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# Oxidants and Antioxidants in Medical Science

## Review Article

### Physical activity as antioxidant and palliative beneficial option in human immunodeficiency virus infection

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#### Key Words

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#### Abstract

Human immunodeficiency virus (HIV) infection is characterized by chronic activation of immune system as a consequence of persistent circulating virus. Evidences for *in vivo* oxidative stress, as an imbalance between oxidant and antioxidant status, were reported to arise during infection evolution. The high active antiretroviral therapy (HAART) has impact on the decline of mortality and morbidity associated to HIV infection but clinical and basic evidences of toxicity are still reported. With increased longevity HAART is prolonged and due to resistance against antiretroviral therapy (ART) new aspects are developed in order to manage HIV infection. In this context, effective non-pharmacological measures, such as regular physical activity have been used. Updates on research confirm that physical activity could mitigate the deleterious oxidative damage by stimulating resistance to oxidative challenge. This paper briefly reviews the wide pathophysiological pathways related to HIV infection, oxidative stress and immune dysfunction and then discusses in detail the benefits of training schedule for infected HIV infected individuals. This constitutes a complementary strategy promoting beneficial pleiotropic effects.

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## INTRODUCTION

Aerobic respiration and oxygen-dependent biosynthesis have significant advantage for life. During both processes free radical and reactive oxygen species (ROS) generation play a major role in the evolution of plants and animals as an essential part of the basic biology and physiology [1]. ROS generation occur as by-product of  $O_2$  metabolism or by enzymes for neutralizing the everchanging virulence of micro-organisms as nicotinamide adenine dinucleotide phosphate (NAPDH)-oxidase and catalase (CAT). The ability of the immune system to sterilise a site of infection by rapid production of ROS, such as superoxide anions ( $O_2^{\bullet-}$ ), hydrogen peroxide ( $H_2O_2$ ), hydroxyl radicals ( $\bullet OH$ ), hypochlorous acid (HOCl) and peroxynitrite ( $ONOO^-$ ), can keep the organism alive. ROS also are involved in xenobiotic detoxification. The subjects, who could mount a robust immune response with vigorous yet coordinated ROS production, would be selected for survival [2, 3]. ROS could mediate two consequences in organisms: at low

levels regulate proliferative response activate specific signal transduction pathways [4], and in certain conditions avidly interact with proteins, lipids and nucleic acids. The latter irreversibly alter structure or functions of biomolecules resulting in damage to cellular components [2, 5, 6]. Both of these consequences significantly impact on physiology and/or the development of pathophysiological conditions [4, 7, 8].

Human immunodeficiency virus 1 (HIV-1), identified in 1983, remains a global health threat responsible for a worldwide pandemic. The HIV infections evolve to acquired immune deficiency syndrome (AIDS) accompanied by opportunistic infections caused by protozoa (*Pneumocystis jirovecii*, *Cryptosporidium*), bacteria (*Toxoplasma*, *Mycobacterium avium*, *Nocardia*, *Salmonella*), fungi (*Candida*, *Cryptococcus performans*, *Coccidioides immitis*, *Histoplasma capsulatum*) or viruses (cytomegalovirus, herpes simplex, varicella zoster). Also tumors (lymphomas, Kaposi sarcoma, cervical carcinoma), encephalopathy,

wasting syndrome, and severe metabolic and immunological dysfunctions appear during AIDS [9, 10]. Several reports worldwide have demonstrated that humans infected with HIV are under chronic immune activation characterized by increased generation of ROS and perturbations of the antioxidant defence system. Oxidative stress has been detected in many tissues of HIV infected individuals using different biochemical markers and diverse biotechniques. The oxidative stress characterization has been made in populations from several countries and different risk groups using case and control, cross sectional and interventional studies [11-21]. During the infection course the imbalance in redox status is related to oxidative molecular damage, viral replication, micronutrient deficiency and inflammatory chronic response; all of them implicated in cellular apoptosis and decreased immune proliferation [22]. Those included changes in glutathione (GSH), thioredoxin (TRX), superoxide dismutase (SOD), ascorbic acid (AA), glutathione peroxidase (GPx), tocopherol (TOC) and selenium (Se). In addition, peroxides, isoprostanes and malondialdehyde (MDA) elevated levels were found in both pediatric and adult patients.

Several advances have been made in treating AIDS since the introduction of the highly active antiretroviral therapy (HAART) in 1996. AIDS pandemic has stabilized on a global scale in 2008 with an estimated 33 million people infected worldwide [23]. In more recent years, as the number of available anti-HIV drug classes as well as individual drug potency and tolerability has increased, many patients can expect to suppress viral load below the limit of detection in clinical practice, currently defined as 50 copies per milliliter of blood [24, 25]. However, with very sensitive methods, a residual viremia is still detected in patients received HAART. Moreover, HIV RNA returns to a measurable plasma level in less than two weeks when HAART is interrupted. These observations suggest that even long term suppression of HIV-1 replication by HAART cannot totally eliminate HIV-1, the virus persists in cellular reservoirs because of viral latency, cryptic ongoing replication or poor drug penetration [26].

HAART does not completely solve the immune and metabolic alterations during HIV infection either. 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 illness progression [24]. 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 oxidative stress increased by antiretroviral therapy (ART) toxicity which point at the mitochondria

as toxic target. It could be produced by a common mechanism through mitochondrial dysfunction [27-29].

Physical activity can be defined as any planned structured actions that lead to increase in energy expenditure and heart rate [30]. There are different modes in relation to intensity (aerobic and anaerobic), to muscle contraction (isometric, concentric and eccentric) and to frequency (acute and chronic). During physical activity ROS can be produced mainly, but not exclusively, by the following mechanisms: reactive transport chain, ischemia/reperfusion and activation of endothelial xanthine oxidase (XO), inflammatory response, and autooxidation of catecholamines [31, 32]. Physical activity also leads to the up-regulation of the antioxidant defence mechanism, which helps minimize the oxidative stress effects [33, 34].

Over the past decades, there have been multiple epidemiological studies showing the relationship between physical activity and overall health in non-HIV populations [30]. Physically active adults are less susceptible to viral and bacterial infections when compared with sedentary adults, suggesting that physical activity improves overall immune function [33, 35-40]. This review is intended to analyze original investigations and reviews focused on the effect of physical activity and oxidative metabolism involved in HIV infection evolution.

The article presents data from more than 100 articles separated by reviews, original researches about aerobic and resistance exercise modes and their impact on human status with HIV and non-HIV condition. 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 physical activity", "oxidative stress, HIV, and aerobic exercise", "oxidative stress, HIV and resistance exercise". Further PubMed searching was performed by selecting the "see all related articles" function, thus providing an additional extensive list of publications. Further searching was performed by manual scanning of the reference lists of several review articles as well as original investigations. The search was conducted between January and June 2013. Although we believe to have identified the bulk of investigations within this area by using the above techniques, admittedly, some investigations may have escaped our search and are therefore not included. We apologize to those authors whose work is not cited here.

Finally, potential use of physical activity as antioxidant in HIV naive and treated patients to decrease the effects of some comorbidities such as lipodystrophy by increasing muscle mass, decreasing obesity and overall adipose tissue, and improving immune function by increasing T cells is discussed [41].

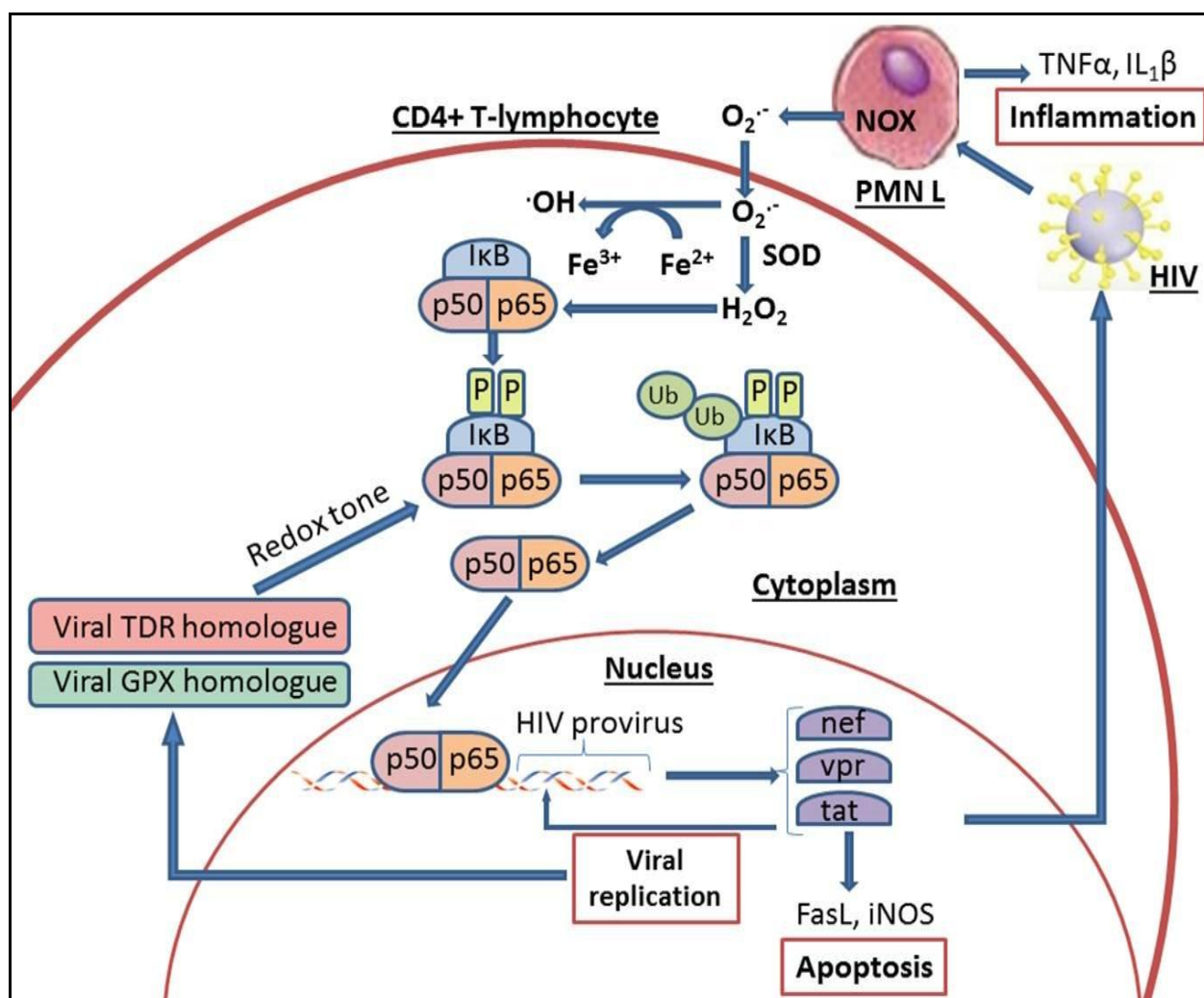
# HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND OXIDATIVE METABOLISM: RELATION TO CHRONIC INFLAMMATION, VIRAL REPLICATION AND APOPTOSIS

Oxidative stress, induced by the increased production of ROS, may play a critical role in the stimulation of HIV replication, the development of immunodeficiency and the degenerative evolution of individuals contributing to the HIV progression. Engagement of HIV envelope with T cell receptor mainly through CD4 generate signals that lead to an increase in free intracellular calcium, which mediate protein kinase (PK) phosphorylation and activation of NADPH oxidase [42]. In this aspect NADPH oxidase enzyme in phagocytic cell (NOX2, gp91<sup>phox</sup>) is critical in host defence against pathogens. This enzyme contribute to an excessive ROS production which may be related to

an increased activation of polymorphonuclear leukocytes or influenced by the pro-oxidant effect of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) produced by activated macrophages during the course of HIV infection [43].

In a previous report oxidative stress was shown to be related to the constitutive production of H<sub>2</sub>O<sub>2</sub> by neutrophils at all stages of the disease, even in the early stages when the number of CD4<sup>+</sup> T cells is still high (Fig.1) [44].

In the literature, disturbs in the metabolism of GSH, TRX, Se, TOC and ascorbic acid on seric and/or tissue antioxidant concentrations are shown. Increased peroxides, isoprostanes, MDA and carbonyl concentrations, and altered GPx, CAT and SOD activities have been reported also [11-13, 15-21].



**Figure 1.** Molecular pathways between HIV, T CD4<sup>+</sup> lymphocyte, polymorphonuclear cell, inflammation mediators and oxidant-antioxidant species. NOX, NADPH oxidase; PMNL, polymorphonuclear leukocyte; SOD, superoxide dismutase; NF- $\kappa$ B (p50p65), nuclear factor of transcription; I $\kappa$ B: inhibitor of transcription factor; HIV: human immunodeficiency virus; nef: HIV regulatory gene; vpr, HIV regulatory gene; tat, HIV regulatory gene; FasL: Fas ligand; iNOS: inducible nitric oxide synthase; TDR, thioredoxin reductase; GPX, glutathione peroxidase; TNF $\alpha$ , tumor necrosis factor- $\alpha$ ; IL $_1\beta$ , interleukin 1- $\beta$ ; Ub, ubiquitine.

These findings could be explained in part by several contributing mechanisms such as: (1) chronic inflammatory activation of immune system; (2) low intake of antioxidant or their precursors from diet in relation to requirements; (3) malabsorption; (4) enhanced cysteine metabolism in peripheral tissues; (5) down regulation synthesis of antioxidant enzymes by viral protein as Tat; and (6) virally encoded regulatory proteins. All of these aspects are influenced by consequent loss of sulphur-group that may account for GSH and antioxidant deficiency during HIV infection. Abnormally high levels of ROS as a consequence of chronic immune system activation by HIV infections could lead to a decline of antioxidant defence molecules and accumulative damage of cellular components generating augmented lipid peroxidation products, oxidized proteins and altered DNA sequences. As a consequence of antioxidant depletion the detoxification capacity of reactive metabolites is reduced and this is probably connected to the peroxides' high levels detected and drug side effects observed in HIV+ patients [7, 45, 46].

Peroxides and aldehydes generated are not only passive results of oxidative reactions, but also cytotoxic products. Both increased and decreased levels of ROS and antioxidant enzymes have been reported in different disease states in which an enhancement of ROS production could be a cause or a consequence of the disease. There is thus experimental evidence that recognize different metabolic events which occur in relation to HIV infection. As a consequence occurs the consumption of antioxidant components, thus contributing to the oxidative stress [12, 44, 47].

Nuclear factor-kappa B (NF- $\kappa$ B) is involved in the early transcription of HIV-1 [14]. NF- $\kappa$ B is bound to inhibitor of kappa B (I $\kappa$ B) in the cytoplasm in its active form, but various factors, such as TNF- $\alpha$  and ROS can cause the release of NF- $\kappa$ B from factor I $\kappa$ B, and NF- $\kappa$ B translocates to the nucleus and binds to DNA. GSH is a major intracellular thiol, which acts as a free radical scavenger and is thought to inhibit activation of NF- $\kappa$ B. TRX is related to redox regulation of I $\kappa$ B also [4, 47]. Thus, ROS may potentially be involved in the pathogenesis of HIV infection not only through direct effects on cells instead off through interactions with NF- $\kappa$ B and activation of HIV replication too (Fig.1).

NF- $\kappa$ B pathway activation is a key indicator of cellular responses and central to signals transmitted through a myriad of receptors. NF- $\kappa$ B activation by multiple innate immune receptor families, such as toll-like receptors (TLR), retinoic acid-inducible gene (RIG)-I-like receptors (RLR) or nod-like receptors (NLR), is a major mechanism for induction of inflammatory and immune responses. TLR, RLR or NLR recognition of viral single or double stranded viral RNA, initiates

almost immediate anti-viral responses that elicits and drives adaptive anti-viral immunity gene sets related to the inflammatory process [2, 43].

Some viral proteins interfere with host T cell functions and promote rampant virus replication. Taylor *et al* [48] pointed out several regions of HIV-1 with the potential to encode selenoproteins, a viral GPx homologue and a viral TRX reductase (TDR) homologue. These could be contributing to Se host deficiency. Host Se status is based on the antioxidant properties of amino acid selenocysteine, the catalytic center of selenoenzymes as GPx family. This enzyme regulates biologic oxidative homeostasis by neutralizing metabolically produced ROS [48, 49].

The viral selenoproteins have been suggested could be involved in regulation of NF- $\kappa$ B controlling HIV replication. Viral TDR homologue expression could be contributed to activation of NF- $\kappa$ B while reducing cellular GPx levels via Se sequestration. Whereas the viral GPx homologue, as a late expressed gene, would be expected to deactivate NF- $\kappa$ B by decreasing oxidant tone. Notable another viral TDR homologue action is in the synthesis of deoxyribonucleotides, via ribonucleotide reductase, enhancing stimulation of proviral DNA synthesis activities [47]. These Se-deficient conditions found in HIV individuals contribute to oxidative stress leading to impaired immune systems and RNA viral mutations, which can modify its virulence and pathogenic effects [4] (Fig.1).

*In vivo* studies have shown that oxidative stress might lead to immunodeficiency at cellular and humoral levels. The role of oxidative stress in lymphocytes depletion during HIV infection may result from different mechanism such as impairment of proliferation, as suggested in animal models, but also from apoptosis [42, 47]. Several investigators have proposed that apoptosis, could be initiated by oxidative stress, and is the direct cause of lymphocyte lost in patients infected with HIV. These investigations provide evidences that infection-induced oxidative stress contributes to CD4+ T lymphocytes depletion by increasing their rate of apoptosis, particularly Fas/APO-1/CD95 induced apoptosis. The pro-oxidant stimuli can also increase the pathogenic effects of HIV and is associated with a progressive increase of plasma viral load too [1, 3, 50]. The proportion of lymphocytes expressing Fas was shown to be elevated in HIV-infected individuals in relation to diseases progression. The increased Fas expression was found by some investigators to be in CD4+ T lymphocytes and by others in both CD4+ and CD8+ T cells [2, 42].

In previous work, it has been demonstrated that viral Tat protein released by HIV-1-infected cells interferes with calcium homeostasis. Also interferes in activation of caspases and induces mitochondrial generation with

accumulation of ROS, all being important events in the apoptotic cascade of several cell types [51]. Observations showed that free ROS-induced apoptosis by a non cytokine/mediated mechanism was significantly enhanced in HIV-infected subjects even in the very early stages after infection.

### **HIV INFECTION, HAART AND REDOX ALTERATION**

The combined HAART varies depending on therapeutics objectives, cost and availability on the market. In the latest years, a relevant decline of the morbidity and mortality of HIV infection has been observed due to the use of HAART. It have led to a decrease of viral load, and a quantitative and qualitative improvement of the immune functions in patients, specially CD4<sup>+</sup> T-lymphocyte count, having as a consequence a decrease of infectious complications and a global clinical improvement [9, 10].

HAART consists of different combinations of viral inhibitors such as: nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), fusion inhibitor, co-receptor inhibitor, and integrase inhibitor. The main reasons for combining different anti-HIV drugs in the treatment of AIDS as **(i)** synergy, **(ii)** lower toxicity, and **(iii)** prevention of drug resistance development have remained and are used as clinical guidelines recommended [23, 25].

On the other hand, HAART does not completely solve the immune and metabolic alterations during HIV evolution. Instead hepatic toxicity from zidovudine (AZT), didanosine (ddI), and zalcitabine (ddC) was reported early in the epidemic. Recent reports continue to point at the mitochondria as toxic target for NRTI and also the activation of the P450 hepatic system by PI [27, 29, 52].

Mitochondrial toxicity as an important side effect of antiretroviral therapy in HIV infection is linked pathophysiologically to clinical and experimental settings with long-term significance. Clinical and basic evidences of HAART mitochondrial toxicity in relation to: **(1)** energy deprivation secondary to mitochondrial (mt)DNA depletion; **(2)** oxidative stress producing structure damage and altered functions; and **(3)** mtDNA mutations resulting from oxidative mtDNA damage, aberrant mtDNA replication and, altered mtDNA transcription are reported [27, 28, 52].

### **Mitochondrial dysfunction hypothesis and oxidative stress during HIV infection and antiviral treatment**

Mitochondria are indispensable to eukaryotic cells due to their extensive involvement in critical metabolic processes. Mitochondria posses a double-membrane structure and contain their own genome along with

their own transcription, translation, and protein assembly machinery. As such, they are able to maintain genomic independence from the nucleus. However, most proteins in the organelle are encoded by nuclear (n)DNA and imported into it. The generation of mitochondria is mainly influenced by extra-mitochondrial transduction signal [1, 53]. The most well-known and best-characterized function of mitochondria is the production of adenosine triphosphate (ATP) through oxidative phosphorylation. The process is carried out by the respiratory chain which contains 87 polypeptides encoded by both mtDNA and nDNA. This result the unique biochemical process achieved by a well coordinated effort of the products from two separate genomes. Glycolysis can also generate ATP and provides a compensatory mechanism when the phosphorylation becomes inefficient as a consequence of defect in respiratory chain. The normal electrons flow could be compromises as a consequence of certain mtDNA mutation. It can lead to an increase of bifurcation and ROS generation [53].

DNA polymerase- $\gamma$  (DNA pol- $\gamma$ ) is the eukaryotic mtDNA replication enzyme. It is encoded by nDNA and contains two subunits. The DNA pol- $\gamma$  activity is inhibited by NRTI used commonly during antiviral treatment of HIV/AIDS patients. This inhibition produces mtDNA depletion which leads to a decreased energy production. This event is cumulative and toxic manifestations increase with duration of exposure [51].

NRTI have been divided into classes of mtDNA replication inhibitors according to the relative importance of DNA chain termination, or internalization of the analogue into nascent mtDNA and substitution for the natural base. Competition with the native nucleotide and NRTI at the nucleotide binding site of DNA pol- $\gamma$  appears to be a crucial event with potentially hazardous consequences [28, 52]. Deletion mutants (truncated mtDNA templates) may be replicated more quickly and efficiently than native mtDNA counterparts owing to enzyme activity. Abundance of defective mtDNA may reach a threshold of energy depletion like that of heritable mitochondrial illnesses, including those that show mtDNA depletion. [27, 28, 52].

Oxidative stress as a consequence of mitochondrial toxicity may amplify some of pathophysiological and phenotypic events in NRTI toxicity. Mainly oxidative stress is implicated in mutations of mtDNA based on: **(1)** lack of known repair enzymes for mtDNA error excision; **(2)** lack of histones protecting mtDNA; and **(3)** a subcellular proximity of mtDNA to oxidants [51]. The results of these events are extensive strand breakage and degradation of deoxyribose.

Hydroxyl radical's oxidation to mtDNA results in

formation of oxidized base 8-hydroxydeoxyguanosine (8-OHdG), leading to GC → AT transversions unless repaired. It can lead to mispairing and point mutation. Although most of the components of a mitochondrial base excision repair system have been identified, it is unclear how efficiently this repair removes the wide spectrum of adducts that may occur from oxidative damage. Mitochondrial oxidative damage was supported indirectly by the co-existence of MDA on or near the inner mitochondrial membrane. This last could lead to cross-linking, deletion errors in transcription or mtDNA polymerization [2, 28].

An accumulation of mtDNA defects may result in myocytes with oxidative capacity that vary from normal to severely impair in a so-called myocardial bioenergy mosaic in the NRTI treated cells. Pathophysiological events not will occur until the thresholds of damage were severe enough to impact on organ function [3, 7, 27, 52].

From early in the era of HAART, spectrums of changes in body fat have been reported to occur in 20-80% of subjects receiving these therapies. Abdominal obesity, hypertension, abnormal serum lipids, and evidence of insulin resistance observed resemble simulates features of the dysmetabolic syndrome (syndrome X). Moreover, there is also evidence that the loss of subcutaneous fat *per se* in persons with HIV is associated with insulin resistance [9, 45, 54, 55].

A high lactate/piruvate ratio (consistent with abnormal mitochondrial function) was detected in the blood of patients with HAART toxicity. Controversy exists regarding potential mechanism. Although extensive experimental data may lack to support the hypothesis, it is reasonable to consider the possibility of subclinical mitochondrial dysfunction and resulting anaerobic metabolism may relate to this observation [27, 28]. The experimental literature show evidences of mitochondrial changes in selected tissues from rats, mice, other rodent species and primates with a variety of NRTI dosing schedule. Even current human therapeutic doses or NRTI doses that are below those currently used clinically, mitochondrial defects are demonstrated in tissues. Respect to mitochondrial toxicity of NRTI, cardiomyopathy (CM) was reported by many authors in relation to AZT and/or other NRTI. CM is reported in AIDS, but remains controversial [25, 52]. Features of AIDS CM are shared with the documented AZT myopathy. Clinical features of AZT CM occur after prolonged treatment.

Fatal hepatomegaly with severe steatosis, severe lactic acidosis and adult Reye's syndrome in NRTI-treated HIV seropositive patients were all pathogenetically linked to induced hepatotoxicity [7, 44].

Lipodystrophy also observed in HAART treated patients consist of two components that may be

analyzed together or independently: fat accumulation and fat atrophy [7, 28]. Lipodystrophic syndrome in HIV-1 infected patients is characterized by an abnormal distribution of fat tissue with subcutaneous lipoatrophy of the face, arms and legs, and an increase in visceral fat of abdomen and back of the neck or by subcutaneous fat loss in the arms and legs without accumulation of abdominal fat (lipoatrophy). Fat accumulation is seen within the abdominal cavity, the upper back (dorsocervical fat pad), the breast, and in subcutaneous tissue. Fat atrophy is ascribed to stavudine (d4T), lesser extent to AZT and ddI. Mechanism may involve altered mitochondrial biogenesis and/or oxidative changes, and possibly adipocyte apoptosis. Adipose tissue is now recognized as a main site for the release of hormonal signals that influence CNS, peripheral tissues and the subsequent alteration in overall metabolism. A meta-analysis of 5 series with 5435 HAART recipients showed fat accumulation in 9 to 34% and fat atrophy in 12 to 40% [28, 29]. Although the mechanisms involved in the onset of lipodystrophy are still unknown, mtDNA depletion has been observed in peripheral adipose tissue, peripheral blood mononuclear cells, and skeletal muscle of lipodystrophic patients [29].

To date, no effective therapies are available to reverse HAART-related lipodystrophy, although switching to a d4T, AZT, or NRTI-sparing regimen seems to be the best option. Mitochondrial toxicity from NRTI may impact on peripheral nervous system function and as the epidemic continues, these side effects are increasingly important. Clinical distal dysesthesias, areflexia, distal sensory loss, and mild muscle weakness were common. Sural nerve biopsies for patients with ART neuropathy showed axonal degeneration and mitochondria with disrupted cristae. Attenuation and prevention of these effects could improve efficacy of HIV treatment and it will resound in HIV subjects' quality of life [24, 46, 56, 57].

### Clinical evidences

Since different groups have tested the symptom effects of HAART in these populations, it was therefore appropriate to test the effect of HAART on surrounded marker as mitochondrial toxicity and oxidative stress indexes during progression of treatment and infection [27, 52, 55, 58, 59]. Authors assessed oxidative stress indexes in HIV+ individuals before HAART treatment show altered indexes after period under treatment. Works about HAART influences on oxidative stress indexes noticed a decrease in the antioxidant system, an increase in damaged molecules and a failure to repair oxidative damage.

Ngondi *et al* [59] assessed the effect of different HAART in oxidative stress parameters and found an increase in lipid oxidation while antioxidants decrease.

They did not find differences related oxidative stress damage with antivirals combination. They showed significant differences in lineal association between some parameters as sulphhydryls and albumin with CD4+ T lymphocytes count and with viral load [59].

Hulgan *et al* [60] quantified plasma F2-isoprostanes as oxidative stress index. They planned different strategies and found that this index augmented in 120 HIV+ individuals treated with HAART but they could not distinguish differences due to drugs or HAART combinations [60]. During long term follow-up they did not find association with peripheral neuropathy or cardiovascular risk in their studies context. Meanwhile Masia *et al* [58] found increased plasma peroxide associated with established cardiovascular risk factors in the study context.

Gil *et al* [61] shows that both combinations used for six months produced an increase in oxidative stress indexes paralleled to beneficial change on both HIV progression marker and body mass index (BMI). A beneficial change in CD4+ T cell count and viral load were observed in about 80% for both treated groups. These are in accordance with the therapeutically HAART effects reported [9] but when redox indexes are considered in simultaneous variable analysis, significant differences appear between therapy combinations comparisons. Differences could be achieved to the manner and accumulative impact on redox toxicity by each individual antiviral drug as well as the combinations [52].

Although the relation is suggested there is still a debate about whether oxidative stress plays a direct role in HAART toxicity. DNA pol- $\gamma$  inhibition favors to an energy deprivation and increase ROS formation. Oxidative stress-mediated cell damage results in part via ROS reactions mainly due to NRTI. This antiviral class has been implicated as a cause of several insidious and sometimes irreversible chronic toxicities [2, 3].

Previous works describe some clinical and metabolic benefits during replacement of antiviral treatment and antioxidant interventions. Lipotrophy, as consequence of antiretroviral treatment, was improved recently replacing d4T (used for >3 years) with abacavir or AZT in 16 HIV individuals during 48 weeks. For that mitochondrial indices and fat apoptosis were evaluated. Also pilot studied with exercise and antioxidant supplementation are carried out indicating that antiretroviral associated mitochondrial toxicity during HIV infection could be reversed while others found it during dietary micronutrient intake improvement in treated patients [55, 62-71].

Theoretical enhance in oxidative stress occurs as a dynamic process of immune reconstitution too. In most of HIV patients the treatment aiming to reduce and

control viral replication could produce clinical deterioration as newly inflammatory process occurs when HIV becomes a chronic condition [19, 54]. Immune reconstitution is related to lymphocytes redistribution, systemic immune activation changes, modification of lymphocytes turnover rate, and other events [42, 47]. This hypothesis will require larger prospective studies including immunological assessments. Long term clinical implications of oxidative stress and how it is related to antiretroviral therapy associated disease should be studied.

The behaviour characterization of total antioxidant capacity and other redox indexes in HIV patients point to the multifactorial feature of the infection. Some authors consider oxidative stress not as an epiphenomenon, but rather as having a central role in HIV disease. Considering previously data oxidative stress has a dominant pathogenic action in the HIV infection and some counteract interventions have been developed including those with nutritional, antioxidant supplementation and alternative non-pharmacological option as physical activity [16, 55-57, 65-69, 71-82].

The complexity and multifaceted nature of the process of redox regulation make it essential to better understand the key players in the process and then to design a targeted means of controlling these players.

#### **PHYSIOLOGICAL ASPECTS OF REDOX REGULATION DURING PHYSICAL ACTIVITY**

Most of the O<sub>2</sub> consumed by aerobic organism is used in the mitochondria for oxidative phosphorylation, where it is reduced to water. However, a small but significant fraction of O<sub>2</sub> consumed may leave the electron transport chain to produce ROS; approximately 2-5%. Several studies have shown that ROS and oxidative damage in biological tissues is increased after acute and/or chronic exercise, which coincides with the presence of tissue damage [35, 83, 84]. Mitochondria and XO are relevant sources of ROS during aerobic physical activity. ROS produced during it act as signals that regulate molecular events in muscle cell adaptations to the event. Radak *et al* [33] found that XO has been implicated in ROS production during anaerobic exercise and Vina *et al* [84] found that XO is also involved in ROS generation during resistance exercise [33, 85]. Chronic exercise of moderate intensity (training) positively alters the oxidative homeostasis of cells and tissues, by decreasing the basal levels of oxidative damage and increasing resistance to oxidative stress [78, 86].

There is growing evidence that the continued presence of a small stimulus such as low concentrations of ROS is in fact able to induce the expression of antioxidant enzymes and other defence mechanisms. The basis for this phenomenon may be encompassed by the concept of hormesis, which can be characterized as a particular



dose-response relationship in which a low dose of a substance is stimulatory and a high dose is inhibitory [87, 88].

In fact, regular physical activity causes adaptations in the antioxidant capacity, protecting cells against the harmful effects of oxidative stress, thus preventing cellular damage [33, 78, 88]. Training is also able to alter the metabolism of purines, reducing the availability of substrate for XO in the trained muscle and plasma content of hypoxanthine and uric acid [36].

While excessive prooxidant production, arising from any form of extreme aerobic or anaerobic physical activity (*i.e.*, marathon, aerobic/anaerobic overtraining) may have the potential to result in significant cellular disruption. There are presently exist no “cause and effect” data to indicate that such an increase in ROS resulting from acute exercise actually causes ill-health and disease. To the contrary, and in accordance with the principle of hormesis, a low grade of oxidative stress appears necessary for various physiological adaptations. Such a repeated exposure of the system to increased ROS production from chronic training leads to an up-regulation in the body’s antioxidant defense system. Associated shift in redox balance in favor of a more reducing environment provides adaptive protection from ROS during subsequent training sessions, as well as when exposed to non-exercise related conditions [83]. Taken together, exercise-induced antioxidants may operate in a similar fashion to all other principles of exercise science. That is, in order for an adaptation to occur (*e.g.*, increased antioxidant defense, hypertrophy, and strength), the physiological stimulus applied (in this case ROS production) must exceed a certain minimal threshold, effectively overloading the system. If overload is achieved, the physiological capacity of the body will expand or adapt. Also improved immune function occurs playing a critical role in regulating the inflammatory process, a primary contributor to chronic disease which ultimately leads to improvements in health and/or human performance [35, 38, 41].

The results of studies that addressed whether physical activity increases oxidative stress are not consistent, perhaps because of the different levels of training of the subjects, the different types of physical activity and intensities used, and the various measures of oxidative stress employed. Basically, we can say that most, but not all, of the studies found, reported some increase in oxidative stress of selected outcome measures in response to some types of physical activities [40].

#### **HIV INFECTION, REDOX IMBALANCE AND PHYSICAL ACTIVITY**

Physical activity has been used as non-pharmacological treatment to promote improvement in anthropometric,

cardiorespiratory, muscular and psychological outcomes in HIV infected individuals [64, 66-68, 70, 81, 89-91]. The training regular responses are assumed as similarly to the HIV negative individuals. Physical activity due to higher oxygen uptake may promote an increase in ROS production by mitochondria and can therefore influence on the redox state of the cell. Also muscular damage subsequent to physical activity can cause inflammation and release superoxide by NADPH from neutrophils. In turns it promotes a transient increase in the ROS production which conceivable produces an exposure/withdrawal in an environment of redox imbalance [92]. It has been suggested as a factor responsible for adaptation of exercise-induced antioxidant mechanisms [33, 37-39, 78, 83, 86, 93, 94].

Up today different groups worldwide have been researched about the influences of diverse schedule or program of physical activity in HIV-AIDS individuals. Until the efficacy and safety of pharmacological interventions are rigorously studied in persons with HIV, the cornerstone of management for central fat accumulation should be diet and physical activity, as extrapolated from populations not infected with HIV [38, 39, 93].

For central fat accumulation, the goal should be to decrease intake of saturated fat and excess caloric energy. Respect to aerobic exercise, it is expected to augment the effects of dietary change because intra-abdominal fat (mesenteric and omental adipose tissue) is metabolically more active than peripheral fat in responding to lipolytic stimuli, such as increases in epinephrine. In persons without HIV, intensive aerobic exercise can decrease intra-abdominal adipose tissue by 17-20%. In addition, aerobic exercise increases peripheral glucose disposal in obese persons, even in the absence of weight loss, and should be beneficial for subjects with insulin resistance. A recent report suggests that an aerobic exercise program with a moderate-fat, low-glycemic-index, high-fiber diet can reverse aspects of lipodystrophy [66, 69, 70, 95, 96].

Some investigations have shown significant benefits of aerobic exercise in HIV-infected persons in the areas of cardiorespiratory capacity, immune status, and metabolic activity as well as psychological variables such as a reduction in symptoms of depression and anxiety [74, 75, 77, 80-82, 97, 98]. These benefits have been observed in as little as 6 weeks of training from aerobic activity at any intensity if performed at least 2 to 3 sessions per week. However, a comparison across intensities is difficult, as most of the studies did not equalize the dosage of exercises across the intensity range.

Physiological variables measured in aerobic exercise interventions in HIV-infected populations include body composition and high-density lipoprotein (HDL)



cholesterol. A 16-week intervention in a group composed of men and women developed a lower intensity aerobic exercise regimen (~40%, maximum oxygen consumption ( $VO_{2max}$ )), twice a week for 45 min. There were significant increases in  $VO_{2max}$  and HDL cholesterol, as well as significant decreases in total abdominal adipose tissue, total cholesterol, and triglycerides. Similarly, other group reported a significant increase in  $VO_{2max}$  as well as decreases in BMI, waist-to-hip ratio, body density, and body fat after a 12-week moderate-intensity aerobic exercise intervention (~60%) performed for 30 min a day, 3 days a week.

The immunological benefits of physical activity, specific to those with HIV infection, include the effects on CD4+ T lymphocyte counts and HIV viral load. Participants in one study with aerobic physical activity, showed enhanced production of natural antibodies that, in turn, can potentially delay disease progression [80]. These results suggest that physical activity can positively affect immunological factors that usually cause disease progression in HIV. Broadbent and Gass [99] found that 52 weeks of physical activity increases CD4+ and CD25+ percentages in older men. Another study reported an inverse relationship between regular physical activity and viral load, a finding that had not been previously supported in the literature. However, most reports indicate that exercise does not positively or negatively impact CD4 count or viral load [72]. The inconsistency of these results emphasizes the need for additional studies that control for the amount and intensity of the physical activity intervention, as well as the stage and progression of the disease. Overall, existing literature indicates exercise interventions are physically and immunologically safe in both children and adults with HIV.

Respect resistance physical activity a conducted a 16-week randomized intervention study of a supervised home-based progressive resistance training and aerobic exercise program in 40 HIV-infected women with increased waist-hip ratio and self-reported fat redistribution. Cross-sectional muscle area and muscle attenuation were measured by computed tomography. Cardiorespiratory fitness was determined by calculated  $VO_{2max}$  and strength by 1-repetition maximum. Cardiorespiratory fitness ( $VO_{2max}$ ) was markedly lower at baseline than reported values for healthy female subjects [97]. Subjects randomized to exercise had significant improvement in  $VO_{2max}$  and endurance. Strength increased at the knee extensors, pectoralis, knee flexors, shoulder abductors, ankle plantar flexors, and elbow flexors. Total muscle area and attenuation increased in the exercise group. No significant difference was seen in lipid levels, blood pressure, or abdominal visceral fat between the groups, but subjects randomized to exercise reported improved energy and

appearance. A 16-week, supervised, home-based exercise regimen improved measures of physical fitness in HIV-infected women. The effects on strength were most significant, but improvements in cardiorespiratory fitness, endurance, and body composition were also seen.

Also combined aerobic and resistance schedule of physical activity are studied. Comparison between the levels of oxidative stress markers and the immunological response profile in HIV-infected and non-HIV subject participating in a single session of aerobic exercise followed by one session of resistance exercise, both at moderate intensity are reported [97, 100]. The exercise protocol consisted of a single session of 20 min on a cycloergometer followed by a set of six resistance exercises. The activity of glutathione S-transferase (GST) and CAT were measured in plasma samples, GSH and thiobarbituric acid reactive substances (TBARS) were measured in erythrocytes. CD4+ and CD8+ T cells, viral load, complete blood count, and white blood count were also assessed. All measurements were performed at three times: baseline, after aerobic exercise, and after resistance exercises. At baseline, the HIV group had lower GST activity than controls, but after the exercise session GST values were similar in both groups. Compared to the control group GSH was significantly lower in the HIV group at baseline, after aerobic and resistance exercises. The control group presented higher TBARS values after aerobic exercise compared to the HIV group. The neutrophil count was lower in the HIV group after aerobic and resistance exercises. Similarly, the exercise session did not significantly change CD4+ T count and viral load among HIV subjects, suggesting that exercise was performed at a safe intensity, as previously demonstrated in another study [100].

These data indicate that HIV-infected subjects had lower antioxidant activity at rest. Physical activity stimulated the enzymatic activity similarly in both groups. The main results of study indicate a similar enzymatic response in both HIV-infected and non-HIV subjects. However, TBARS levels were elevated only in control group. This suggests that physical activity stimulates the antioxidant mechanism similarly in both groups, but TBARS levels were not similar. Therefore, it suggested that the use of exercise training as an antioxidant strategy might be followed in HIV-infected individuals.

The increase of the antioxidant capacity after physical activity in HIV-infected individuals has been suggested by different authors responding as similar as non infected [64, 66, 72, 76, 81, 97, 100]. This effect could produce adaptation and promotes greater tissue resistance to oxidative challenge.

Studies have reported a 22-45% prevalence of depression among HIV-infected people. This high prevalence indicates that depression is a disease that needs to be assessed in all patients with HIV. Depression has been linked to altering the course of infection due to immune function impairment. HIV-infected patients who participate in regular physical activity have higher life satisfaction scores measured by psychological parameters when compared with those who are sedentary [81].

A relatively strong body of literature illustrates the beneficial effects of combined aerobic and resistance exercise training for those infected with HIV. The advantage of combined exercise training is enhanced cardiorespiratory function in a population that is typically deconditioned with the strength and muscle mass gains of resistance training.

Based on these results physical training (mixed aerobic and resistance) may be safely performed by HIV infected individuals. The physical schedule program constitutes a complementary strategy providing induction of antioxidant response which produces a beneficial adaptation capable to mitigate the deleterial effects of oxidative stress [33, 79].

Results to date indicate that moderate- to high-intensity aerobic, resistance, and combined aerobic and resistance exercise regimens can be safe and elicit favorable and beneficial changes in the HIV-infected population. These benefits can include changes in body composition, functional capacity, muscular strength, total and HDL cholesterol, cognitive function, depression and anxiety, overall health, and quality of life. Most studies indicate no beneficial effect of exercise training on HIV status, viral load, or immune function. However, aerobic exercise has shown no negative effect on immunity or disease progression [39, 98, 101]. The effects of resistance or combined exercise programs on immunity have yet to be determined.

Despite this lack of consistency in results regarding whether exercise increases oxidative stress, many studies have sought to determine whether antioxidant supplements would benefit those who exercise regularly. Earlier studies found no advantage of antioxidant supplements on exercise performance, but there is little theoretical basis to believe that they would have an effect [79, 98, 102].

Moreover, several factors govern human performance, thus making it difficult to detect effects of a supplement intervention [103]. Other studies examined whether supplements reduced measures of oxidative stress. And, just as the studies to examine exercise-induced oxidative stress produced varied results, so did these studies regarding supplementation. The type of supplement, timing of the supplement, and the outcome measures were different among the studies, making any

overall interpretation difficult.

At this time, the only statement that can be made is that exercise may or may not result in harmful oxidative stress, and antioxidants may or may not reduce it, if it occurred at all.

Based on findings it is uncertain whether an increase in oxidative stress that occurs with exercise is necessary for muscle adaptation to occur, or whether it is harmful, causing muscle damage that impairs the ability to perform or train. There is growing evidence that ROS can serve as signals that stimulate adaptive processes [33, 78, 86].

At what level of increased oxidative stress the potential benefits will outweigh the risks are not clear. A prudent recommendation for athletes is to ingest a diet rich in antioxidants rather than taking supplements.

## **CONCLUDING REMARKS**

Advanced in HIV research allow the scientific community to better understand the molecular and clinic mechanisms. Oxidative stress underlying HIV evolution causes a very wide spectrum of genetic, metabolic and cellular response from diverse tissues overwhelms the organism. This impact contributing to the spectrum of malignancies associated to HIV infection. The oxidative stress evaluations will therefore become potential utility factors to follow antiviral combinations effects, as well as the usefulness of antioxidant and alternative therapies. The counteract actions strategy to diminish the impact of oxidative damage may contribute both restoration of immune response and down regulation of HIV replication. Also these actions may attenuate the toxic effects of HAART which will impact on quality of life of HIV infected individuals.

Regular physical activity can positively affect the HIV-infected individual psychologically, and emotional wellness has been linked directly related to immune health while not imposing deleterious effects on the immune system. Continued research is needed to further define the effects of optimal nutrition and physical activity on the immune system as HIV-infected individuals grow older. As the evidence for the benefits of physical activity on immune and metabolic functions in persons with HIV grows, recommendations for regular exercise should become an integral part of their care across all ages.

## **COMPETING INTERESTS**

The authors declare that they have no competing interests.

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