specificity [26].

Reciprocally, the virus may be spread upon activation of non-productively infected CD4⁺ memory T-cells in the context of immune responses to HIV or other antigens. During the asymptomatic phase of infection, when the fraction of infected cells is much lower than the fraction of activated cells, these bursts would predictably continue in a local, recurrent and asynchronous fashion and CD4⁺ T-cell depletion might be driven by several mechanisms [12]. It has been suggested that the relentless activation of native cells into the activated/memory pool may not be fully compensated for by replenishment of new native cells from the thymus or by the generation of viable memory cells [9]. Alternatively, chronic stimulation of resting T-cells might have negative effect on the homeostatic regeneration of these cells. The relevance of this process to CD4⁺ T-cell depletion is underscored by the observation that disease progression is associated with immune activation and vice versa [3, 12].

IMPAIRED PRODUCTION OF NEW CD4⁺ T-CELLS

This mechanism focuses on mature CD4⁺ T-cells, but these cells are often derived from early progenitors that may also express CD4⁺ T-cells. Such progenitors, including multi-lineage and lineage-restricted haematopoietic progenitor cells are uniquely endowed with the capacity to persist with long half-lives and to generate large numbers of differentiated progeny rapidly upon stimulation. If these cells are destroyed or rendered non-functional, mature progeny could be made [23]. Evidence for suppression of multi-lineage and lineage-specific haematopoiesis has been available since the beginning of the AIDS epidemic [27].

Laboratory findings showed that when late-stage patients initially presented with opportunistic infections, they were not just lymphopenic, but anaemic, neutropenic and thrombocytopenic as well. These findings led to multiple diagnostic bone marrow biopsies, the results of which were frequently abnormal. Microscopic examination revealed hypercellularity or hypocellularity, plasmocytosis, myeloid or erythroid dysplasia and a variety of other pathological changes [28]. Phenotypic and functional analysis of bone marrow progenitor cells showed a decrease in the number of lineage-restricted colony forming units and in some, but not all instances, infection and/or apoptotic death of CD4⁺ T-cell progenitors. Although the mechanisms associated with such cytopenias remain unclear, they are often reversed upon the provision of effective antiretroviral therapy [29].

The thymus, housing many CD4⁺ T-cells in varying stages of maturation, is another critical target organ for HIV infection. Examination of paediatric and adult specimens has revealed thymocytes depletion, loss of corticomedullary demarcation and development of thymic medullary beta-cell follicles. These changes are associated with immunohistochemical visualization of structural proteins within thymocytes and are evidence of viral replication. Although it has proven difficult to study the thymus in HIV infected humans, the frequency of circulating CD4⁺ and CD8⁺ native T-cells have been found to decrease as disease progresses [10]. In addition cells bearing TCR excision circles also decrease in frequency with age and as a function of HIV disease progression [8]. In return, signs of thymopoiesis return after treatment of some individual with effective antiretroviral therapy particularly if they are younger and have evidence of plenty thymocytes by computed tomography [8]. It has also been noticed that peripheral lymphoid organs undergo marked alterations after HIV infection. These changes include the accumulation of virus on and eventual destruction of the follicular dendritic cell network, decompartmentalization and depletion of both the CD4⁺ and CD8⁺ T-cell populations. Thus, HIV infection leads to profound disruption of the bone marrow, thymus and peripheral lymphoid organs and where measurable quantitative and qualitative defects in important CD4⁺ T progenitor cells [10]. With these cells eliminated or no longer functional, the immune system cannot be sustained.

OXIDATIVE STRESS

The role of oxidative stress in the destruction of immune cells has been elucidated [30-34]. Specifically, the severe depletion of total antioxidant status in the AIDS stage of HIV supports that indicated increase reactive oxygen species

production correlated with increased viral load and decreased CD4⁺ T-cell count [32]. The center for disease control (CDC, 1992) also reported that low antioxidant status was significantly related to reduce CD4⁺ T-cell count [43]. Laboratory-evidenced report shows that viral tat protein increased the apoptotic index by increasing production of intracellular reactive oxygen species. Antioxidants that are naturally endowed to protect the immune defence system or consumed and hence depleted in the process of protecting the cells against reactive oxygen species-induced oxidative damage. The depletion of these antioxidants (which includes antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase, glutathione transferase, caeruloplasmin, vitamins such as vitamin A, E and C and minerals such as selenium and zinc) lead to the generation of more reactive oxygen species which consequently leading to immune depression which further enhances HIV viral replication and further suppression of the immune system/ destruction of immune cells, followed by opportunistic infections as a result of depressed immune system and development of AIDS.

CD4⁺ T-CELL COUNT AND PROGNOSIS

The CD4⁺ T-cell count has been shown in numerous clinical trials and natural history studies to be an independent risk factor for progression to AIDS and ultimately death. However, it has two major limitations: it is subject to considerable variation, for instance, inter-assay variability, diurnal variation, changes due to inter-current illness and thus it reflects existing damage to the immune system [35-38].

LINKING CD4 GENE EXPRESSION AND T CELL DEVELOPMENT

The control of CD4 gene expression is essential for proper T lymphocyte development. Signals transmitted from the T-cell antigen receptor (TCR) during the selection process are believed to be linked to the regulation of CD4 gene expression during specific stages of T cell development [39]. Thus, the control CD4 gene expression is an ideal model system for studying the molecular mechanisms that drive T cell development. Studies on characterization of transcriptional control elements in the CD4 locus and the factors that mediate their function has led to significant insights into the mechanisms in which the T lymphocyte develops its mature functional characteristics.

HOW DOES HIV CAUSE DEPLETION OF CD4 LYMPHOCYTES? A MECHANISM INVOLVING VIRUS SIGNALING THROUGH ITS CELLULAR RECEPTORS

HIV infection causes an acquired immunodeficiency, principally because of depletion of CD4 lymphocytes. The mechanism by which the virus depletes these cells, however, is still obscure. Since the virus predominantly infects CD4 lymphocytes *in vivo*, some have assumed that HIV replication directly kills the infected cells or that the anti-HIV immune response destroys them [40]. However, a large number of studies do not support this concept. Rather, the data strongly indicate that CD4 lymphocyte depletion is by an indirect mechanism. Several theories on various direct and indirect mechanisms are reviewed. The most plausible mechanism, which is backed by *in vivo* data, involves the consequences of HIV contact with resting CD4 lymphocytes,

which cannot support virus replication. HIV binding to, and signaling through, CD4 and chemokine receptor molecules on resting CD4 lymphocytes and other cell types [which extensively occurs as the rare, productively infected cells (ie: infected cells producing virus) migrate among other cells through the lymphoid tissues back into the blood] induces upregulation of L-selectin and Fas. When these resting, HIV-signaled CD4 cells return to the blood, they home very rapidly back to peripheral lymph nodes and axial bone marrow, and their disappearance from the blood is likely due to their leaving the circulatory system. Approximately one-half of these cells that have been induced by HIV to home to lymph nodes are subsequently induced into apoptosis during the process of trans-endothelial migration when secondary signals are received through various homing receptors. These cells are not making HIV, which would explain the observation that CD4 cells not making HIV are the predominant cells dying in the lymph nodes of HIV+ subjects. These studies indicate that the principal mechanism of CD4 T-cell depletion by HIV is due to its use of CD4 as its primary receptor and the signaling induced through this receptor on non-permissive (resting) T-lymphocytes. This unique mechanism of viral pathogenesis, if correct, leads to the possibility that HIV might not cause depletion of CD4 lymphocytes if it used some other receptor to infect CD4 lymphocytes.

COMPUTATIONAL MODELING OF HIV AND CD4 CELLULAR/MOLECULAR POPULATION DYNAMICS

Computational models can facilitate the understanding of complex biomedical systems such as in HIV/AIDS. Untangling the dynamics between HIV and CD4+ cellular populations and molecular interactions can be used to investigate the effective points of interventions in the HIV life cycle. With that in mind, it has been developed as a state transition systems dynamics [41] and stochastic model that can be used to examine various alternatives for the control and treatment of HIV/AIDS. The specific objectives of these studies were to use a cellular/molecular model to study optimal chemotherapies for reducing the HIV viral load and to use the model to study the pattern of mutant viral populations and resistance to drug therapies. The model considers major state variables (uninfected CD4+ lymphocytes, infected CD4+ cells, replicated virions) along with their respective state transition rates (viz. CD4+ replacement rate, infection rate, replication rate, depletion rate). The state transitions are represented by ordinary differential equations. The systems dynamics model was used for a variety of computational experimentations to evaluate HIV mutations, and to evaluate effective strategies in HIV drug therapy interventions.

CHRONIC CD4⁺ T-CELL ACTIVATION AND DEPLETION IN HIV-1 INFECTION: TYPE I INTERFERON-MEDIATED DISRUPTION OF T-CELL DYNAMICS

The mechanism of CD4⁺ T-cell depletion during chronic human immunodeficiency virus type 1 (HIV-1) infection remains unknown. Many studies suggest a significant role for chronic CD4⁺ T-cell activation. It has been assumed that the pathogenic process of excessive CD4⁺ T-cell activation would be reflected in the transcriptional profiles of activated CD4⁺ T-cells [42]. Here the researchers demonstrate that the

transcriptional programs of *in vivo* activated CD4⁺ T cells from untreated HIV-positive (HIV⁺) individuals are clearly different from those of activated CD4⁺ T cells from HIV-negative (HIV⁻) individuals. The researchers observed a dramatic up-regulation of cell cycle-associated and interferon-stimulated transcripts in activated CD4⁺ T cells of untreated HIV⁻ individuals. Furthermore, we can find an enrichment of proliferative and type I interferon-responsive transcription factor binding sites in the promoters of genes that are differentially expressed in activated CD4⁺ T cells of untreated HIV⁻ individuals compared to those of HIV⁺ individuals. We confirm these findings by examination of *in vivo*-activated CD4⁺ T cells. Taken together, these results suggest that activated CD4⁺ T cells from untreated HIV⁻ individuals are in a hyperproliferative state that is modulated by type I interferons [42]. It provides a new model for CD4⁺ T-cell depletion during chronic HIV-1 infection.

CONCLUDING REMARKS

Conclusively, based on experimental studies, different mechanisms combined to provide explanations for HIV-mediated depletion of CD4⁺ T-cells. These mechanisms range from accelerated destruction of matured CD4⁺ T-cells, chronic activation, oxidative stress to impaired production of CD4⁺ T-cells. The altered immune systems lead to failure in signal network, followed by failure in the immune system to respond to invading organisms (imbalance between production and destruction of CD4⁺ T-cells) enabling HIV-infected persons to become vulnerable to opportunistic infections that typify AIDS. Studies required, which could possibly provide detailed explanations pertaining to immune response in HIV-1 infection. Research works throw more light onto new insights and the mechanism involved in HIV-1 infection probably leads to the development of an effective vaccine against HIV.

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