Oxidants and Antioxidants in the Pathogenesis of HIV/AIDS

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Abstract: Human immunodeficiency virus (HIV) has predominantly been considered the main cause in the progression of acquired immunodeficiency syndrome (AIDS). However, many researchers believe that there are co-factors involved along the way that may play a critical role in its development. Elevated levels of reactive oxygen species (ROS) have been established to be present at the onset of infection. Additionally, the delayed response by the immune system upon infection may be due to an initial depletion of antioxidants, which play a critical role in scavenging excess ROS to maintain normal physiological conditions. This pro-oxidant/antioxidant imbalance results in a condition known as oxidative stress (OS). OS has been reported to be an integral element in the progression of many diseases, including AIDS. Therefore, it is presumed that antioxidant treatment may provide a promising and cost-effective therapeutic approach in treating HIV-infected individuals on a global scale.

Although HIV infection presents one of the most arduous complications to humans worldwide, awareness of its origin, adverse effects, and potential treatment remain confined to a limited population. The aim of this article is to inform the reader of how AIDS developed into a global epidemic so rapidly, while emphasizing the relationship between oxidants and antioxidants in the pathogenesis of HIV/AIDS. A basic review of reduction/oxidation (redox) reactions is provided to understand how such simple introductory concepts can have such profound effects on the body. This serves as an essential building block to the topics that follow: ROS, antioxidants, and OS in HIV disease. Moreover, it allows for us to better define and elucidate OS as an often-overlooked link between HIV-infection and the progression of AIDS, as well as potential antioxidant treatment.

Keywords: HIV, AIDS, reactive oxygen species, antioxidants, oxidative stress.

INTRODUCTION

In 1981, the first cases of atypical skin lesions and an aggressive disease of Kaposi's sarcoma appeared in homosexual men [1]. These accounts marked the initial onset of a condition that became known as Acquired Immune Deficiency Syndrome (AIDS). Within twenty years, AIDS became a global epidemic; an estimated 20 million people died, and an additional 36 million people were living with its causative agent – human immunodeficiency virus (HIV) [2]. A large majority of those infected lived in non-industrialized countries with inadequate financial support to handle the pandemic.

HIV weakens the defensive role of the human immune system. Once HIV infects a person, the body attempts to overcome the virus by generating antibodies to fight it off. However, in a rate-limiting process, progression of the disease weakens the body's immune system to thwart off and even defend from infection. As the immune system becomes compromised, several opportunistic infections develop that give rise to AIDS.

Sub-Saharan Africa represents the hardest hit region by AIDS in the world today [2]. At the end of 2001, approximately 40 million people in the world were living with HIV/AIDS, 70% of which were from that region [3]. It is estimated that more than one million United States' residents are living with HIV/AIDS today [4]. About 20% of these people are unaware of their HIV-positive status, and thus, pose a great threat of onward transmission [5]. Treatment cost, delivery and effectiveness may account for the large differences seen throughout the world.

Several studies have attributed oxidants as critical role players in the genesis of AIDS. Many have suggested that the mechanisms responsible for the progression of AIDS could be reversed through administration of antioxidant reducing agents. The discovery of HIV led to a broadening of the view that oxidative stress (OS) may have a principal contribution to both the expression of HIV and development of AIDS [6, 7]. Around the same time, empirical observations from unrelated areas of AIDS research appeared to confirm this postulate of an oxidative role [8-10]. Studies even began to report the potential use of reducing agents to suppress HIV expression [11-13].

Although the global prevalence of AIDS has recently stabilized, regional differences in trends and modes of transmission have led to a major push by clinical researchers to propose plausible solutions to prevent its onset and halt the progression of the disease's severe symptoms. In light of this, HIV has offered multiple targets for potential therapy. Several reports have pointed to the use of antioxidant treatment as a means to neutralize the adverse effects of oxidants. This article provides an insight to both oxidants and antioxidants in the pathogenesis of HIV/AIDS, while

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also reviewing antioxidants as therapeutic agents in slowing the progression of this life-threatening disease.

I. THE OXYGEN PARADOX

Oxygen is essential to sustaining normal cell function, and ultimately, aerobic life. All living aerobic organisms require dioxygen as an electron acceptor for efficient energy production and a signaling molecule in biological processes [14]. However, it is constantly facing a paradox in which the breakdown of its products may be detrimental to cell function and survival [15].

Ever since the term 'radical' was introduced, there have been innovative developments in the science of medicine and physiology. Free radicals are chemically unstable species. In general, free radicals are atoms or molecules with an open-shell, unpaired electron configuration generated by an incomplete one-electron reduction. These unpaired electrons are highly reactive, and can go on to activate a wide-range of mechanistic pathways, thereby inflicting much damage [16].

A. Reactive Oxygen Species

Oxygen is central to the generation of ROS. ROS can participate as beneficial molecules through cell signaling processes, but also as detrimental through inducing irreversible cell damage and death [14, 15]. ROS production is initiated with the rapid uptake of oxygen and the subsequent activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, catalyzing the synthesis of superoxide anion ($O_2^{\bullet}$-). The chemically unstable ROS byproducts from aerobic cellular metabolism react almost instantaneously with neighboring species in their vicinity. The interaction of these stability-seeking agents causes them to propagate a cascade of reactions. This can then activate patho-physiological processes in the surrounding environment, which may ultimately disrupt and damage living cells, and potentially, cause tissue injury. There are a variety of reactive species, some of which include hydrogen peroxide (H_2O_2) and hydroxyl radical ($OH^{\bullet}$), as well as the common ROS subclass – reactive nitrogen species – such as nitric oxide ($NO^{\bullet}$), nitric dioxide ($NO_2^{\bullet}$) and peroxynitrite ($ONOO^-$). Although the physiological function of the cellular membrane is to act as a permeability barrier, separating the intracellular and extracellular environments, some ROS, such as H_2O_2, are able to penetrate through the membrane barrier. Once inside the cell, ROS can be oxidized even further and elicit their effects. Therefore, reducing oxidants to physiological levels presents a complicated task.

B. Antioxidants

Antioxidants are either naturally occurring or synthetic biomolecules that prevent free radical induced damage by averting the formation of radicals, scavenging them, or promoting their decomposition in the body. Their neutralizing capabilities reside in their ability to donate an electron to ward off the deleterious effects of the highly reactive radicals or by converting ROS into different, less harmful, molecules. Antioxidants come in a variety of forms, ranging from those generated endogenously by the body to others administered exogenously as dietary supplements. When the natural balance between oxidants and antioxidants within the body is disturbed *via* antioxidant deficiency or increased ROS production, oxidative stress results. The subsequent adverse effects have appeared to be diminished, and sometimes resolved, through bodily antioxidant defense and supplementation [17].

C. Oxidative Stress

Excessive levels of ROS may be generated through over stimulation of the otherwise tightly regulated NADPH oxidase or by other mechanisms that generate ROS in a non-regulated fashion. An overload of free radicals and oxidants leads to their accumulation in the body, a phenomenon known as oxidative stress (OS). Generally, free radical production is counterbalanced by several mechanisms that include both enzymatic and non-enzymatic antioxidants. However, in times of imbalance between ROS and the body's antioxidant scavengers, OS ensues. OS may be a consequence of excess ROS production and/or reduced antioxidant capacity. The inability of the human biological system to detoxify and reduce oxidants or to repair detrimental damage disrupts physiological homeostasis. OS has been implicated in the pathogenesis of many other human diseases including cancer, diabetes, Parkinson disease, and even AIDS [18].

II. HIV: AN OXIDATIVE ROLE

AIDS is a particularly insidious disease with HIV compromising immune function. Rather than competing with the immune system, the virus targets for complete destruction. One of the key focuses of HIV is for annihilation of helper T-lymphocytes (CD4 cells), which provide receptor sites for HIV to bind. The competition between HIV and helper CD4 cells commences as the virus accumulates in the lymph nodes. There the virus multiplies at an extraordinarily high rate. At the same time, the helper CD4 cells are proliferating at a great rate. However, the degree at which the virus is generated is much greater to that of the CD4 cells. It is believed that HIV does not kill by gradually undermining the immune system's ability to produce helper CD4 cells, but rather by overwhelming the finite regenerative capacity of the system. Furthermore, AIDS is triggered when the infecting virus mutates and diversifies into so many different strains that the immune system is suddenly overpowered. The diverse variations of HIV strains are different enough from the original to elude the immune system [19].

Ever since its first isolation in 1984, HIV has generally been accepted as the causative agent of AIDS. However, the discovery of HIV also led to a broadening of the view that ROS play a critical role in the expression of HIV and the development of AIDS [20]. It has been reported that the virus induces OS by disturbing cellular antioxidant defense and initiating oxidative reactions [21]. Advanced cases of HIV infection renders individuals susceptible to opportunistic infections, which take advantage of the progressive immunodeficiency caused by HIV. Since cellular redox status is a normal physiological variable, any imbalance may elicit cellular response through proliferation, transcriptional activation, or apoptosis [17]. For this reason, recent reports suggest that OS is a principal mechanism in the progression of AIDS [21-23].

A. $CD4^+$ Depletion

Cellular CD4 immunodeficiency at an early stage is a hallmark of HIV infection. Several antigens may bind to receptor sites and trigger apoptosis in $CD4^+$ T-cells. Apoptosis is a normal process of programmed cell death that the body utilizes in destroying infected cells. However, when T-lymphocytes become infected, their elimination results in a weakened immune function at a time in which the body needs it most. The body is faced with a dilemma of promoting apoptosis to eliminate HIV, yet consequently lowering the body's resistance to HIV [24].

Since OS can induce apoptosis, ROS may trigger apoptotic pathways responsible for the initial T-cell depletion upon HIV infection. A study that examined the relationship among $CD4^+$ T-cell count, spontaneous apoptosis, and Fas expression from HIV-1 infected patients found an increase in both Fas expression and apoptosis, which was consistent with CD4 depletion [25]. Aires *et al.* support these findings, noting a significant increase in Fas expression on $CD4^+$ T-cells from HIV-positive individuals compared to HIV-negative individuals [26]. Therefore, increased Fas expression on $CD4^+$ T-cells and OS at the time of infection correlate to the elevated levels of apoptosis found in HIV-infected individuals, and hence, T-cell depletion in HIV disease [27]. This phenomenon has been well documented to enhance disease progression [25, 26]. If it were possible to suppress ROS levels at the onset of infection through antioxidant treatment, this would reduce Fas expression, activated apoptotic pathways and T-cell depletion, thereby slowing disease progression.

B. Macrophages

Macrophages are white blood cells derived from monocytes. They play a protective role by engulfing and digesting cellular debris. In times of infection, macrophages dispose of pathogens and enhance immune system response by stimulating lymphocytes. Macrophages are among the first cells infected by HIV. They are thought to serve as a reservoir, protecting HIV from neutralizing antibodies, and to bud HIV-1 primarily at the plasma membrane [28, 29]. Macrophages can then transfer the virus during activation of other immune cells. While T-cells die within a few days of HIV infection, macrophages appear to exist for months, continuing to release HIV. It has been shown that transmission of HIV from macrophages to $CD4^+$ T-cells occurs rapidly [30]. In addition, activation under OS conditions during HIV-infection were found to enhance inflammatory response and impair phagocytic response, causing ineffective clearance of apoptotic cells and the establishment of a chronic inflammatory state [31]. Both of these may be causative reasons behind the large T-cell depletion seen at the early stages of infection.

C. Tat

The transactivator gene (tat) of HIV encodes for the tat protein that activates immature T-lymphocytes. Tat is thought to be responsible for the burst of HIV replication that occurs when infected T-lymphocytes are stimulated. This gene is unique in that it is composed of two separate segments of DNA within the genome. Mutant strains of HIV that lack tat react far less actively when antigens stimulate the T-lymphocytes. Tat transforms T-cells into host cells suitable for HIV infection. It is believed that the gene encodes a protein that increases the expression of HIV genes leading to an increase in viral synthesis. Elevated levels of tat have been reported during times of HIV-infection, enabling proliferative infection of neighboring cells [32]. Tat can also act as a toxin in uninfected cells, activating cell death pathways [33]. The rapid spread of infection depletes T-cells and contributes to the progressive deterioration of the immune system in HIV disease.

Tat is known to increase HIV transcription rates. It is thought to bind to cellular factors and mediate their phosphorylation. This results in an increase in transcription of all HIV genes [34]. Tat has been shown to induce OS [35]. One study revealed that tat protein expression from HIV-1 infected HeLa cells amplified the activity of tumor necrosis factor (TNF), which stimulated HIV-1 replication through the activation of nuclear factor-kappa B (NF-κB) [36, 37]. Furthermore, this report found NF-κB activation to be involved in the formation of reactive oxygen intermediates, while suppressing the expression of Mn-dependent superoxide dismutase (Mn-SOD) involved in the cellular defense system against OS. Specifically, the C-terminal region of HIV-1 tat suppressed Mn-SOD expression. This induced pro-oxidative condition was reflected in a lowered ratio between reduced and oxidized glutathione. These findings suggest that tat-mediated events affect cellular redox state, and that antioxidant therapy may potentially deplete oxidant levels, reducing NF-κB activation, transcription of HIV, and disease progression.

D. NF-κB Regulation

OS has been implicated in increased HIV transcription through the activation of NF-κB in HIV-infected patients. NF-κB is a transcription factor that controls the transcription of DNA. Its activation is closely modulated by the redox state in the cell. In the cytoplasm, NF-κB is bound to an inhibitory factor (IκB) in its inactive form. However, a pro-oxidant state has been shown to release IκB, thereby activating NF-κB. This permits NF-κB to translocate into the nucleus, where it binds to DNA and transcription of HIV can take place [38].

It is suggested that a reduction in the elevated oxidant levels found in the cytoplasm upon infection may be attained through antioxidant treatment. Subsequently, NF-κB would remain bound to IκB and unable to pass through the nuclear membrane to transcribe. Glutathione, a major intracellular thiol, has been associated with inhibition of NF-κB by scavenging free radicals within the cytosol [39]. Since Fas activation is associated with NF-κB, inactivation or impairment of the Fas membrane receptor's binding site may not only lower levels of $CD4^+$ T-cell depletion, but also reduce HIV transcription rates. This could potentially decrease disease progression.

III. ANTIOXIDANTS: A THERAPEUTIC APPROACH

AIDS presents a vexing, yet extremely complicated, disease with many facets and implications. OS following HIV-infection depletes $CD4^+$ T-cell count through apoptosis,

while also enhancing HIV replication and transcription. These processes seem to rely upon the activation of NF-κB during redox impairment. A recent study found a significant depletion in antioxidant levels of vitamins A, C and E in HIV-positive children [40]. It was suggested that an increase in OS from free radicals overwhelmed the antioxidant system. Furthermore, studies support that antioxidant deficiency leads to a more rapid HIV-associated disease progression. Since oxidative agents and antioxidant deficiency have such a tremendous role in advancing disease, researchers believe that antioxidant supplementation may suppress HIV viral loads, thereby restoring immune function and potentially slowing the progression of AIDS [41].

A. *N*-Acetyl-Cysteine

N-acetyl-cysteine (NAC) is the acetylated precursor of both L-cysteine and reduced glutathione (GSH). NAC maintains intracellular thiol levels during OS, while restoring depleted GSH levels from infection. GSH is one of the body's most important and powerful natural antioxidant and detoxifier. It is known to aid in the transport of nutrients to lymphocytes and phagocytes, as well as in the protection of cell membranes. Oral NAC supplementation has shown positive results in improving the quality of life and well being of patients faced with a wide range of genetic defects, metabolic disorders, and infections, including HIV infection [42, 43].

Several studies have implicated intracellular GSH depletion and ROS generation to regulate HIV. GSH deficiency has been associated with impaired T-cell function and survival in HIV disease [44]. De Rosa *et al.* examined oral administration of NAC on effective GSH replenishment in impaired T-cell function and survival in 81 HIV-infected individuals for eight weeks [45]. Results revealed a significant increase in whole blood GSH and T-cell GSH levels in NAC-treated subjects. These findings suggested a clinical role for NAC therapy in protecting against OS and improving immune function in HIV-positive patients.

A recent study looked at the effect of NAC on gp120 [46]. This HIV envelope glycoprotein is released during infection of macrophages and generates OS, which contributes to disease progression. Results indicated that lipid peroxidation (LPO) caused by gp120 was countered by NAC. A recent report that looked at both gp120 and tat demonstrated similar findings [47]. NAC reversed both gp120- and tat-induced OS. Therefore, since gp120 and tat induce OS, which plays a critical role in viral transcription and replication, NAC treatment may inhibit and suppress pro-oxidants, thereby extending latency and alleviating deleterious effects from low GSH levels.

B. Vitamin A

Vitamin A is a group of fat-soluble compounds that plays an important function in bone growth, reproduction, vision, cell division, and cell differentiation. It is an essential component of the immune system that regulates white blood cell production to prevent, thwart off, and destroy bacteria and viruses that cause infection. Vitamin A is stored in the liver and is made up of two classes: preformed vitamin A and provitamin A carotenoid. Preformed vitamin A is absorbed in the form of retinol. It is found in the liver, milk and animal foods, and is the most readily used form by the body. Provitamin A carotenoids are those that can be converted Vitamin A. Carotenoids can be found in colorful fruits and vegetables. Beta-carotene has shown a provitamin role in vitamin A deficiency, as it is the most efficient form made into retinol. Studies have suggested an antioxidant function of beta-carotene in reducing free radicals [48].

Vitamin A deficiency has been shown to induce OS [49]. Moreover, most HIV-infected individuals present this condition, especially children and pregnant women [50, 51]. Most AIDS-related deaths and growth failure cases in HIV-infected children have been found to be associated with vitamin A deficiency [51]. Vitamin A therapy in HIV-infected children has shown protective effects against morbidity and mortality by lowering respiratory tract infection and severe diarrhea [52, 53]. Several observational studies of HIV-infected pregnant women have displayed low serum vitamin A levels with an increased risk of mother-to-child transmission (MTCT). One study assessed the effect of antenatal vitamin A supplementation on the risk of MTCT from HIV infection [54]. Although findings suggest that vitamin A deficiency is associated with MTCT, its role in lowering MTCT rates is insignificant.

A recent systematic review examining randomized controlled trials of HIV-infected women confirmed this result [55]. The five trials included 7528 women and showed no evidence of a positive effect on prenatal and/or postnatal vitamin A supplementation for the risk of MTCT of HIV. Interestingly, prenatal vitamin A treatment was found to significantly improve birth weight. Nevertheless, the review suggested that data does not support vitamin A supplementation for HIV-infected women, despite the improvements in birth weight. Proper dosage and duration may play a role in these results.

Furthermore, while reports suggest a beneficial role for carotenoid supplementation in treating diseases associated with OS, clinical studies have observed harmful effects. One report suggested that the carotenoid cleavage products formed during oxidative attack might alter the course of antioxidative action [56]. It seems certain that because vitamin A is essential in immune response of macrophages, which are one of the first cells at the onset of HIV-infection, it may significantly, directly or indirectly, be responsible for the depletion of a large number of $CD4^+$ T-cells and disease progression. Therefore, studies analyzing both the pharmacokinetics and pathogenesis of how vitamin A deprivation causes immunodeficiency in HIV-infected patients are necessary for potential therapeutic use.

C. Vitamin C

Vitamin C, also known as ascorbic acid (AA), is a water-soluble antioxidant necessary for normal tissue growth and repair in the body. Since the body is unable to manufacture AA, it must be incorporated in one's daily diet. AA is commonly found in a variety of fruits and vegetables. It is an essential antioxidant for enhancing superoxide anion and hydroxyl radical scavenging, and boosting immune response. AA has been shown to prevent LPO damage to OS-induced cells [57]. There has not been much study with AA and its

role in treating HIV-infected individuals. While one report revealed sustained high dosages of vitamin C to be toxic and immunosuppressive to T-cells, physiologically sustainable dosages may be beneficial for warding off the adverse effects of ROS and improving immune response at the time of infection [58]. Future studies monitoring both AA dosage and duration are essential in elucidating its role in HIV-infection.

D. Vitamin E

Vitamin E is a lipid-soluble vitamin. Its antioxidant properties are involved in protecting vitamin A and essential fatty acids from oxidation, thereby preventing the breakdown of tissues. Similarly to vitamin C, humans cannot generate vitamin E; thus, it must be supplemented into a daily diet from corn, lentils, wheat, rice or nuts. Vitamin E is a family of eight isomers; α-tocopherol is the only form that is actively maintained in the human body and found in the largest quantities in the blood and tissues, specifically in cell membranes. Vitamin E deficiencies and OS have been associated with HIV-seropositive patients [59, 60]. A study of 296 HIV-infected men showed a decrease in the risk of progression of AIDS by doubling their vitamin E intake [61].

In addition, while AZT remains one of the primary medications used to reduce viral levels of HIV-1, it has been shown to cause bone marrow toxicity. It was found that a concentration of 1 to 100 micromol/L were able to significantly increase the growth of bone cells in culture [62]. This suggests that combination therapy of AZT and vitamin E may have the similar anti-viral effects, while suppressing bone marrow toxicity.

Vitamin E supplementation has also been found to reduce NF-κB levels in HIV-1 infected lymphocyte cell cultures and lower oxidant production in lymphocytes, thereby reducing viral replication and inhibiting cell death [13, 63]. Vitamin E has been suggested to have a protective role in cell membranes by preventing LPO due to its lipophilic nature, as well as elevating the activity of other antioxidants to aid in the scavenging of free radicals [64]. One study revealed that vitamin E acetate completely blocked NF-κB activation in HIV-1-infected cell cultures, while vitamin E had a minimal effect [65]. Additional studies are needed to confirm this report of a different redox form of Vitamin E having promising results, as well as in determining therapeutic values of the time dependence and proper dosages essential for potential clinical application.

IV. CONCLUSION

Once the first incident of HIV infection was reported in 1981, its implications and symptoms brought much concern to clinicians and researchers. Its global spread presented a serious problem. The subsequent opportunistic diseases from infection and slow progression to AIDS were alarming. Novel advances in diagnosis and treatment brought much hope to researchers. They believed that if it were possible to catch the infection at an early stage and the agents that led to its life-threatening consequences, treatment might alter the course of these agents and save lives. However, as most virologists had known, this would be no simple task.

ROS were found to play a critical role in accelerating and controlling the progression to AIDS. In addition, antioxidant depletion was found to be a common sign at the onset of HIV infection, which resulted in severe OS. This imbalance gave way to pro-oxidants that activated replication and transcription pathways of the virus. Therefore, it was thought that antioxidant supplementation might suppress the effects of OS and slow the progression to AIDS. Although several reports are optimistic in their therapeutic use for HIV infection, further studies are essential to verify these results. Limitations remain with regards to the stage of infection, proper antioxidant dosage and duration, and resistance to treatment. Randomized trials utilizing appropriate dosages of antioxidant(s) are essential in investigating their role in altering the course of HIV infection.

V. EXPERT COMMENTARY

HIV/AIDS has developed into a global problem that shows no sign of ceasing any time soon. Several studies indicate new advances in diagnosing and treating the infection, yet almost all remain costly. Antioxidants offer a promising, natural, and inexpensive remedy that may not only alter the course of HIV infection to AIDS, but also prove invaluable in reaching out to poverty-stricken countries.

VI. FIVE-YEAR REVIEW

There has been extensive study in the pathogenesis of HIV/AIDS over the past few years. An overwhelming number of treatment studies focus on the use of protease inhibitors and antiretroviral agents rather than antioxidants. However, a majority of these reports face tremendous difficulty due to the ever-mutating HIV strains. Although the mutations have no effect on the virus, the genetic flexibility permits drug resistance and the virus to escape the body's immune system.

A majority of research has focused on the use of highly active antiretroviral therapy (HAART) to suppress HIV viral replication and the progression of HIV disease. The hope is that daily treatment will stop any further weakening of the immune system, and thus, allow it to recover from any injury already caused. Reports have revealed HAART regimens that have successfully controlled AIDS and its related disorders, as well as reduced the amount of active virus to undetectable levels at times [66, 67].

However, recent studies have indicated a rise in prevalence of HIV-1-associated neurocognitive disorders and related side effects following the era of HAART [68-70]. An *in vitro* study investigated whether HAART drug combination of AZT and Indinavir (IDV) may alter the blood-brain barrier (BBB) endothelial cells, which may exacerbate this condition [68]. Following 72 hours of treatment, the viability of the cells was significantly reduced in a dose-dependent manner and levels of ROS were highly elevated. AZT+IDV treatment also induced apoptosis in endothelial cells. Interestingly, pretreatment with NAC reversed some of the pro-oxidant effects of AZT+IDV. The authors suggested that this AZT+IDV combination treatment might affect the BBB in HIV-infected individuals treated with HAART drugs.

An additional study investigated the related side effects of Efavirenz (EFV), which is another widely used treatment for HIV-1 infection [69]. Similar to previously discussed study, viability was reduced in a concentration-dependent manner and EFV triggered apoptosis. EFV also lowered cellular proliferation and directly affected mitochondrial function in a reversible fashion by decreasing mitochondrial membrane potential and increasing superoxide production. As previously demonstrated, this study found the toxic effect of EFV treatment to be partially reversed by antioxidant pretreatment.

The elevated levels of ROS in each study indicate HAART generates ROS, thereby provoking the onset of OS, which has already been well established to occur upon HIV infection. Hence, while the oxygen faces a paradox, so does HAART: although viral loads may be suppressed, it is at the expense of elevated ROS levels that are known to only activate HIV transcription pathways and promote cell death. Therefore, since NAC treatment has been demonstrated to suppress some of the pro-oxidant effects of antiretroviral treatment, antioxidants in combination with HAART may reverse neurocognitive disorders and additional opportunistic infections associated with HIV-1 infection, while still working to reduce viral loads.

Since a substantial amount of evidence reveals a role of ROS in inducing OS following HIV infection, and OS as a causative factor in the progression of many diseases, including AIDS, a turn of focus should be put on antioxidants as natural and inexpensive therapeutic agents to suppress the consequently life-threatening disease. Future studies should be undertaken to determine the correct dosages and duration of antioxidant treatment necessary to curb the adverse effects of HIV infection. Furthermore, comparative studies may serve to identify co-factors that contribute to the development of AIDS. With a better understanding of the co-factors that assist in progressing the disease, there is tremendous hope of improved diagnosis and treatment to perhaps alter the course of HIV infection and prevent the onset of AIDS.

VII. KEY POINTS

- Ever since the first reported HIV-infected case in 1981, AIDS has progressed into a global pandemic.
- Simple redox reactions play a major role in biological function.
- ROS represent a class of high energy, reactive molecules that can inflict serious damage.
- Antioxidants work to achieve a balance between beneficial and destructive oxidant production.
- OS results from an imbalance between oxidant and antioxidant species.
- Sustained OS disrupts cellular structure and function, which is mediated by redox pathways, contributing to cell and tissue damage, and is a main component in the patho-physiology behind a multitude of diseases.
- The HIV hypothesis of AIDS overshadowed the oxidative pathway alternative.
- HIV-infected individuals suffer from chronic OS upon viral infection.
- ROS are believed to facilitate the progression of AIDS.
- Apoptosis plays a key role in $CD4^+$ T-cell depletion.
- NF-κB has an obligatory role in HIV replication and transcription.
- Although the roles of many antioxidants are not completely understood, their deficiencies have been linked to OS in HIV-positive patients.
- Antioxidants reveal a potential role in slowing the progression of HIV disease.
- Limitations remain in antioxidant trials, including infection duration, antioxidant dosages, and resistance to treatment.
- Randomized trials utilizing appropriate dosages of antioxidants are necessary to investigate their role in altering the course of HIV infection.
- While many studies indicate HAART to reduce viral loads to undetectable levels at times, it has shown to come at the expense of elevated ROS levels.
- The combination of some antioxidants and HAART reveals promising results in lowering viral loads and the generation of ROS from antiretroviral treatment.

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CONFLICT OF INTEREST

None Declared.

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