

# Immune Modulators of HIV Infection: The Role of Reactive Oxygen Species

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## Abstract

A continue loss of CD4<sup>+</sup> T lymphocytes, immune response dysfunction and chronic immune activation (IA) are hallmarks of untreated chronic HIV-1 infection. ROS and the subsequent oxidative stress have been connected with chronic activation of the immune system, viral replication, immune dysfunction, programmed cell death, and neurological damage, all considered to be major contributing issues in HIV-1 diseases progression. It has been demonstrated that HAART partially restore the antioxidant capacity by suppressing HIV, and it has been suggested that antioxidant therapy in combination with HAART could protect the blood brain barrier from oxidative stress-induced damage. Several mechanisms have been proposed to explain how HIV could modulate ROS generation and several HIV proteins have been shown to modulate ROS production. This review is intended to highlight the role played by ROS as modulators of the immune system during the course of HIV infection, which could explain its contribution to disease progression, opening the scope to new strategies for drug design and future treatment.

**Keywords:** HIV-1; Reactive oxygen species (ROS); Immune activation IA; AIDS; Nef; Tat; Treg

## Introduction

Since the human immunodeficiency virus-1 (HIV-1) pandemic developed more than twenty-five years ago, millions have died from Acquired Immunodeficiency Syndrome (AIDS), and an estimate of 34 million people worldwide are living with HIV in 2010 [1]. HIV-1 is responsible for a chronic disease and is an important causes for morbidity and mortality worldwide [2], due to a progressive immunodeficiency associated to both quantitative and qualitative deficit of CD4<sup>+</sup> T lymphocytes, compromising innate immunity mechanisms as well [3]. Direct infection, apoptosis of activated cells (infected or non-infected cells) [4], cytotoxicity of infected cells [5], impaired renewal due to deficient thymopoiesis [6], and thymic involution [6,7], can result in a massive depletion of CD4<sup>+</sup> T cells [8]. Typically, untreated individuals infected with HIV-1 develop AIDS, which is associated with opportunistic infections, malignancies and, eventually death; while paradoxically, a few others maintain undetectable plasma viral loads without any therapy and remain asymptomatic for many years [9].

Although a variety of clinical trials have been conducted in order to control the progression of HIV infection by focusing on oxidative stress, their precise targets and reaction mechanism have remained unclear [10]. The aim of this review is to discuss and highlight the role of ROS as modulators of the immune system during the course of HIV infection, which could explain its contribution to the immunopathogenesis of the disease, opening the scope to new strategies for drug design and treatment.

ROS are a group of highly reactive free radicals [11], produced mainly by phagocytic cells such as neutrophils and macrophages [12]. There are several sources of ROS within the intracellular compartment, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs), xanthine oxidase, the mitochondrial electron transport chain, peroxisomes, and the endoplasmic reticulum (ER) [12,13]. Due to its highly unstable nature, superoxide readily produces a number of other compounds [14]; when it is catalyzed by superoxide dismutase (SOD) results in hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) production,

which promotes either oxidation or disulfide bond formation [15]. Additionally, H<sub>2</sub>O<sub>2</sub> generates hypochloric acid (HOCl) when it is combined with Cl<sup>-</sup> in a reaction catalyzed by myeloperoxidase; both H<sub>2</sub>O<sub>2</sub> and HOCl are present in the phagosome to kill microbes. H<sub>2</sub>O<sub>2</sub> also interacts with transition metal ions, such as ferrous and ferric ions, to produce hydroxyl radicals (OH•), which is the most highly oxidizing member of the ROS family, reacting rapidly with DNA, lipids, and proteins [16].

NOXs and mitochondria are major cellular sources of ROS [17]. The NOX family comprises seven members (NOX1-5 and DUOX1-2) with NOX2 NADPH-oxidase [18]; each of these isoforms have a core catalytic subunit called NADPH oxidase (NOX) and dual oxidase (DUOX) subunits, and even five regulatory subunits. Several NADPH oxidase isoforms depend on a small GTPase (Rac1 or Rac2) for their activation [19]. NOX2 NADPH oxidase is composed by functional transmembrane heterodimers, gp91phox and p22phox (also known as cytochrome b558), and four regulatory cytosolic subunits p40phox, p47phox, p67phox, and Rac2. The components can further be located in different biological membranes, such as: nuclear, endoplasmic reticulum, endosome, phagosome, and mitochondria, which has been associated with its function within these intracellular and extracellular locations [20].

Some members of the NADPH oxidase family are expressed in virtually all mammalian cells [19]. Brain tissue (that is, neurons,

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astrocytes and microglia), constitutively express NOX1 oxidase, NOX2 oxidase and NOX4 oxidase [21], presumably reflecting physiological roles for NOX oxidase-derived ROS.

### General effects of ROS in immune response

ROS have a critical role in several physiological events such as regulation of redox-dependent signaling cascades, by acting as cofactors for hormones production [19], intracellular signaling post-T-cell activation [22], antigen cross-presentation [23], autophagy [16], both apoptotic and necrotic cell death pathways [24-26] and chemotaxis [27], by increasing CCR5, and CXCR4 expression [28,29], major determinants of HIV interaction with mononuclear phagocytes and T lymphocytes.

ROS can also orchestrate Th2 responses, by inducing lipid oxidization which trigger thymic stromal lymphopoietin (TSLP) production by epithelial cells, a cytokine known to be involved in Th2 differentiation, which suppresses the production of Th1 molecules such as IL-12 and CD40 by DCs, in lymph node; and induce DC-derived chemokine CCL7, which mediates basophils recruitment [30]. Interestingly, NOX2 oxidase-derived superoxide from macrophages is essential for Treg generation, contributing to control T cell-mediated inflammation [31]. Besides, NOX2 deficiency affects both FoxP3 and ROR $\gamma$ t expression in CD4<sup>+</sup> T cells, which is traduced as increased Th17 cells and diminished Treg development in a ROS-dependent and T-cell-intrinsic manner [32].

On the other hand, excessive ROS production by an overactive NADPH oxidase system, both in phagocytic and non-phagocytic cells, may set in motion a vicious cycle of radical and non-radical oxidant generation in various cellular compartments, which disrupts redox circuits that are normally controlled by thiol-dependent antioxidant defenses, and induces a state of oxidative stress. In fact, many adverse effects of ROS are attributable to the oxidation of important signaling proteins, including kinases and phosphatases, and activation of the pro-inflammatory redox-dependent transcription factor NF- $\kappa$ B; this leads to the expression of adhesion molecules, leukocytes proliferation and migration [19,33]. ROS may also oxidize and activate matrix metalloproteinases, responsible for tissue remodeling [34]. ROS may initiate the assembly of multiprotein signaling complexes known as inflammasomes, which activate caspase-1, leading to the processing and secretion of the pro-inflammatory cytokines interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-18 [35].

Several studies suggest that ROS affect the intrinsic apoptotic pathway in neuronal cells, with mitochondria being the major source and primary target [36]. ROS may oxidize mitochondrial pores that lead to cytochrome c release and caspase-9 activation due to the disruption of the mitochondrial membrane potential [37,38]. ROS generation change the intracellular redox status as well, with subsequent effects on specific kinases, phosphatases, and transcription factors, increasing cell susceptibility to apoptotic stimuli [39-41]. ROS are also involved in T lymphocytes cell death process [22], hence, inhibition of superoxide generation upon T-cell receptor engagement, rescue from activation-induced cell death [42]. Sustained Jun N-terminal kinase (JNK) activation is ROS dependent in T cells and, during T cell neglect-induced death increased levels of ROS has been detected [43].

Thus, ROS are important signaling molecules that regulate many signal-transduction pathways and play critical roles in cell survival,

death, and immune defenses [17], involving them in many different diseases including cancer, neurological disorders, among many others [44,45].

### ROS and HIV-1 infection

An increased oxidative stress condition has been repeatedly described in chronically HIV-1-infected patients, based on: elevated extracellular and intracellular ROS levels [46-53], systemic reduction in glutathione (GSH) and thioredoxin concentrations [54], disturbance of mitochondrial membrane potential [55], and changes in expression and activation status of cell death receptors [56], which may lead to host cell death [52,57]. An increased HIV-1 replication, induced by ROS, has been observed in reservoir cells [58]. These effect is mediated by H<sub>2</sub>O<sub>2</sub>-induced LTR activation during middle stage of infection, where a great deal of oxidative stress occurred [59].

It has been demonstrated that HAART partially restore the antioxidant capacity by suppressing HIV [60], and it has been suggested that antioxidant therapy in combination with HAART could protect the blood brain barrier from oxidative stress-induced damage, could be considered as a viable therapeutic option for patients with HIV-associated dementia (HAD) [61]. However protease inhibitors (PIs) for HIV, enhance ROS production in several types of cells including macrophages, vascular smooth muscle cells, umbilical vein endothelial cells, adipocytes, and pancreatic  $\beta$ -cells, and contributed to intestinal barrier integrity disruption [62] suggesting that ROS greatly contribute to HIV PIs-induced side effects [63].

### Effects of HIV induced ROS on immunity

There is no doubt about the crucial role played by ROS in the immunopathogenesis of HIV infection. HIV induced ROS have been connected to decreased immune cell proliferation, loss of immune function [50,58,64], followed by a cellular dysfunction and cell death, loss of memory T cell response [65], T helper imbalance, related to premature Treg response [66], which are highly susceptible to HIV infection [67], premature ageing of immune system because of a direct and quantitative shortening of telomere [68], altogether disturbing the adaptative immune response.

ROS has been connected to several critical signaling pathways during HIV Infection. Thus, ROS induce HIV LTR activation by early NF- $\kappa$ B activation, by inducing both I $\kappa$ B degradation and covalent modification of p65, CBP/p300-induced hyperacetylation as well as phosphorylation of p65 [59], these events may explain the explosive increase in viral replication after the middle stage of infection [69] and, can promote HIV replication in macrophages [10]. Cross link of death receptors such as DR5, induced production of ROS and subsequent apoptosis in HIV-1 infected monocyte-derived macrophage, associated with JNK phosphorylation [70], a kinase known to be involved in the apoptotic signaling pathway initiated by stress or toxic stimuli [71]. Besides, HIV infection facilitates TRAIL-induced cell death in monocyte-derived macrophage (MDM) by down regulating the TRAIL decoy receptors and intracellular c-FLIP, dependent of ROS generation and subsequent JNK phosphorylation [70].

Excessive ROS production is also explained by polymorphonuclear chronic activation during HIV infection [48] or, through a pro-oxidant effect of TNF- $\alpha$ , as released by activated macrophages, which may be accompanied by a concomitant deficient antioxidant defense system [72]; altogether increasing the susceptibility to cell death. Indeed,

oxidative stress is the common mediator of programmed cell death in HIV/AIDS on this subpopulation [57]. Previous results show that neutrophils from HIV infected patients have increased basal levels of superoxide production [73], particularly before AIDS is established, which is associated to their dysfunction [48]. In fact, apoptosis could be responsible for HIV-related neutropenia [74], which could occur either spontaneously or triggered via death receptors such as Fas/FasL [75,76]. Spontaneous cell death during HIV infection is at least partially mediated by ROS, because it can be significantly reduced in the presence of oxygen radical scavengers [57].

### Effects of HIV induced ROS on different cells

Oxidative stress not only affects HIV infected human CD4 T lymphocytes, macrophages, dendritic cells and neutrophils, human hepatocytes has been documented to be affected as well during the disease [77]. HIV virions and its envelope gp120 protein, induce ROS production within hepatocytes, hepatic stellate cells (HSC) and other immune cells through its interaction with CCR5 or CXCR4 chemokine receptors [78,79], and during HIV/HCV co-infection, leads to accelerated hepatic fibrosis development, higher rates of liver failure and death, compared with patients with HCV only [80]. Thus, HIV regulate hepatic fibrosis progression through the generation of ROS, in a NF- $\kappa$ B -dependent fashion, and a subsequent increment of pro-fibrogenic genes [81]. Oxidative stress has been recently involved in endothelial cell dysfunction, vascular injury, and pulmonary arterial hypertension, during HIV infection [82]. A unifying mechanism of HIV-related ROS effects is currently unknown, despite the intensive efforts unraveling the immunopathogenesis of the disease; which may make difficult to design the appropriate therapeutic approach capable of controlling oxidative stress.

### ROS and mucosal integrity during HIV infection

A prominent role of the intestinal mucosal integrity has been postulated has been connected with chronic immune activation during HIV infection. Gut mucosa is a compartment where the interchange between HIV and the host's immune system, takes center stage [83,84]. Within 1-2 weeks, infection becomes systemic, with extensive viral replication and CD4<sup>+</sup> T-cell depletion in the intestinal lamina propria [84-87], because of a direct infection or apoptosis of bystander cells [88]; associated to enteropathy [89] induced by proinflammatory molecules, and cytotoxic effects that provoke intestinal epithelial apoptosis [90], and immune activation. The T regulatory response that has been described as premature in this region, because the immunosuppressive effects of cellular immune response precede clearance or control of viral replication [88,91].

ROS play an important role in epithelial intestinal cells injury, contributing to gut mucosal barrier dysfunction. The ROS-induced gut mucosal injury, implies loss of epithelial integrity between the cellular tight junctions and enteric bacterial translocation, which can be attenuated by radical scavenger [92]. Oxidative stress is known to exist in IBD epithelium, and activate TACE (TNF-alpha converting enzyme), a pleiotropic metalloprotease also known as ADAM17, which is required for TNF- $\alpha$  production [93].

Current evidence also indicates that Th17 cells are even more profoundly depleted than CD4<sup>+</sup>CCR5<sup>+</sup> T cells in the intestinal mucosa of HIV- infected individuals [94]. Loss of Th17 cells [95], is associated with loss of the integrity of the gut mucosal barrier, allowing microbial translocation products from the gut, associated to increased plasma levels of lipopolysaccharide (LPS) and soluble CD14 (sCD14), in the

absence of overt bacteremia, which correlates with systemic immune activation [96,97] and mortality prediction in HIV infection [98]. NOX2 deficiency or ROS depletion significantly promotes development of effector Th subsets such as Th17 cells, and suppressed development of natural and inducible Treg cells. ROS is essential for immune homeostasis by controlling Th17/Treg balance. Increased generation of ROS attenuated Th17 cell differentiation and its related immune response [99]. It is likely that disruption of the precise fine-tuning between generation and elimination of ROS may cause inflammation in multiple tissues in a T-cell-dependent manner [32].

### Effect of HIV proteins on ROS production

Several mechanisms have been proposed to explain how HIV could modulate ROS generation: 1) by inactivation of the GDP-bound form of RhoA and activation of p190 RhoGAP-A protein [100]. A previous report showed that Rac-dependent ROS production, leads to downregulation of RhoA through oxidative inactivation of low molecular-weight protein tyrosine phosphatase, and the subsequent activation of p190 RhoGAP-A [101]; 2) by phosphorylation of p47phox [52] and association with p22-phox [102] inducing a direct activation of the NADPH oxidase complex, 3) by activation of p66ShcA, a protein involved in phosphatidylinositol 3-kinase/Akt/PKB signaling module, a pathway which is upstream of NADPH [103], 4) by activating the PI3K/ Akt pathway, turning on the NF- $\kappa$ B Transcription factor [104] and inducing p42/44 MAPK activation [105].

Several HIV proteins (structural and regulatory) have been shown to modulate ROS production [61,102,105-109] (Figure 1). Thus, HIV regulatory protein Tat has pro-oxidant function, which could induce long terminal repeat region (LTR) transactivation, and this effect is prevented by NADPH oxidase inhibitors [104]. Furthermore, Tat can reduce SOD synthesis [110,111] and intracellular glutathione (GSH) levels [112]. Exposure of microglia and astrocytes to HIV-1 Tat leads to ROS generation, which activates signal transduction processes leading to expression of proinflammatory cytokines, as well as adhesion molecules on endothelial cells, microglia, and astrocytes [113-115]. On the other hand, inhibition of NADPH oxidase, significantly attenuates inflammatory mediators (TNF- $\alpha$ , IL-6, CXCL10, IFN- $\gamma$  and MCP-1) in microglia, astrocytes and macrophages [116,117].

HIV-1 Nef is another regulatory protein that also has pro-oxidant properties. The effect of Nef on ROS activation has been previously demonstrated in different cells [53,102,106,107]. Nef has been detected in brain, where it associates with astrogliosis and recruitment and activation of monocytes/macrophages [118]. HIV-1 Nef increases oxidative stress in primary human astrocytes [119] and led to their rapid cell death [120]. Furthermore, ROS-induced astrocyte death is thought to play a role in the occurrence of HAD [121,122].

Several pathways could explain Nef modulating effects on ROS: Nef may induce superoxide production by activating PAK (p21-activated kinase) in a Cdc42/Rac dependent manner [107]. Through the interaction with Hck (hemopoietic cell kinase), Nef may induce phosphorylation and membrane translocation of p47-phox, a mechanism that could explain activation of superoxide, bypassing the typical pathway stimulated by pro inflammatory cytokine GM-CSF [106]. Additionally, through its association with p22-phox [102], Nef could directly affect NADPH-activity, a possibility that requires further investigation.

A hypothetical predictive model of protein-protein association, between p22-phox and Nef, showing low values of free energy



between the molecules (-1117.6), is shown in Figure 2. In particular, residues VRGE (126-129) from p22-phox (gray) corresponding to an intracellular portion of the protein and residues RRQDI (105-109) from Nef (black), demonstrated the highest probability of interaction.

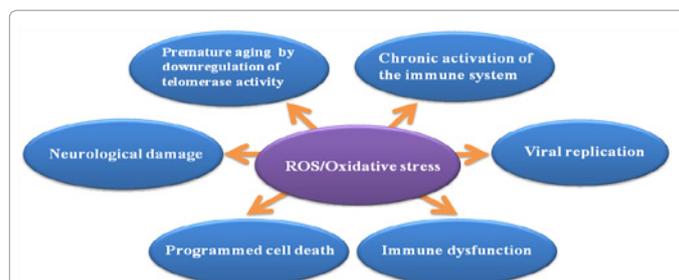
Vpr an HIV protein that contribute to HIV-1 pathogenesis has been proven to increase ROS and HIF-1(a biomarker of oxidative stress) expression in human microglial cells, promoting mitochondrial dysfunction as well as oxidative stress [108,123]. Oxidized phosphatidylcholine (OxPC), formed from phospholipids in response to oxidative stress, were identified in atherosclerotic lesions [124] to be induced by rVpr, in a ROS-dependent manner, because it is reverted by the addition of N-acetyl-L-cysteine (NAC), a ROS scavenger molecule [125]. In this model, ROS are likely generated as a result of mitochondrial dysfunction, since Vpr binds ANT (adenine nucleotide translocator), a member of the permeability transition pore complex [126], and disrupts the MMP [127]. Additionally, HIV-1 gp120-induced neurotoxicity use ROS as signaling and effector of oxidant damage. Antioxidant gene blocks gp120-induced proapoptotic signaling *in vitro* and protects cell viability *in vitro* and *in vivo*, therefore specifically hypersensitive to gp120-induced apoptosis, signaling for which involves ROS intermediates [109].

### The triad: immune chronic activation, oxidative stress and HIV infection

A continue loss of CD4<sup>+</sup> T lymphocytes, immune response dysfunction and systemic immune activation (IA) are hallmarks of untreated chronic HIV-1 infection [128], and it is now well established that chronic IA, is an important mechanism that contribute to immune response impairment and disease pathogenesis [129-131]. Within the multiple biological process described to be altered and involved in AIDS, a great deal of innate immune components have been clarified not only to be affected, but more importantly, to play a crucial role during disease progression [132,133]. Thus, IA is manifested in many ways including increased proinflammatory cytokines and chemokines [134] and oxidative stress [135,136], among others. Reactive oxygen species (ROS) are important molecules that regulate many signal-transduction pathways and play critical roles in cell survival, death, and immune defenses [17], and overproduction of ROS leads to oxidative stress, directly associated with toxic effects on cells and tissues [137], involving molecular damage of cellular components such as nucleic acids, proteins, or lipids [138,139]. Furthermore, ROS and the subsequent oxidative stress, have been connected with chronic IA during HIV [48], viral replication [125], immune dysfunction [1,140], programmed cell death [57,141], and neurological damage [142], all considered to be major contributing factors in HIV-1 diseases progression [143,144] (Figure 3).

Immune system exhaustion [145] associated with constitutively activation of lymphocyte populations [146] and expression of programmed death-1 (PD-1)[147], has been associated with impaired immune reconstitution in patients on ART [148].

A number of factors have been identified for sustained chronic IA, which are both directly or indirectly related to HIV replication, they include: the innate and adaptive immune responses against HIV, the translocation of bacterial products as a consequence of compromised integrity of the mucosal barrier, and the potential bystander stimulation of lymphocytes and macrophages by HIV gene products [96,149]. Such



**Figure 3: ROS/oxidative stress during HIV infection.** Oxidative stress during HIV infection has been associated with: premature aging through downregulation of telomerase activity, chronic activation of the immune system, neurological damage, viral replication, programmed cell death and immune dysfunction.

IA is manifested in many ways including: increased T-cell turnover [96,150], increased frequencies of T-cells with activated phenotype [151], polyclonal B-cell activation [152], increased serum levels of proinflammatory cytokines and chemokines [96], enhanced oxidative stress [135,136] and premature development of regulatory T cells (Tregs) [151]. Immune exhaustion is an aberrant component of the immune chronic activation during HIV-1 infection and is associated with ongoing virus replication [153], and elevated intracellular cyclic AMP (cAMP), which inhibits T cell activation capability [154]. In T cells, cAMP triggers a protein kinase A-Csk-Lck inhibitory pathway that inhibits proximal T cell receptor (TCR) signaling events [155]. This mechanism may also be involved in the inhibitory function of Tregs [156]. Therefore, anti inflammatory therapy has been suggested to download the immune activation in order to improve T cell-dependent functions *in vivo* [157].

Chronic IA of innate immune cell is also evident during HIV infection. Hence, pDCs are highly susceptible to HIV-induced activation due to its interaction with the cellular receptor CD4, and the subsequent production of type I interferon. Also, pDCs during HIV infection show high levels of the chemokine receptor CCR7 [158], indoleamine 2,3-dioxygenase, tryptophan depletion and the subsequent suppressive effects by contributing with Treg generation. Increased levels of IDO and tryptophan depletion is mediated in part by TLR activation, [146] and by oxidative stress, which creates a niacin "sink" effect that depletes both niacin and tryptophan [159]. These events are associated with inhibition of HIV-induced CD4 T cell proliferative responses *in vitro* [160], and increment of regulatory T cells (Treg) in lymphoid tissues, where IDO is overexpressed [146]. Thereby, the dysregulation of innate immunity could contribute both to the numerical depletion of CD4 T cells and to the progressive loss of functional responsiveness of lymphocytes.

### Concluding Remarks

ROS are important molecules that regulate many signal-transduction pathways and play critical roles in cell survival, death, and immune defenses, their overproduction leads to oxidative stress, directly associated with toxic effects on different cells and tissues. ROS and oxidative stress have been connected with chronic IA during HIV infection and diseases progression.

Several pathways have been involved in ROS/oxidative stress during HIV/AIDS; however the molecular mechanism of ROS/HIV modulation is currently under study. Demonstrating protein-protein association between HIV proteins and elements involved in ROS production (for instance the association between p-22phox and Nef, which affects superoxide production) could unmask potential targets for therapeutic intervention. Further studies may contribute to develop specific therapeutic strategies, which combined with antiretroviral therapy, would improve life expectancy and quality of infected patients.

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