Epidemiology: Open access
ISSN: 2161-1165

del Valle, Epidemiology (Sunnyvale) 2014, 4:4
DOI: 10.4172/2161-1165.1000171

Review Article Open Access

Altered Redox Regulation as Cofactor in Comorbidities and Accelerated Aging in HIV Infection Evolution and Antiretroviral Treatment

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Received date: Aug 12, 2014, **Accepted date:** Sep 15, 2014, **Published date:** Sep 22, 2014

Abstract

Metabolic issues persist in HIV patients who are otherwise stable with and without antiretroviral treatment. Metabolic alterations are associated to chronic inflammation, severe mitochondrial toxicity and oxidative stress as critical factors influencing HIV disease outcomes even during antiretroviral treatment. These aspects could also be involved in comorbidities and premature aging. Both factors should be managed during therapy and they should be focus of intense ongoing investigation.

The aim of this mini-review is to describe essential mechanisms of in vivo reactive oxygen species generation, antioxidants pathways, and oxidative stress involved in HIV disease. Potential impact on reactive oxygen species, oxidative damage, cellular function, and how these responses change could mediate aging in pathophysiological situations are discussed. Accrual experimental and clinical reports analyses allow us a better understanding of various inter-related contributing factors. In addition, oxidative stress as an often-overlooked link between HIV-infection and the progression of aids, during antiretroviral treatment, is analyzed. Potential long-term consequences of antioxidant treatment require on-going investigation in order to obtain important clinical issues that have recently been reported. Currently, the most practical advice is to start antiretroviral therapy early and to manage traditional risk factors of non–aids-related conditions.

Keywords: HIV; Antiretroviral; Comorbidities; Oxidative stress; Aging

Introduction

Human immunodeficiency virus (HIV) infection has worldwide proportions with long-term impact [1,2]. HIV infection is mainly ECR-14-170developed and based on two species: HIV-1 and HIV-2, both of which cause numerical and functional decline of CD4 cells resulting in progressive immunodeficiency. Complex immune dysfunction in HIV-positive individuals predisposes them to both pathogenic and opportunistic infections [3,4]. How viral and human interrelation conduces to polypathies in HIV infection is a revisited topic and has not yet been completely defined.

HIV infection primarily induces chronic activation of innate immune responses, fulfilling the double function of limiting viral replication in the initial stages of infection and enhancing the generation of efficient adaptive immune responses [5]. In particular, production of interferon (IFN)-α and IFN-β by plasmacytoid dendritic cells (pDC) may be triggered through Toll-like receptor (TLR) engagement, and have both immune-stimulating and anti-viral activity, including that against HIV [6]. Recent evidence demonstrates that some of these mechanisms may have negative regulatory effects on T cell function that subsequently results in its functional impairment, despite the persistence of an activated T cell phenotype. This imbalanced response has two major consequences: (1) progressive depletion of T cell subsets due to deregulated production of pro-apoptotic cytokines; and (2) progressive loss of T cell function due to immune suppressive mechanisms associated with innate immunity [7,8].

As immunological effector mechanism, reactive oxygen species (ROS) generation occurs as by-product of oxygen (O_2) metabolism or by specialized enzymes also for neutralizing the ever-changing virulence of microorganisms. The ability of immune system to sterilize a site of infection, by rapid production of ROS (superoxide anions $O2^-$, hydrogen peroxide H_2O_2, hydroxyl radicals ·OH, hypochlorous acid HOCl, peroxynitrite $ONOO^-$, etc.) can keep organisms alive. The subjects, who could mount a robust immune response with vigorous yet coordinated ROS production, would be selected for survival [9,10].

During the HIV infection, ROS generation has been recognized as chronic, overlapping the antioxidant system and related to oxidative molecular damage, viral replication, micronutrient deficiency and inflammatory chronic response. These phenomena are all implicated in apoptosis and decreased immune proliferation [11-14] and included changes in glutathione (GSH), thioredoxin (TRX), superoxide dismutase (SOD), ascorbic acid (AA), glutathione peroxidase (GPx), tocopherol (TOC) and selenium (Se). In addition, peroxides (PO), carbonyls (CO), isoprostanes (isoP) and malondialdehyde (MDA) elevated levels were found in both pediatric and adult patients, naïve or treated with antiretroviral drugs [15-21].

As a result of mechanism interactions, different opportunistic and degenerative diseases arise with HIV evolution and contribute to cardiovascular disease, cancer, kidney and liver disease, osteoporosis, and cognitive impairment. Life expectancy of HIV infected individuals is significantly reduced in comparison with HIV-negative counterparts [22].

Some anti-HIV drugs classes are associated with lactic acidosis, hyperlipidemia, glucose intolerance, diabetes mellitus, fat redistribution, wasting, and atherosclerosis. These features could be related with OS increased by antiretroviral (ART) toxicity which indicate out mitochondria as toxic target. It could be produced by a common mechanism through mitochondria dysfunction which contributes to cell senescence and accelerated aging during ART treatment [23].

This review is intended to analyze original investigations and reviews focused on the effect of oxidative metabolism involved in HIV infection and related to comorbidities and accelerated aging in naïve and treated subjects. Finally, potential use of antioxidant in HIV naïve and treated patients trying to counteract oxidative deregulation is discussed. This work presents data from around 70 reviews and original research about HIV and oxidative stress, in naïve and antiretroviral treated patients. In an attempt to identify the relevant literature, a comprehensive search was performed using PubMed and Google Scholar. The following search terms were included in multiple combinations: oxidative stress, HIV and aging, oxidative stress, HIV, and antiretroviral, oxidative stress, HIV and antioxidants.

Further PubMed search was performed by selecting the "See all related articles" function, thus providing an additional extensive list of publications.

Further search was performed by manual scanning of reference lists of several review articles, as well as original investigations. Search was conducted from February to June 2014.

Although we believe most significant researches within this field were identified, we may have overlooked some investigations that are not included.

ROS generation, biological functions and oxidative stress in physiological condition

ROS are highly reactive molecules that originate mainly from the mitochondrial electron transport chain (ETC). Almost all cells and tissues continuously convert a small proportion of molecular oxygen into superoxide anion by the univalent reduction of molecular oxygen in the ETC. ROS are produced by other pathways as well, including the respiratory burst taking place in activated phagocytes, ionizing radiation's damage on cell membranes components, and as byproducts of several cellular enzymes including NADPH oxidases (Nox), xanthine oxidase (XO), and uncoupled endothelial nitric oxide synthase (eNOS). Furthermore, endoplasmic reticulum as essential organelle produces ROS [8,9].

ROS are linked to various physiological processes, in order to maintain a state of homeostasis; living organisms are striving to keep those highly reactive molecules under tight control with the help of an intricate system of antioxidants. Organisms continuously must confront and control the presence of both pro-oxidants and antioxidants. Balance of both is regulated and extremely important for maintaining vital cellular and biochemical functions [24]. This balance often referred to as the redox potential, is specific for each organelle and biological site, and any interference of the balance in any direction might be deleterious for cells and organisms. Changing the balance towards an increase in the pro-oxidant over the capacity of the antioxidant is defined as oxidative stress (OS). A variety of enzymatic and non-enzymatic antioxidants present in human cell become insufficient to avoid cellular ROS interaction and might lead to oxidative damage. Changing the balance towards an increase in the reducing power, or the antioxidant, might also cause damage and can be defined as reductive stress [24].

ROS are deeply involved in both arms of the immunological defense system, the innate and the acquired responses. ROS generation represents one of the first lines of defense mounted against invading pathogens and constitutes essential protective mechanisms that living organisms use for their survival. Some physiological roles in immune defense, antibacterial action, vascular tone, and signal transduction are argued. Transient over production of ROS in viral infections is generally related to pro-oxidant effect of inflammatory cytokines and/or polymorphonuclear leukocyte activation exerting also intracellular signal transduction cascades within cells and thereby upregulating the cellular response. In regulatory mode, it also contributes to decrease the cell activation threshold [25,26].

Every biological molecule which is present in our body is at risk of damage by free radicals. Such damaged cell molecules can impair cell functions or can lead to cell death ultimately resulting in disease. While ROS are known to function as harmful products of aerobic metabolism, especially when present at high concentrations, more recently low levels of these prooxidant molecules have been discovered to modulate transcription factor activation [27,28]. A growing number of molecules, such as many kinases, phosphatases, and transcription factors, in a wide range of signal transduction pathways, are thought to be modulated by intracellular redox status [27]. Moreover, a few transcription factors, such as the small GTP-binding protein Rac, are known to activate ROS-generating enzymes (e.g., NADPH oxidase) and produce ROS as a modulator of downstream molecules [29].

ROS regulation of transcription factors can occur by direct modification of critical amino acid residues, primarily through the formation of disulfide bonds, at DNA-binding domains or via indirect phosphorylation/dephosphorylation as a result of changes in redox-modulated signaling pathways.

Activation of AP-1 by *in vivo* adenovirus administration is redox-modulated and involves the participation of redox factor-1 (Ref-1). Ref-1 is a unique molecule that has two distinct enzymatic functions a DNA repair enzyme and a redox regulatory transcription factor [30].

Furthermore, it is believed that phosphorylation of IkB, inhibitory subunit of NF-kB, is a key step in NF-kB redox activation. ROS-mediated phosphorylation of IkB, leading to its ubiquitination and degradation, allows the NF-kB complex to be translocated to the nucleus and acts as a transcriptional activator [30].

At the cellular level, OS generated by ROS and ROS-modified molecules can influence a wide range of cellular functions. Direct consequence of OS is the damage to various intracellular constituents. For example, when lipid peroxidation occurs, changes in cellular membrane permeability and even membrane leakage can be manifested [28]. Oxidative damage to both nuclear and mitochondrial DNA has detrimental effects, leading to uncontrolled cell proliferation or accelerated cell death [31].

Apoptosis, also known as programmed cell death, plays an important role in all stages of an organism development. While there are controversies in the literature regarding the role of apoptosis in aging, age associated increase in apoptosis have been observed in several physiological systems, including the human immune system, human hair follicle, and rat skeletal muscle.

In the intrinsic apoptotic pathway, it has been shown that proteins of the mitochondrial permeability transition pore complex, which controls mitochondrial membrane potential, are the direct targets of ROS [31]. These proteins include the adenine nucleotide translocator in the inner membrane, the voltage-dependent anion channel in the outer membrane, and cyclophilin D at the matrix [32]. Prooxidants capable of induction of mitochondrial permeability potential include not only chemicals, such as t-butyl hydroperoxide and diamide but also lipid peroxidation products such as 4-hydroxynonenal [31]. Moreover, it has been increasingly recognized that oxidative damage to organelles, such as lysosomes and endoplasmic reticulum, stimulates crosstalk between these organelles and mitochondria and induction of apoptosis via intrinsic signaling pathway.

As molecular and cellular defects accumulate during life span of organisms, resulting in redox balance perturbation and ROS endogenous generation, it will influence further the regulation of a number of physiological functions (e.g., metabolism and stress tolerance) and, ultimately, accelerate aging process [33].

ROS can induce expression of several genes involved in signal transduction. A high ratio for GSH/GSSG is important for the protection of the cell from oxidative damage [34].

Disruption of this ratio causes activation of redox sensitive transcription factors, such as NF-kB, AP-1, nuclear factor of activated T cells and hypoxia-inducible factor 1, which are involved in the inflammatory response. Activation of transcription factors via ROS is achieved by signal transduction cascades that transmit the information from outside to the inside of cell. Tyrosine kinase receptors, most of the growth factor receptors, such as epidermal growth factor receptor, vascular endothelial growth factor receptor, and receptor for platelet-derived growth factor, protein tyrosine phosphatases, and serine/threonine kinases are targets of ROS. Extracellular signal-regulated kinases, JNK, and p38, which are the members of mitogen-activated protein kinase family and are involved in several cellular processes including proliferation, differentiation, and apoptosis, also can be regulated by oxidants [35].

Cellular defense system includes redox buffers such as the thioredoxin, NAD(P)H, ascorbic acid, and thiol-containing molecules including GSH, cysteine and protein thiols. Reductive cellular environment creates the electrochemical gradient necessary for electron transfer in oxidation-reduction reactions occurring in biological systems [32].

Elucidation of free radicals role in pathogenesis of different diseases has led to a medical revolution that is reassuring a new paradigm of healthcare.

Oxidative stress and its pathophysiological implication in aging and diseases condition

ROS association to aging has been well documented. Modern science and research have begun to unravel the molecular components of free-radical biology and biological inter-relationships of these components in mediating various disease processes for a better understanding and exploitation in biomedical/clinical sciences [32,35].

Redox-sensitive transcription factors and OS are often associated with origin and progression of many human disease states via four critical steps; membrane lipid peroxidation, protein oxidation, DNA damage and disturbance in reductive equivalents of the cell; which leads to cell destruction, and altered signaling pathways [8,9,31].

The unregulated condition has been implicated in various diseases like cancer, cardiovascular diseases, neurological disorders, diabetes, and aging. Different mechanisms are involved such as "mitochondrial oxidative stress" which can be exemplify by pro-oxidants shifting of the thiol/disulphide redox state and damage on glucose tolerance; "inflammatory oxidative conditions" and increased activity of either NADPH oxidase or xanthine oxidase-induced formation of ROS; or by both [32,33].

In physiological aging, mitochondrial dysfunction and low-grade inflammation occur. Loss of subcutaneous fat is common and may be due to various factors.

ROS are also tumorigenic by virtue of their ability to increase cell proliferation, migration, and survival, and by inducing DNA damage, all contributing elements to tumor initiation, promotion, and metastasis [36-38].

Immunosenescence generally refers to the well-known effects of aging on adaptive immune system function. The immune system of very old individual (>70 years of age) is characterized by increased population of terminally differentiated CD8+ cells effector (which appear to be resistant to apoptosis), reduced levels of naive CD8+ cells, a reversed ratio of CD4+ to CD8+ cells, increased T-cell activation, increased levels of many inflammatory markers, and reduced T-cell proliferation. Most of those outcomes are accelerated by the presence of chronic persistent infections [8,25,36,37].

It is suggested that a reduction in elevated oxidant levels found in cytoplasm upon any infection may be attained through antioxidant treatment. Subsequently, NF-κB would remain bound to IκB and wasn't unable to pass through the nuclear membrane to transcribe genes. Glutathione, a major intracellular thiol, has been associated with inhibition of NF-κB by free radicals scavenging in cytosol [10].

Aging is an inherently complex process that is manifested in organisms at genetic, molecular, cellular, organ, and system levels. Although the fundamental mechanisms are still poorly understood, a growing body of evidence points toward ROS as one of the primary determinants of aging.

"Oxidative stress theory" holds that a progressive and irreversible accumulation of oxidative damage caused by ROS impact on critical aspects of aging process and contribute to impaired physiological function, increased incidence of disease, and a reduction in life span [30,31,33,34].

Even with a well-described definition and a familiar set of characteristics, aging remains one of the most poorly understood of all biological phenomena, due in great part to its inherently complex and integrative nature, as well as the difficulty in dissociate the effects of normal aging from those manifested as a consequence of age-associated disease conditions [33].

As a result, while disciplines ranging from physiology and genetics to epidemiology and demography have developed a large number of theories that attempt to explain why we age [24,39], definitive mechanisms to explain the process across species and systems remain equivocal.

OS in a physiological setting can be defined as an excessive bioavailability of ROS, which is the net result of an imbalance between production and destruction of ROS (with the latter being influenced by antioxidant defenses) [38]. However, despite a large body of evidence supporting notion that ROS are produced in cells and can

inflict damage, a causal link between ROS increase and aging has still not been clearly established [7,8,10,33,36-41].

In recent years, several related theories containing ROS approximation have also been proposed.

Evidences suggesting that mitochondrial DNA damage is increased with aging support mitochondrial theory of aging in recent reports [39,40]. Another consideration is cellular senescence theory of aging emphasizes the importance of cellular signal responses to stress and damage. Those signaling responses subsequently stimulate pathways related to cell senescence and death [42,43]. At the cellular level, ROS have been found to modulate various signals leading to accelerated mitogenesis and premature cellular senescence [25,28]. An additional theory that has gained more attention in recent years is molecular inflammatory theory of aging, whereby activation of redox-sensitive transcriptional factors by age-related OS causes the upregulation of proinflammatory genes expression. As a result, various proinflammatory molecules are generated, leading to inflammation processes in various tissues and organs [37,43].

Oxidative stress in HIV natural infection

Several researchers have demonstrated that humans infected with HIV are under chronic OS characterized by perturbations of the antioxidant system [15-21].

Immune activation is increased in HIV-infected patients because of residual HIV infection; and other viruses, such as cytomegalovirus reactivation; increased bacterial translocation; and altered gut permeability. Markers of bacterial translocation, such as lipopolysaccharide, and of innate immunity activation, such as sCD14, together with indications of elevated immune activation, have been linked to neurocognitive and cardiovascular comorbidities and to mortality [14,25,35,44].

HIV itself may also cause mitochondrial toxicity and OS contributing to lipoatrophy also during natural infection [45-48].

Initial HIV infection, evaluated by the nadir CD4 cell count, has also been related to the occurrence of different comorbidities. This could be explained, at least in part, by persistent low-grade viral replication in reservoirs. Macrophages participate in HIV reservoir and are resident in a number of affected tissues, such as adipose tissue, liver, bone, vascular wall, and brain. If infected macrophages are activated and release both, ROS and proinflammatory cytokines inside these tissues they could participate on local inflammation and related redox-mediated signals of transcription factor activation. That activation in turn could mediate other virus replication and infection instauration [11,14].

“Chronic T cell activation” hypothesis is supported by observations series of which collectively suggest that increased T cell activation expression markers, such as CD38 and HLA-DR. Those also correlate with disease progression and CD4 T cell depletion better than plasma virus levels which may ultimately lead to their malfunction, exhaustion, and death.

Persistence of HIV particles provide a chronic stimulus for mechanisms normally associated with innate immune responses. That chronic innate immune activation suppresses functional T cell-mediated adaptive immune responses while sustaining the activated phenotype of T cells with disruption of lymphoid architecture and multifactorial immune suppression, including decreased CD4 and CD8 T cells [14,25,26], which resembles many of the alterations observed during HIV infection.

Cells of myeloid lineage including monocytes, macrophages and dendritic cells play an important role in the initial infection and therefore contribute to its pathogenesis. This is mainly because these cells are critical immune cells responsible for a wide range of both innate and adaptive immune functions [37].

In previous work, it has been demonstrated also that viral Tat protein liberated by HIV-1-infected cells interferes with calcium homeostasis, activates caspases and induces mitochondrial generation and accumulation of ROS, important events in the apoptotic cascade of several cell types [11,14]. Those aspects contribute to the spectrum of malignancies associated to HIV infection.

Also mitochondrial dysfunction and its impact on chronic inflammation during HIV natural evolution have been suggested [45-47].

Once HIV has established as chronic infection, newly produced virions interact preferentially with cells expressing CD4. CD4+ T cell subset depletion in HIV/aids patients is the most dramatic effect of apoptosis mediated by redox abnormalities and induction of Fas/APO-1/CD95 receptor expression. High proportion of lymphocytes expressing Fas was shown to be elevated in HIV –infected individuals. Generally these studies demonstrated that the proportion of Fas-expressing cells increases with disease progression. Increased Fas expression in CD4+ lymphocytes was found by some investigators and others were found in both CD4+ and CD8+ T cells [50,51].

Therefore, if we consider that increased immune activation and long-term chronic inflammation are major players in the aging process in the general population, it is obvious that these processes are more prevalent in HIV-infected patients than in the general population, even when the infection is well controlled. HIV-infected patients will be more prone to develop, in advance, age-related diseases [22,35,52].

Oxidative stress during antiretroviral treatment

Most significant advance in medical management of HIV infection has been the treatment of patients with antiretroviral (ART) drugs. In latest years, a relevant decline of morbidity and mortality of HIV infection has been observed due to the use of combined therapy named High Active Antiretroviral Therapy (HAART) [53,54]. This treatment can suppress HIV replication to plasma HIV RNA undetectable levels (<50 copies/mL) and improves the immune function in patients, especially CD4 T lymphocytes subsets. Also HAART can successfully prevent aids-related morbidity and mortality, resulting in increased lifespan of HIV-infected patients. In turn, the course of HIV disease has evolved from a universally fatal infection to a manageable chronic illness [55,56].

However, it has become evident that patients taking otherwise effective antiretroviral drugs remain at increased risk of non–aids-related morbidity and mortality. Many of these conditions are classically associated with normal aging process but appear to be occurring at an earlier age in HIV-infected persons. These conditions include premature onset of cardiovascular disease, neurocognitive disease, bone disease, and cancer [57-60].

Thus, the emerging picture of HIV-infected patients’ health that are being successfully treated with antiretroviral therapy in terms of viral suppression is as follows: lifespan is not normalized by antiretroviral treatment; the risk of age-associated diseases is higher than expected;

inflammation remains elevated and predicts age-associated events; and CD4+ count often remains low and predicts also age-associated events [60].

Hepatic toxicity from ART was reported early in epidemic, and recent reports continue to point out the mitochondria as toxic target and OS as a consequence of therapy [61-66]. Since HAART does not completely eliminate HIV, it is likely that the final outcome of treatment will depend not only on the effective reduction of viral load (VL), but also on recover ability of immune system and residual virus control [60]. Previous studies have suggested a role of OS in HIV replication stimulation, immunodeficiency development and also in treatment consequences, this last contributing to an organism damage vicious cycle [65].

The prevalence of insulin resistance and type II diabetes are increased in treated patients.

OS interaction events in disease progression have become intricate in HIV-infected patients with HAART. Virus control with HAART may not, as one might expect, reduce OS levels, on the contrary [61-63].

Combinations of anti-HIV drugs containing Nucleoside Reverse Transcriptase Inhibitors (NRTI) are generally used during HIV infection as clinical guidelines recommended. Additional adverse effects and/or regimen adherence difficulties have serious consequences such as loss of serum HIV suppression, development of drug-resistant HIV strains, and increased probability of opportunistic illness develop [60]. NRTI are associated with lactic acidosis, hyperlipidemia, glucose intolerance, diabetes mellitus, atherosclerosis, fat redistribution and wasting syndrome; all of these could be related to increased OS and its toxicity [31,55,64]. Phophorylated-NRTI mitochondrial toxicity may amplify some of the pathophysiologic and phenotypical events in infection.

Picture of immunosenescence closely resembles observations in patients receiving long-term antiretroviral therapy, suggesting that ongoing HIV-related immune dysfunction and inflammation during antiretroviral treatment underlies premature aging in HIV-infected persons [52,59].

Collectively, these observations support an emerging relation that posits residual inflammation and suboptimal CD4+ count gains with a hypercoagulable state resulting from several ongoing factors. These include residual viral replication, persistent viral expression, the loss of immunoregulatory cells that should dampen immune activation, increased lymphoid fibrosis, and microbial translocation. Other contributed factors to ongoing inflammation include chronic infection with CMV, hepatitis C virus (HCV), or hepatitis B virus (HBV), and thymic dysfunction. How these factors combine to affect CD4+ cell gains, immune function, and early morbidity and mortality is not known [59,60]. The phenomenon of ongoing viral production under suppressive antiretroviral therapy is also being investigated. Use of a super-sensitive assay in a University of California San Francisco cohort of patients achieving undetectable viral load on a standard assay during antiretroviral treatment showed that over years of follow-up, virus was detectable at approximately 80% of the measurement time points [67]. This evidence of ongoing viral production, and perhaps replication, suggests that adding another drug to current regimens may be a rational strategy for further reducing viral expression and potentially reducing inflammation.

The study and enhancement of surrogate markers of HIV disease progression, including OS indexes, continues to be an important area of research particularly with the advent of therapies that claim to halt or slow the process of immunological decline [68-72]. Additional markers and combinatorial analysis that add value to T-CD4+ lymphocyte subset would therefore be useful i.e. in the decision of when to start/ stop or change therapy.

Considering factors related to the virus and the treatment, others environmental factors could also prematurely induce aging, such as smoking, sedentary lifestyle, low-nutrition diet and resulting fat gain, or drug use. Even if difficult to do, these factors need to be aggressively taken in count.

However, recent studies have indicated a rise in prevalence of HIV-1-associated neurocognitive disorders and related side effects following the era of HAART [57].

Previous studies found ART side effects with simultaneous lowered cellular proliferation and directly affected mitochondrial function in a reversible fashion by decreasing mitochondrial membrane potential and increasing superoxide production. Those events could impact on different biological manner to organisms [60,73].

ROS elevated levels in HAART previous studies are suggested thereby provoking OS scale, which has already been well established to occur since 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 also activate HIV transcription pathways and promote cell death.

Some studies and clinical research found that some ART toxic effect could partially be reversed by previous and concomitant antioxidant treatment [74,75].

Since antioxidant treatment has contributed to suppress some of pro-oxidant effects of antiretroviral treatment, antioxidants in combination with HAART may impact on others like neurocognitive disorders, additional opportunistic infections associated with HIV-1 infection, and reducing viral load [76,77].

Integrative analysis

Researchers at the Modena University metabolic clinic recently reported a higher prevalence of age-related morbidities (cardiovascular disease, hypertension, renal failure, bone fracture, and diabetes mellitus) in HIV-positive individuals. These morbidities occurred at an earlier age, and that polypathology was more frequent than in HIV-negative controls [35].

Substantial evidence from various researches provides a strong link between aging and OS, also related to antiretroviral effect and OS in HIV infection. It is important to note that data from diverse experiments suggest alternatives to the OS theory of aging and have produced results implicating other causal factors for changes in aging processes, such as a lowering of body temperature and associated hypometabolic state, telomerase shortening and alterations in gene expression [78,79]. These factors have been associated with an increased production of prooxidants and induction of OS. Despite some contradictory results, evidences produced during the past decade have provided valuable information on biological systems that impact on aging.

Recently, several studies have demonstrated that young organisms are capable of initiating an array of regulatory processes in response to OS, including the activation of stress-gene expression and

modification of stress-responsive signal transcription pathways. In contrast, there is compelling evidence that these regulatory processes are altered in old organisms [80,82,83].

Therefore, stress-induced cellular injury appears to be exaggerated with advancing age [33,34].This failure to effectively respond to cellular challenge has been postulated to contribute to a reduction in stress tolerance and the development of various pathologies and diseases. Factors such as these are likely to contribute to the cellular dysfunction and reductions in stress tolerances that are hallmarks of aging [10,39].

Telomeres cap the ends of chromosomes and consist of hexameric TTAGGG repeats and the protective 'shelterin' protein complex [79].Telomerase is a ribonucleoprotein consisting of a reverse transcriptase (TERT) and its RNA moiety (TERC). An 'end replication problem' causes telomeres to shorten during each replication cycle to yield persistent DNA damage and growth arrest (senescence) and limited regenerative capacity of tissues [80,81]. Its expression causes cellular immortality. Although shortening and/or damage to telomeres is associated with proliferative arrest of cells in vitro, it remains unclear how accurately these diseases recapitulate the processes of tissue aging in humans. All of these enzymes exhibit some evidence of reverse transcription [81].

More recently, an inhibitory effect of NRTI phosphates on human peripheral blood mononuclear cell TERT indicated that different phosphorylated NRTI (including lamivudine, abacavir, zidovudine, emitricitabine and particularly the nucleotide analog tenofovir) were inhibitors of TERT. TERT activity is vital to telomerase functions and because of the key role of telomerase in aging theories, it was hypothesized that this inhibition could contribute to the premature aging in HIV/AIDS, and help promote the looming epidemic of premature aging in that population [59,78].

Whether HIV itself or the comorbidities associated are most responsible for frailty and other geriatric symptoms is unclear, but it is widely agreed that inflammation related to HIV, other infections such as CMV, and chronic conditions or lifestyle factors plays a major role in driving more rapid aging and increased morbidity and mortality [52,82].

Future perspective

HIV infection results in prolonged continuous stimulation of pDC, which is maintained beyond the acute-early phase and throughout the infection evolution. This uncontrolled chronic innate immune activation may lead to a deregulated adaptive immune response, characterized by functionally impaired T cells and increased levels of phenotypic markers of activation [52].

In this context, antioxidants may produce immune modulation and can be used for prophylaxis or therapy of certain diseases along with the mainstream therapy.

Supplements of exogenous antioxidants can act directly to quench the free radical or free radical reactions, prevent lipid peroxidation and also boost the endogenous antioxidant system and hence deliver the prophylactic or therapeutic activity. Many novel approaches and significant findings have come to light in the last few years [74].

Several clinical studies and basic research have shown that depletion of endogenous enzymes in certain pathological condition may be mitigated by the use of exogenous antioxidants. Sustained interest in the antioxidants use for human disease prevention and management offers opportunities for newer and better therapeutic entities development with antioxidant activity [72]. Parallel identification, development of natural or synthetic antioxidants and their suitable formulation can provide enormous scope for better treatment of several diseases. On-going studies continue to produce epidemiological evidence suggesting that antioxidant rich foods or antioxidant supplements reduce the risk of chronic disease and promote wellness. Several factors like poor solubility, inefficient permeability, and instability due to storage of food, first pass effect, and gastrointestinal degradation need to be improved. Antioxidants are to be developed as drug targets. Therefore modification in dosage form, physicochemical characteristics, biopharmaceutical properties and pharmacokinetic parameters are important to consider in drug development process. Therapeutic and nutritional fields progression related antioxidants has not only been punctuated by some successes, but by various spectacular failures as well [74]. Today, varied diet (natural and healthy food with antioxidant activity) remains the best advice in garnering the benefits of antioxidants and the many other bioactive components available from food. Concurrently, it is also necessary to avoid oxidant sources (cigarette, alcohol, exposure of chemicals, stress, etc.) to keep on healthy [36,39]. Continued research is needed to identify the therapeutically important constituents and dietary components that have antioxidant action, quantify these components and assess their potential for in vivo antioxidant activity and their interactions with target tissue. It is also imperative to reveal the relationship between intake of antioxidants and their dose-dependent functional effects. In the light of present understanding the appropriate role for antioxidants in human health will become more apparent. As clinical evidence emerges and our understanding of genomic differences improves, the specific role of antioxidants with variation of species or genetic differences need to be identify. The future holds great promise for discoveries of new knowledge about free radical biology and antioxidants, and for turning this basic knowledge into practical use for ensuring a healthy life [9,10]. Developing coordinated research collaborations involving biomedical scientists, phytochemical researchers, nutritionists and physicians is a critical step evaluating the impact of antioxidants in health and disease for the coming decades

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 and its treatment [83,84]. Furthermore, comparative studies may serve to identify co-factors that contribute to the development of aids. With a better understanding of the co-factors related in disease evolution, there is tremendous hope of improved diagnosis and treatment to perhaps alter the course of HIV infection and prevent the onset of aids.

Acknowledgment

This work was partially supported by the Ministry of Public Health, Republic of Cuba (Project No. 131094). Special thanks to Dr. Daniel Limonta who critically revise manuscript.

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