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Improvement IL-10 and Reactive Oxygen Species (ROS) in HIV Patients : Narrative Review

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ABSTRACT

Human Immunodeficiency Virus (HIV) infection is still a frightening health problem for the world community. This virus infection causes a set of symptoms of the disease characterized by a weakening of the immune system. This set of symptoms is known as *Acquired Immune Deficiency Syndrome* (AIDS). Due to the decline in the immune system, HIV sufferers will be susceptible to various infectious diseases that can be fatal. This study aims to determine how IL-10 and Reactive Oxygen Species (ROS) levels increase in HIV patients. This study used a Narrative Review design. Articles were searched from Google Scholar, PubMed, Science Direct, and EMBASE/Elviser databases using relevant keywords, then selected based on established criteria and research objectives. There is Increased levels of IL-10 and Reactive Oxygen Species (ROS) in patients result in a decrease in the immune system, this is characterized by increased virus replication, macrophage deactivation and depletion of the number of lymphocyte cells, so that the progression of infection towards AIDS can occur. HIV infection causes mitochondrial dysfunction and increased production of *Reactive Oxygen Species (ROS) in CD4* $^{+}$ T lymphocytes . Various viral proteins, such as *envelope proteins* Gp120, Tat, Nef and Vpr, are able to increase ROS production. through various different pathways. The increase in ROS that occurs can increase mRNA expression through activation of *Nuclear Factor Kappa B* (NFκB), increasing IL-10 mRNA expression will ultimately increase IL-10 levels

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is still a frightening health problem for the world community. This virus infection causes a set of symptoms of the disease characterized by a weakening of the immune system. This set of symptoms is known as *Acquired Immune Deficiency Syndrome* (AIDS). Due to the decline in the immune system, HIV sufferers will be susceptible to various infectious diseases that can be fatal.[1]

The first HIV outbreak occurred due to the transmission of the SIV virus from African primates to humans. Wildlife hunters in Africa were the first group suspected of being infected

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with the virus in the early 20th century. Based on genetic analysis, it is estimated that HIV-1 spread to North America in the 1960s. In the mid-1980s, this type of virus, especially the M subtype, spread massively throughout the world, causing a global HIV pandemic. Meanwhile, in the same decade, HIV-2 is thought to have entered Portugal and France, and from there they spread with low prevalence in Europe, South America and Asia.[1]

In 2017, an estimated 36.9 million people worldwide were infected with HIV , with 1.8 million new cases (UNAID S , 2018). The sub-Saharan region, especially southern Africa, is the region with the highest number of infections. Around 75% of the world's HIV cases are in this region and two-thirds of the number of new cases reported come from this region.[2]

Since the introduction of antiretroviral drugs (ARVs), the epidemiology of HIV worldwide has changed. Although the prevalence of HIV sufferers increases every year, the number of HIV incidents tends to decrease. This increase in prevalence is thought to be due to the increase in the coverage of HIV sufferers who receive ARVs, so that they have a higher life span. It is estimated that more than 50% of HIV sufferers have received ARV drugs. This is in line with the decline in the number of deaths due to HIV/AIDS, from a peak of 1.9 million people in 2005 to 1 million people in 2016. In 2002, the reported incidence of HIV was 3.3 million people, while in 2012 the number decreased to 2.2 million people. The main cause of the decline in HIV incidence, due to the decline in HIV transmission that occurs among heterosexuals, but among homosexuals the incidence of HIV is still stable.[2]

In 2017, HIV was estimated to have infected 36.9 million people, with the number of new cases reaching 1.8 million people worldwide (UNAIDS, 2018). Asia is the region with the second largest spread of HIV after Africa. It is estimated that there were 4.8 million HIV sufferers in Asia in 2012, with the largest number of sufferers in China and India, while Thailand was the country with the highest HIV prevalence (1.1%).[2]

In Indonesia, the latest data from the Ministry of Health shows that by the end of September 2024, 35,415 new cases of HIV and 12,481 new cases of AIDS had been found. This data shows an increase compared to the same period in the previous year. In addition, by June 2024, 38 provinces in Indonesia had reported HIV/AIDS cases, with 512 of the 514 districts/cities also having reported.[3]

The HIV virus will specifically infect $CD4^+$ T cells that play a key role in the immune system, and cause a decrease in the number of these cells in the blood which then causes a progressive decline in the immune system. In addition to the reduction in $CD4^+$ T cells , the decline in the immune system in HIV patients is also caused by disruption of cytokine regulation that affects the function of various immune cells. Increased interleukin 10 (IL-10) is one of the main causes of this dysregulation. Increased IL-10 causes an immunosuppressive condition by inhibiting the $CD4^+$ T cell response to HIV infection.[4]

Interleukin 10 is a cytokine that acts as an immunoregulator. This cytokine functions to suppress the adaptive and innate immune systems. Interleukin 10 is generally produced by various types of cells, including T cells, *Natural Killer* (NK) cells, monocytes and B cells, in response to viral infections. Several studies have shown that in HIV infection conditions, there will be an increase in IL-10 production, where this increase is correlated with disease progression.[5]

Increased IL-10 in HIV infection is known to cause harmful effects. Interleukin 10 is known to be able to reduce the production of Th1 cell cytokines, such as IL-2 and IL-12, and inhibit antigen presentation and cellular immune responses. This shows that IL-10 is involved in reducing T cell function in response to HIV infection. Previous *ex vivo* studies have shown that inhibition IL-10 is able to increase the activity of $CD4^+$ and $CD8^+$ T cells . Therefore, inhibition of IL-10 is expected to be able to restore T cell function and increase its ability to control viruses.[6]

In addition to cytokine regulation disorders, in HIV infection, oxidative imbalance conditions can also be found. This is characterized by reduced levels of *glutathione* (GSH) in plasma and other body fluids. In addition, GSH levels in erythrocytes and T cells also decrease in

line with the progression of HIV. In addition to functioning as an intracellular defense system against oxidative stress, GSH also plays a role in the mechanism of the immune system, through increased IL-2 synthesis and increased cytotoxic and *natural killer activity* from T cells. Low GSH levels in HIV infection are also closely related to low survival rates. Free radicals are unstable and highly reactive molecules because they contain one unpaired electron in their outermost orbital, so to achieve stability, free radicals react with surrounding molecules to obtain an electron pair. Prevention of damage caused by free radicals in the human body can be done by producing antioxidants endogenously in the body's defense system. However, the current levels of antioxidants are unable to fight free radicals that cause disease, one of which is due to oxidative stress.[7]

In this literature review, we will describe the role of IL-10 and Reactive Oxygen Species (ROS) along with the development of the disease. so that can be assessed how Reactive Oxygen Species (ROS) can affect IL-10 in HIV/AIDS patients. Based on this article, it is expected to be a theoretical basis for further research related to advanced therapy or vitamins that can be given to improve the health status of HIV patients .

METHOD

The method of writing this research is a literature review or *Narrative Review*, in search literature, writer use a number of site seeker academic namely: (1)*PubMed Central*, (2)*Google Scholar, (3)Scince Direct* and (4) *EMBASE/Elsevier,* These databases were selected based on their comprehensive coverage of HIV disease and clinical research. Four subtopics of the research question were searched on the four search sites with different keywords using *Boolean Operators* using *mesh terms*, as follows: 1)References regarding the subtopics IL-10 and HIV/AIDS were searched with say key: *(IL-10) OR (Interleukin-10)* AND *(HIV)* OR *(AIDS).* 2)References regarding the subtopic Reactive Oxygen Species and HIV/AIDS are searched using the keywords: *(*Reactive Oxygen Species*)* AND *(HIV)* OR *(AIDS).* 3)References on the subtopic of oxidative stress and HIV/AIDS were searched using the keywords: *(oxidative stress)* AND (*HIV)* OR *(AIDS).* 4)References about subtopic T cell or T lymphocyte on HIV/AIDS searched with keywords: (T cell) OR (T lymphocyte) AND (*HIV)* OR *(AIDS)*

After obtained a number of reference from results search with say key which has determined, reference the Then selected based on criteria inclusion and exclusion first before assessing its relevance to the criteria: 1)The form of publication or writing can be a case report, case series, literature review/literature study, *original article*, *systematic review,* or *meta-analysis.* with say key and or topic which relevant with purpose of writing *a Narrative Review* this. 2)Writing published in *peer reviewed journals* . 3)The year of publication of the article is within the last ten years, namely 2014-2024, unless the study or publication has relevant theories, topics and/or findings that are related and support the objectives of *the Narrative Review* being worked on. 4)Articles or publications that are not written in an international language, namely English, are not included as references. 5)If *full articles* from a publication No can accessed, so excluded from the reference list. The method of citing references and writing bibliographies in this *Narrative Review* will refer to the *Vancouver method.* Irrelevant studies will be excluded from this study. If agreement is difficult to reach, voting will be carried out to get the final decision.

RESULTS AND DISCUSSION

Pathogenesis and Clinical Manifestations of HIV/AIDS Infection

Human Immunodeficiency Virus (HIV) can be transmitted through sexual contact or direct contact with the blood of HIV sufferers through transfusions or wounds from contaminated needles. HIV can enter the body through the body's mucous membranes, especially the genital

mucosa, the presence of open wounds on the skin or mucous layers, or be passed from mother to fetus. [7] The main factor that most influences the increased risk of HIV transmission is the amount of viral RNA contained per mL of plasma (*viral load*). Every increase of 1 $\log^{10}$ *viral load* causes a 2.4-fold increase in the risk of transmission.[8]

The primary target of HIV infection is active $CD4^+$ T cells, however, the virus can also attack dendritic cells or monocytes or macrophages, depending on the route of entry into the body. If it enters through sexual contact, HIV will infect dendritic cells or monocytes/macrophages first, then infect $CD4^+$ T cells, but if it can enter through direct contact with blood, then HIV can directly infect $CD4^+$ T cells.[9] Experiments on Rhesus monkey models infected with *Simian Immunodeficiency Virus* (SIV) intravaginally, showed that dendritic cells of tissue found in the vaginal mucosa, are the first cells to contain SIV DNA. Dendritic cells are cells that can act as *antigen presenting cells (APC), which can present antigens to naive* T lymphocytes. After capturing the virus, dendritic cells will carry the virus to the lymph nodes and present it to activated $CD4^+$ T lymphocytes after interacting with dendritic cells.[10]

HIV virus enters the cell through a direct fusion mechanism with the plasma membrane. After entering the body, the gp 120 and gp 41 proteins found in the HIV *envelope layer* will be recognized by the CD4 receptor found on the surface of $CD4^+$ T lymphocytes, monocytes or macrophages and several other target cells. These receptors are mostly MHC class II receptors. After binding, there will be a conformational change in the gp120 domain which causes the domain to bind to CCR5/CXCR4, which is a chemokine receptor. As a result, a stable bond is formed between the virus particle and the cell membrane, which allows the N terminal part of the gp 120 protein to penetrate the plasma membrane. Furthermore, the HR-1 and HR-2 sequences of the gp 41 protein form a hairpin-like structure, which results in fusion between the virus and cell membranes. After fusion, the virus core will be released into the cell cytoplasm, in addition to the release of the capsid layer mediated by the MA, Nef and Vif proteins.[10]

As soon as the viral RNA enters the cell, the viral RNA will be converted into double-stranded DNA, through the activity of the *reverse transcriptase enzyme*. Furthermore, the DNA that has been formed will be carried into the cell nucleus through the pores in the cell nucleus with the help of the Vpr protein, and randomly joins the nuclear DNA, so that it becomes part of the host cell DNA. This process occurs through the mediation of the *integrase enzyme*. This viral gene will also replicate and be passed on during the division of the infected cell. [11]

The viral DNA that has been combined with the host DNA can be transcribed by RNA polymerase II from the host cell. The transcription results are complete viral RNA, and several mRNAs that will be translated into *envelope proteins* and other regulatory proteins. These regulatory proteins function to regulate the viral transcription process, resulting in viral RNA or mRNA. This regulatory ability distinguishes HIV from other *retroviruses. After that, various viral proteins and RNA are transported to the cell membrane to be assembled and released as immature viruses*. The proteolysis process mediated by the protease enzyme causes the virus to become *mature,* which has a distinctive core.[11]

Two days after infection, HIV can be found in the lymphoid tissue and quickly spreads throughout the lymphatic system. Eventually, the virus can reach the bloodstream and its replication can be detected in plasma five days after infection. After 10-14 days after infection, HIV can be detected throughout the body, including the nervous system. Transmission of HIV through blood and organ donation can occur 5-6 days after infection. Transmission from mother to child can occur after 12 weeks of pregnancy, but transmission generally occurs in the last trimester of pregnancy and a small portion at birth. In addition, HIV can also be transmitted through breast milk.[11]

Immediately after infection, HIV will replicate very rapidly, 106 copies /mL of HIV RNA can be found, peaking at 4-8 weeks after infection. Along with the emergence of a specific immune response to HIV, viral replication will decrease drastically, even to undetectable levels. This is due

to the clearance of cells containing the virus and clearance of the virus from the circulation. Clinically, at this time flu-like symptoms can arise, such as fever, headache, nausea and anorexia. These symptoms can resolve on their own without treatment. This stage is known as the acute infection phase.[11]

Six months after the acute infection phase, most patients will enter the asymptomatic phase. In this phase, the level of viral RNA reaches the *set point*, which is a condition where the virus cannot be detected. During this asymptomatic phase, there is a dynamic balance between the host's immune system and HIV, where the cellular and humoral immune responses remain high so that the viral RNA is still at low levels.[12] However, viral replication continues to occur, especially in the lymphoid tissue area. This condition may last for several years. In this phase, patients usually do not show clinical symptoms. In many patients, minor opportunistic infections can also be found, such as thrush and *herpes zoster*. In addition, thrombocytopenia can also be found in this phase. There is a driving factor that ends this phase, namely the presence of mutations that occur during the viral replication process. These mutations increase the induction of virulent viruses with increased cytopathic ability and changes in cell tropism.[13]

After being infected for 10 years or more, about 50% of infected people who do not receive ARVs will show symptoms of the disease, such as a decrease in $CD4^+$ lymphocyte cells to below 200-350 cells/µl and loss of specific immune response of $CD4^+$ and $CD8^+$ T lymphocyte cells, a dramatic increase in plasma virus, and the emergence of clinical symptoms. Symptoms that often appear are long-lasting fever (> 1 month), weight loss, fatigue and diarrhea that does not go away. This phase is called the chronic symptomatic phase, which can develop into AIDS. In this phase, the HIV virus has mutated, making it more virulent. In addition, chemokines produced by activated lymphocytes cannot block the entry point of the virus into cells. As a result, there is an increase in virus replication and a decrease in $CD4^+$ T lymphocytes, causing immune system deficiency. This condition causes opportunistic infections, malignant tumors and damage to the central nervous system which leads to death.[14]

Immune Response to HIV Infection

Immunologically, some time after infection, the body will respond by activating the natural immune system, namely by activating macrophage cells, *natural killer cells* , complement and the release of various pro-inflammatory cytokines. In addition, there is also activation of the adaptive immune system, in the form of humoral and cellular immune responses. [15]

Activation of the humoral immune response is characterized by the formation of neutralizing antibodies that function to clear the virus from circulation through the formation of a complex of viruses, antibodies and complement. One of the antibodies that plays an important role in clearing the virus is antibodies against the p24 protein of the virus, which is the core protein of the virus. These antibodies arise within a few weeks after infection. In addition to antibodies against p24, there are antibodies that recognize the V3 region of the gp120 protein of the virus. The presence of these antibodies results in the virus being unable to enter the host cell and perform cell fusion or recognize the gp41 protein in *the envelope*. Other types of antibodies can interfere with the interaction between the HIV *envelope* and the CCR5 receptor, thereby preventing the virus from entering the cell.[16]

T lymphocytes (cytotoxic T cells) that play a role in lysing infected cells. These cells specifically recognize MHC class I which presents various HIV proteins, including core proteins, *reverse transcriptase enzymes, envelope* proteins and regulatory proteins. These $CD8^+$ T cells play a major role in suppressing viral replication, especially during the early stages of infection. However, the response of these cells to HIV infection can decrease, even disappear in progressive disease. This is caused by several factors, including decreased expression of *major histocompatibility complex* (MHC) class I molecules required due to the presence of HIV

accessory proteins, such as Tat, Nef and Vpu; increased expression of cell killing inhibitors; and the accumulation of selective $CD8^+$ T cells that lack IL-2 receptors. In addition, the decrease in this cell response is also caused by the ability of HIV to mutate and reduce the $CD8^+$ T cell population with high antigen concentrations.[17]

$^+$ T cells, the cellular response to HIV infection also involves activated $CD4^+$ T cells and macrophages. These cells release various chemokines that can block the chemokine receptors (CXCR4 and CCR5) used by HIV to enter cells. As a result, there is a sharp decrease in the number of viruses and virus-producing cells in the lymphatic tissue.[18]

Although the immune system can eliminate HIV, not all viruses can be eliminated. A large number of viruses trapped in *follicular dendritic cells* and latently infected cells can be a source of viruses that can continuously infect $CD4^+$ T cells that reside or migrate in the lymphatic system. The mechanism by which HIV can evade the immune system is not yet clearly understood, but there are several mechanisms that are thought to cause this. These mechanisms include the destruction of most $CD4^+$ T cells which are crucial to the effectiveness of the immune system, the occurrence of mutations that cause antigen variations, and a decrease in the ability of MHC class I on infected cells to present viral antigens, so that they cannot be recognized by $CD8^+$ T cells.[19]

2.2 Interleukin 10 (IL-10)

Interleukin 10 is an anti-inflammatory cytokine that functions to inhibit the activity of Th1 cells, NK cells and macrophages.This interleukin is the main cytokine in the regulation of the cytokine system that plays a role in suppressing the expression of pro-inflammatory cytokines during repair during infection. As a result, tissue damage can be prevented.[20]

Interleukin 10 is one of the cytokines of the IL-10 cytokine family. Other members of this family are IL-19, IL-20, IL-22, IL-24 and IL-26. Together with interferon, the IL-10 cytokine family forms the 2nd class of the α-chain cytokine family. In addition to IL-10, other cytokines included in this class are type 1 interferon and γ interferon. The production of these cytokines is regulated by the gene encoding IL-10, located on chromosome 1 at location 1q31-32, which spans approximately 4.7 kb and contains four introns and five exons. There are various genetic variations in the IL-10 gene, but the most widely studied are two microsatellites composed of 2 dinucleotide repeats, namely IL10G and IL10R, and three types of *single nucleotide polymorphisms* (SNPs), namely -1082 (G / A), -819 (C / T) and -592 (C / A). This is because both types of microsatellites and three types of SNPs affect IL-10 secretion. In humans, IL-10 is a protein composed of 160 types of amino acids with a molecular weight of 18.5 kDa, in the active form as a homodimer with a molecular weight of 37 kDa.[20],[21]

Interleukin 10 was initially known to be produced only by Th2 cells to inhibit cytokine production from Th1 cells, but it is now known that IL-10 expression is not specifically owned by Th2 cells alone, but also by various cells involved in the adaptive and natural immune systems. Currently, IL-10 is known to be produced by various cells in the adaptive immune system, such as Th1, Th2, Th17, Treg, $CD8^+$ and B cells. In addition, IL-10 is also produced by various cells in the natural immune system, such as macrophages, dendritic cells, mast cells, NK cells, eosinophils and neutrophils. Several studies have also shown that these cells can also be produced by human cancer strain cells.[18],[22]

IL-10 activity is mediated by a specific receptor found on the cell surface, the IL-10 receptor (IL-10R). This receptor is composed of 2 different types of chains, namely IL-10R1 and IL-10R2. Both types of chains are members of class II cytokine receptors, in the form of transmembrane glycoproteins. The extracellular portion contains 210 amino acids and has several protected amino acid positions as its secondary structure. The intracellular portion has varying thickness and does not show striking amino acid sequence similarities. The IL-10R1 receptor is

generally found on the surface of immune cells, while the IL-10R2 receptor can be found on the surface of most cells and tissues.[23]

The binding between IL-10 and its receptor occurs in 2 stages. Initially, IL-10 will bind to IL-10R1, forming the IL-10/IL-10R1 complex. The presence of this complex causes a conformational change in IL-10 that causes this cytokine to bind to IL-10R2. Therefore, IL-10 will not react to cells that only have the IL-10R2 receptor. The binding between IL-10 and its receptor causes the activation of 2 members of the Janus kinase family, namely Jak1 which is associated with IL-10R1 and Tyk2 which is associated with IL-10R2. [24] This causes the phosphorylation of 2 tyrosines found in IL-10R1. As a result, the STAT 3 molecule, which is a transcription factor, will bind to each other and be phosphorylated by Janus kinases. In addition, in certain types of cells, STAT 1 and STAT 5 molecules are also activated. Next, these STATs that have been bound to each other will migrate into the nucleus, and bind to STAT-binding elements of various promoters, to induce transcription of the appropriate genes.[25][26]

HIV infection and IL-10

Interleukin 10 is a cytokine that plays a key role in the process of suppressing the immune response to viruses. Interleukin 10 can inhibit the proinflammatory response that occurs during infection, both in the natural immune response and in the adaptive immune response. This actually aims to prevent tissue damage caused by excessive adaptive immune responses.[27][28] However, in HIV infection there is an increase in IL-10 levels which causes the viral infection to become persistent.[29]

There are several mechanisms of IL-10 increase in HIV infection involving the Nef, Tat and Env proteins of the virus. The Nef protein is known to be able to increase the expression of IL-10 mRNA and IL-10 protein in PBMC cultures by involving the calcium/camodulin phosphodiesterase pathway.[30] The Tat protein of the virus has also been shown to increase IL-10 production in PBMC cultures. Unlike the Nef protein, the increase in IL-10 due to the Tat protein occurs through activation of the protein kinase C (PKC) pathway which causes increased activity of the transcription factor NF κ B and the MAP kinase protein ERK1/2, thereby increasing IL-10 production.[29] The Env protein of the virus can also increase IL-10 production through activation of the T bet transcription factor pathway in $CD4^+$ cells.[31]

Increased levels of IL-10 in HIV infection are a major factor causing decreased T cell function. As explained above, IL-10 inhibits proliferation and cytokine production, and reduces the ability of T cells to respond to the presence of the virus. Several studies have also shown that IL-10 expression correlates with HIV viremia.[32] Research conducted using *lymphocytic choriomeningitis virus* (LCMV) in mice, as a model of chronic viral infection, shows that inhibition of the IL-10 pathway can increase the immune response of T cells, resulting in clearance of the LCMV virus and the formation of memory T cells against the virus. Other studies have shown that inhibition of IL-10 causes increased T cell activity, both $CD4^+$ and $CD8^+$. [33]This increase is characterized by increased proliferation and expression of IFN-γ, TNF-α, and IL-2. However, this increase can only occur in the pre-AIDS phase. In the post-AIDS phase, IL-10 inhibition fails to enhance T cell responses.[34]

T cells in HIV patients have a tendency to undergo apoptosis, inhibition of IL-10 has been shown to reduce the tendency of apoptosis of these cells. This suggests that IL-10 also plays a role in the decrease in the number of important immune cells that occurs during HIV infection. In HIV infection, dendritic cells will also produce IL-10, which causes these cells to become targets for lysis by NK cells. This suggests that IL-10 not only weakens the antiviral response of T cells, but also allows the virus to weaken the immune system by targeting cells needed to produce new T cells.[35]

Oxidative Stress

Oxidative stress is a term first introduced by since in 1985, to refer to a condition of imbalance between oxidants and antioxidants that has the potential to cause damage. Oxidant is a term used to refer to a substance that can oxidize other substances, such as *reactive oxygen species* (ROS) and *reactive nitrogen intermediate* (RNI), while antioxidants are substances that bind to oxidants, thereby preventing oxidation reactions.[35]

In principle, oxidative stress is caused by 2 things, namely reduced antioxidant levels and increased ROS which are oxidants. Decreased antioxidant levels in the body are caused by several conditions, such as mutations in genes that reduce antioxidant defenses. A diet lacking in antioxidants and other essential elements, such as iron, Zn, magnesium, copper also reduces antioxidant levels.[36] Protein deficiency, such as in kwashiorkor, can also reduce antioxidant levels, especially glutathione (Sive et al., 1993). In addition, oxidative stress also occurs due to increased ROS production due to exposure to increased oxygen, the presence of toxins that produce reactive species, such as pesticides, and excessive activation of the natural system that produces reactive species, such as inappropriate activation of phagocytic cells in chronic inflammatory diseases and in persistent viral infections.[36][37]

Oxidative stress conditions, causing increased proliferation, cell damage, cell aging, even inducing cells towards apoptosis. Currently, it is known that oxidative stress contributes to various pathological conditions.[35] Although associated with many diseases, oxidative stress is actually still needed by the body in certain conditions, such as oxidative stress that causes apoptosis in the birth canal of mothers who are about to give birt.[37]

Oxidative Stress in HIV Infection

Currently, HIV infection has been shown to trigger oxidative stress, both in laboratory experiments and in infected patients. In HIV patients, an increase in oxidative stress can be found, which is characterized by increased ROS production, increased oxidized nucleic bases, such as 8-oxoG, and increased lipid peroxide products, such as MDA and alkaline compounds.[38]

HIV is able to increase oxidative stress through its ability to increase ROS production and induce mitochondrial dysfunction . Several proteins owned by HIV are able to increase ROS production through different mechanisms. The *envelope protein* Gp120 increases ROS production through upregulation of cytochrome P450 2E1, proline oxidase (POX) and activation of NOX2 and NOX4 which are part of NADPH oxidase.[38] Tat protein increases ROS through activation of NADPH oxidase especially NOX4, induction of *spermine* enzyme *oxidase* (SMO) which is an enzyme involved in the catabolism process of biogenic polyamines , and disrupts the respiration process that occurs in the mitochondria. [38,39] Vpr protein can interact with *adenine nucleotide translocator* (ANT) which is a *mitochondrial component permeability transition pore* (PTP) which causes Ca^{2+} to enter the mitochondria. As a result, mitochondrial dysfunction occurs which increases ROS production. Nef protein can also increase ROS production through its ability to bind to p22 phox which is a subunit of NADPH oxidase.[35],[39]

In fact, the body has the ability to neutralize ROS produced during the metabolic process. The body has an antioxidant defense system, which consists of various enzymes such as *Superoxide dismutase* (SOD), catalase and *Glutathione peroxidase* (GPx) as well as non-enzyme molecules such as *glutathione* , bilirubin and various types of vitamins and other micronutrients. [40] HIV infection also has an effect on this antioxidant defense system. Several studies that have been conducted have shown a decrease in the antioxidant defense system in HIV infection. There is a decrease in the activity *of* SOD, catalase, GPx , Glutathione *e reductase* (GR), Glutathione *S - transferase (GST*) & *Reduced Glutathione (* GSH) were significantly increased in HIV *patients* .[41]

Glutathione e is the molecule that has been shown to be most affected by HIV infection. The viral Gp120 and Tat proteins have been shown to decrease the synthesis and metabolism of glutathione enzymes. Both proteins decrease the expression of GSS, GR and GPx, which triggers a decrease in total glutathione levels and increases the GSSG/GSH ratio. In addition, the Vpr protein can also trigger a decrease in glutathione levels, by decreasing ATP biosynthesis in mitochondria.[41]

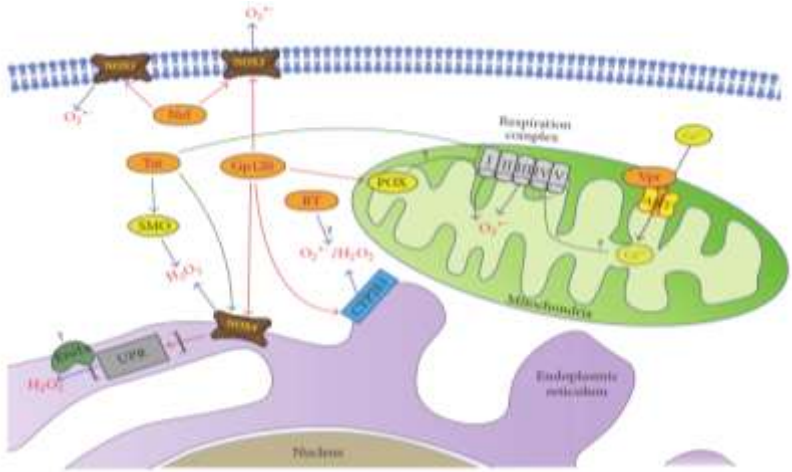

Figure 1. Mechanism of increased ROS in HIV infection.
(Source: Ivanov et al., 2016).

Oxidative stress has been shown to play a significant role in the course of HIV disease, through its ability to affect the immune system. There are several ways in which oxidative stress can affect the immune system, including that oxidative stress conditions can increase HIV viral replication. Increased ROS that occurs during HIV infection can trigger activation of NFκB. Under normal conditions, NFκB actually binds to IκB in the cytoplasm, but the increase in ROS that occurs causes NF κB to be released and enter the nucleus to bind to DNA, especially in the promoter region of *the long terminal repeat* (LTR) of the virus. As a result, HIV gene expression will increase which will ultimately increase virus replication. In addition, increased oxidative stress also activates the TNF-α gene which can worsen the oxidative stress conditions that occur. In addition, chronic oxidative stress that occurs in HIV patients also causes apoptosis in $CD4^+$ T lymphocytes. Oxidative stress also causes cells to produce abnormal chemicals that are sensitive and cause the body to become more sensitive to the toxic effects of some drugs consumed.[42]

Stres oxidative has shown relate with HIV infection. Some complications HIV infection is caused stress oxidative. Other mechanisms may involved, such as improvement *Nitric Oxide Synthase* (NOS) gene expression with overproduction of NO and activation of hepatic NF-kB with consequence improvement level cytokines that induce ROS production. On the other hand, mechanisms regulated by HIV infection regulate the oxidative status through mechanism bait come back.[43]

Improvement *turnover* of mitochondrial proteins and mitoptosis also contribute in regulation of oxidative status with remove damage mitochondria caused by stress oxidative. Some study has show that level oxidant increased in HIV patients, which is shown with improvement lipid peroxidase activity, increased MDA, and increased dismutated SOD activity superoxide O_2^- to H2O2. Antioxidant activity (*glutathione*) peroxidase and catalase) were also found decreased in HIV disease. Profile Immunology in HIV- infected patients is affected by stress oxidative and possibly modulated with treatment antioxidants. Stress oxidative tall found in the serum of HIV-infected patients. Apoptosis mediated stress oxidative improved in lymphocytes HIV patients without symptom. [44]

CONCLUSION

In HIV infection, the virus will specifically infect $CD4^+$ T cells . $CD4^+$ T cells stimulated by the viral Nef, Tat and Env proteins will respond by increasing IL-10 mRNA expression which will ultimately increase IL-10 levels. This increase occurs through the activation of various pathways according to the proteins that activate them. Protein Nef is known to increase the calcium/kamodulinfosphodiester pathway, Tat protein activates the protein kinase C (PKC) pathway and Env protein activates the transcription factor T-bet. Increased IL-10, is the main cause of decreased $CD4^+$ T lymphocyte function. Increased IL-10 causes cytokine dysregulation, inhibits cell proliferation and reduces its ability to respond to viruses. HIV infection also causes mitochondrial dysfunction and increased production of *Reactive Oxygen Species (ROS) in* $CD4^+$ T lymphocytes. HIV infection causes increased production of ROS.

From the article above it can be concluded that there are increased levels of IL-10 and Reactive Oxygen Species (ROS) in patients result in a decrease in the immune system, this is characterized by increased virus replication, macrophage deactivation and depletion of the number of lymphocyte cells, so that the progression of infection towards AIDS can occur.

AUTHOR CONTRIBUTIONS

Indra Frana Jaya KK; Conceptualization, formal analysis, project administration, visualization, and writing-original draft. Legiran; Conceptualization, data curation, formal analysis, methodology, and writing-original draft. Eddy Mart Salim; data curation, methodology, and project administration, Zen Hafy; methodology, visualization, and writing-review & editing,

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