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Oxidative Stress, Redox Regulation and Elite Controllers of HIV Infection: Towards a Functional Cure

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/60806>

1. Introduction

HIV infection has been associated with a high oxidative stress profile. Different stages of the infection are marked with distinct characteristics of redox activity culminating to either potentiation of the disease or an ameliorative process. Both host and viral survival rates require varying degrees of antioxidants to counter the devastating effect of oxidative stress (OS) molecules produced during the onset of the infection. Here, the chapter x-rays and brings to concept the oxidative stress condition and its implication on HIV functional cure. It is obvious that 'excess' free radicals could destroy cell membranes and generate apoptosis, the main cause of lymphocyte-CD4⁺ depletion in HIV infection. The whole scenario demonstrates that measurement of oxidative stress molecule could function as a potentially HIV biomarker and surveillance parameter in addition to CD4 cell count and that its regulation controls the HIV infection processes.

Generally, people with HIV infection have an unbalanced redox system which is related to a depletion of protective system (glutathione peroxidase; superoxide dismutase; vitamins A, C and E; selenium; etc.), activation of immune signalling molecules (cytokines and chemokines) and an increased production of free radicals (superoxide anion, hydrogen peroxide and hydroxyl radicals). Immunological and biological consequences of this condition include activation of lymphocytes and phagocytising cells, chronic inflammation, increased polyunsaturated fatty acid concentration and lipoperoxidation and direct or indirect effect of several pathologic agents. As the search for HIV functional cure intensifies, oxidative stress condition of natural controllers of HIV infection remains an integral success path for a possible disease cure and management.

2. Free radicals in HIV disease progression

2.1. Free radical production and Reactive Oxygen Species (ROS)

Free radicals are chemical species capable of independent existence and which contain one or more unpaired electrons [1]; they are like loose cannons or rather hot pepper ready to cause biological damage. They consistently react with proteins, lipids, polysaccharides and nucleic acids of biological components and thus damage cell membranes, organelles and importantly DNA [2, 3] with the resultant disease condition [4]. It has been estimated that the average person produces about 10,000–20,000 free radicals attacking each body cell daily [5]. In biological systems, oxygen radicals are known collectively as reactive oxygen species (ROS) possessing high chemical reactivity, with original formation in the mitochondria and smooth endoplasmic reticulum as oxygen reduces along the electron transport chain [6,7]. ROS are formed in other processes that include white blood cells such as neutrophils, which specialise in producing oxygen radicals used in host defence against invading pathogens, cellular exposure to abnormal environment such as hypoxias [8], drugs/xenobiotics [9] and ionising radiation [10]. Hypoxic conditions are created when oxygen is limited and mitochondria pump out ROS which alert the cell to the shortage, but how cells sense hypoxia is a subject of much debate; Bell et al. [11] described these extensively. Reactive oxygen species (ROS), namely, hydroxyl radicals (HO^\bullet), superoxide anions (O_2^-), nitric oxide (NO) and hydrogen peroxide (H_2O_2), are constantly generated in aerobic organisms in response to both external and internal stimuli [12]; therefore, metabolic activity initiated by immune cells against stimuli creates electron-deficient free radicals. As highly reactive molecules, they damage other molecules by abstracting electrons from them. High doses and/or inadequate removal of ROS results in oxidative stress which causes severe metabolic malfunctions and damage to biological macromolecules. ROS therefore are the main cause of oxidative stress.

2.2. ROS in HIV infection: Do they differ in the different stages of HIV?

Oxidative stress (OS) means any perturbation in the pro-oxidant to antioxidant balances in favour of oxidation, thus resulting in damage to cells. OS increases the replication of HIV and the amount of certain cytokines, among them is tumour necrosis factor- α (TNF- α) through the activation of nuclear factor-kappa binding (NF- κ B) and indirectly by activation of genes that further promote OS [13]. Oxidant production in HIV infection, however, is through the stimulatory effects of gp125 (an HIV glycoprotein) and tat, the viral-transactivating protein [14]. Mycoplasmas as well enhance the replication of HIV by increasing oxidative stress since they are known to produce H_2O_2 . HIV coinfection with mycoplasma therefore results in the release of H_2O_2 from T-cells.

It has been proposed that CD4⁺ T-cells are depleted by apoptosis and that T-cells are primed to undergo apoptosis upon cross-linking of CD4 by gp120 of the virus [15]. Subsequent activation perhaps by conventional antigens or superantigens induces apoptosis in these T-cells and increases the progression rate. OS have been implicated to play a rather devastating role in the progression of HIV disease. In this case, certain questions are raised, namely, does the OS condition in HIV infection differ in the various stages of the disease? Does the threshold

of OS correspond to the worsening clinical manifestation of the disease as the infection progresses? What is the OS threshold that is associated with the stages of infection?

Generally, chronic OS, with constant generation of free radicals, affects the immune system's fight against HIV through the following mechanisms:

1. *Enhanced HIV replication through activation of NF- κ B and genes (TNF genes) that further promote oxidative stress*
2. *Apoptosis of CD4 T-cells and immune dysfunction*
3. *Causing cells to make sensitive abnormal chemicals*
4. *Making the body more sensitive to the toxic effects of certain drugs*

Clinical and immunological classification systems of HIV infection use a four-stage system for both adults and children. Higher numbers indicate advanced degrees of deterioration in clinical and/or immunological status. The recent WHO clinical staging or case definition recognises four (1–4) stages (clinical stage 1, asymptomatic; clinical stage 2, mild symptoms; clinical stage 3, advanced symptoms; clinical stage 4, severe symptoms) [16] as well as the US Centers for Disease Control and Prevention (CDC) which provided a revised classification system for paediatric HIV infection; here, the immunological status staging is used for HIV surveillance. The ranking of the CDC HIV symptoms seems different from the WHO listing. The US CDC clinical staging categories are N, not symptomatic; A, mildly symptomatic; B, moderately symptomatic; and C, severely symptomatic [17]. Similarly, the current CDC HIV surveillance and staging recognises five infection stages in which a confirmed case can be classified as 0, 1, 2, 3 or U [18]. Zero (0) indicates a negative HIV test within six months of the first HIV infection diagnosis. Stages 1–3 are determined by the CD4 test immunologic criteria based primarily on the CD4+ T-lymphocyte count as indicated below: stage 1, $\geq 1,500$ in one-year-olds/ ≥ 500 in adults; stage 2, 750–1,499/200–499; and stage 3, 750/<200 [18]. If none of the above apply (e.g. because of missing information on CD4 test results), the stage is U (unknown). These four stages may be referred to, respectively, as the seroconversion and primary HIV infection stage, chronic HIV infection, HIV infection with symptoms and AIDS.

An earlier study by Peterhans showed that viruses could generate ROS from phagocytic cells [19]. Currently, it is known that other viruses (DNA, RNA) could cause cell death through generation of ROS in the infected cell [20,21]. There is confirmed increased free radical production in stage 2 of HIV infection than in stage 4 [22]. Invariably, the antioxidant component is decreased in some cells by half of its amount in stage 2 of the infection [22]. Gaman and her colleagues [23] reported similar patterns of OS increase in stage B/C of chronic lymphocytic leukaemia (CLL) patients. Ibeh et al. using serodiscordant HIV patients showed a high OS condition in serodiscordant-seropositive individuals against their seronegative partners [24]. In a further study, he observed an increased oxidative stress condition in different stages of HIV disease in patients undergoing antiretroviral therapy in Nigeria, where over 50% of the nontreatment group was in stage 2 of the infection [25]. These reports indicate differing OS condition in the various stages of HIV infection and possibly in other viral infections and its capability to serve as a potent surveillance tool (Fig. 1). Further studies should focus on

threshold of OS generated and/or needed to determine entrance to the various infection stages. A possible explanation to the observed consecutive more intense overproduction of ROS in the various stages especially in stage 2 is associated partly with changes in the expression of the antiapoptotic/antioxidant compounds Bcl-2 and thioredoxin along the course of the disease by hydrogen peroxide H_2O_2 [26]. It is known that the free radical H_2O_2 plays a central role in activating NF- κ B (NF- κ B activates HIV replication) through the activation of a factor that binds to a DNA-binding protein; NF- κ B in turn stimulates HIV gene expression by acting on the promoter region of the viral long terminal repeat (LTR). NF- κ B regulates cellular responses as a 'rapid-acting' primary transcription factor. This makes it to be a first responder to harmful cellular stimuli such as H_2O_2 . Known inducers of NF- κ B activity include reactive oxygen species (ROS), tumour necrosis factor alpha (TNF- α) and interleukin-1-beta (IL-1 β) [27]. If there is no adequate levels of antioxidants, the activity of NF- κ B increases in excess amounts and accelerates HIV replication. It is estimated that more than one billion T4 cells are killed and over 50 million HIV replenished on a daily basis in AIDS; this characteristic causes an increase in cytokine synthesis and free radical damage of cells [28].

3. Induction of stress responses and stress response genes: A coping strategy

Oxidative stress is a potent biological stress that weakens and damages cellular components. Naturally, cells devise means of coping, avoiding and responding to this call. Perhaps, the coping mechanism may depend on the degree of the stress, allowing the cell not to overstretch its capabilities. Induction of the antioxidant response element or suppression of inflammatory reactions could limit HIV replication in the host. The master transcription factor known as nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is known to regulate the expression of antioxidants through activation of antioxidant response element (ARE). Fan et al. showed that upregulation of Nrf2 increased the ARE-dependent antioxidants and that HIV-1-related proteins downregulated Nrf2 expression in HIV-1 transgenic rats [29]. Increased oxidative stress induces Nrf2 and stimulates key antioxidant defence mechanism [30] in HIV cells. Cells tend to respond differently to different levels of OS. At a medium level of OS, cells are known to undergo a halt on cell growth and differentiation [31]. In this state, the redox-sensitive transcription factors NF- κ B and activator protein-1 (AP-1) are both activated and induce stress protein synthesis through ARE on stress protein genes [128]. Other factors associated with apoptotic pathways are also activated which enables the cell to undergo the characteristic changes known to apoptosis [32, 33]. A higher level of OS is characterised by the pathological changes caused by free radical damage; this becomes apparent and the cell undergoes death characterised by necrosis [34, 35].

However, response to ROS at the cellular level occurs through ARE and oxidative stress-responsive genes (Fig. 1). Following oxidative stress, a signal is transduced by interaction of specific DNA repair enzymes, antioxidant enzymes, heat shock proteins, proteases, protease inhibitors, cytokines and proliferation factors [36]. This adaptive response is biphasic: an 'early' response (1–4 h), which imparts relatively minor protection, and a 'late' response (12–16 h)

which imparts major protection and involves the synthesis of proteins such as repair enzymes [37]. The response also varies with the initiating stress in that some responses are global (e.g. induction of SOD), whereas others are specific to the initiating stress and in other cases, tissue specific (e.g. induction of surfactant proteins in the lung).

4. Lipid peroxidation products: A possible biomarker of HIV disease progression

Lipid peroxidation is a free radical reaction. Any species that has sufficient reactivity to abstract a hydrogen atom from a polyunsaturated fatty acid side chain in membrane lipids may initiate this process [38]. This occurs when hydroxyl radicals and possibly oxygen react with the unsaturated lipids of bio-membrane, resulting in the generation of lipid peroxide radical ($R00^\bullet$), lipid hydroperoxide ($R00H$) and fragmentation products such as hydroxyoctadecadienoic acid from linoleates, F_2 -isoprostanes from arachidonates and neuroprostanes from docosahexaenoates [39], 4-hydroxy-hexanal, 4-hydroxy-2-nonenal and malondialdehyde (MDA) [40] that gives the OS condition. MDA seems to be the most potent biomarker of lipid peroxidation although 4-hydroxy-hexanal and 4-hydroxy-2-nonenal are also specific, sensitive and quantifiable markers (noninvasive) measurable in urine for OS overview [41]. Lipid peroxidation in biological membranes generally proceeds through a complex process involving rearrangement and destruction of the double bonds in polyunsaturated fatty acid. This occurs in three steps, viz. initiation, propagation and termination phases. Peroxidation of membrane lipids can have several outcomes, such as increased membrane rigidity, decreased activity of membrane-bound enzymes, altered activity of membrane receptors (e.g. sodium pumps), altered permeability (increased permissibility), formation of hydrophobic centres that approaches the external phase, alteration of protein structure, mutagenicity (resulting from DNA/RNA damage or binding) and inhibition of growth and protein synthesis [24]. This is caused by the high nucleophilic properties of decomposed aldehyde products formed during lipid peroxidation, which enables them to react with electrophilic sites such as amino and thiol groups [42]. Biomarkers are characteristics that are specific, reliable and can be measured objectively upon evaluation as indicators of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention.

It is now established that HIV infection is associated with formation of lipid peroxidation products. The importance of evaluating these products is to determine or rather to have a fair idea of the degree of damage the infection has caused the cell. Numerous research works have implicated lipid peroxides as a marker of disease prognosis, drug development and evaluation of efficiency of drugs [43, 44]. A number of scientists have suggested the use of OS marker MDA as a potent additional tool for the assessment and surveillance of HIV/AIDS disease [25,39] and a possible predictor of HIV/AIDS disease progression [45]. This is not unlikely knowing that different levels of OS measures as MDA is associated with stages of HIV/AIDS infection classification (Fig. 1).

5. Elite controllers

Elite controllers are referred to as individuals having the ability to spontaneously suppress viral load and maintain HIV control mainly achieved soon after seroconversion. These individuals may not be common in the population, about <1 %, and may best be understood using serodiscordant HIV infection. There is evidence of an increasing number of these individuals in some parts of Africa.

5.1. Serodiscordant infection: Definition

HIV natural resistance can best be described using serodiscordant HIV infection in sexual partners. Serodiscordant HIV infection recognises couples/sexual partners in which one may be either HIV seroconcordant-seropositive or seroconcordant-seronegative or the partners are having different serostatuses [46]. Serodiscordant HIV infection refers, therefore, to partners adequately exposed to HIV infection in which one is HIV positive (seropositive) and the other HIV negative (seronegative).

5.2. Global prevalence

The prevalence of HIV serodiscordant infection in seronegative population has not been well documented. About 0.5 % (one in 200) people are reported in America [47]. Scott-Algara et al. [48] in 2003 reported that between 5 and 15 % of individuals of different populations at risk of HIV infection (regular partners of seropositive subjects, prostitutes and intravenous drug addicts) show no signs of apparent infection by HIV in spite of many years of exposure. However, some studies have indicated an estimate of about 5 % in Africa. Fowke et al. [49] in a cohort study showed that 4.3 % of HIV-1-exposed seronegative prostitutes in Kenya were persistently HIV negative after 12 years of follow-up study. Other reports have shown an increasing number of persistent serodiscordant-seronegatives and the risk of HIV transmission within stable serodiscordant partners across 23 countries of sub-Saharan Africa [50].

5.3. Classification of HIV natural resistance

Those individuals who are serodiscordant-seronegative may possess natural resistance to HIV infection. They can be grouped into two: *highly exposed persistently seronegatives (HEPSs)* and *long-term nonprogressors (LTNPs)*

5.3.1. Highly Exposed Persistently Seronegatives (HEPSs)

They are individuals who are repeatedly exposed to HIV through different routes of exposure but persistently remain seronegative (do not develop antibody to HIV).

5.3.2. Long-Term Nonprogressors (LTNPs)

About 5–10 % of HIV-infected people remain asymptomatic for about 7–20 years after infection despite being on no antiretroviral therapy. Their immune function is well controlled with CD4+

lymphocytes counts above 6000/mm³ coupled with a low plasma HIV RNA. Initially, these were based primarily on immunologic control, i.e. maintenance of high CD4 count, but currently LTNPs are known as elite controllers based on viral load calculations/standards. Those with undetectable viremia (HIV RNA <50 copies/ml) are elite controllers, while those with low but detectable viral load (HIV RNA <2000 copies/ml) are known as viremic controllers [51, 52]. These individuals are referred to as LTNP or elite controllers (ECs) [47]. Other subgroups include typical progressors (TPs) where about 80 % of HIV-infected individuals develop AIDS within the median time of ten years [53] and rapid progressors (RPs) which develop within 2–3 years of infection and exist in 10 % of the population [54].

5.3.3. *Viral fitness*

The phenomenon of viral ‘fitness’ relates to the pathogenicity of certain strains of HIV. HIV replicative capacity (RC) is attributed as a component of viral fitness [55]. RC, therefore, is a measure of the ability of the virus to replicate successfully in a given environment [56] which tends to affect controllers of HIV. In LTNP, a number of genetic defects have been associated with the virus. Such documented defects or genetic lesions include the NF-κB or SP1 site and the nef mutant gene within the long terminal repeats of the virus [57]. According to Learmont et al., some LTNPs have shown to possess this mutant gene (nef) [58]. Also faster rates of disease progression have been observed in Ugandan individuals infected with subtype D compared with subtype A isolates. The current concept is based on the viral load dynamic equilibrium set point that is established between the production of virus (VR) (dependent on the number of activated CD4 cells) and the suppression of replication and elimination of virus-producing CD4 cells by adaptive immunity [51, 52]. Here, the elite controllers fall into extreme low viral load carriers that are undetectable, though other researchers still maintain effective immune clearance of EC as the major factor [58]. From studies, vigorous virus-specific humoral and cell-mediated immune responses have been detected. For example, high titres of potent neutralising antibodies have been found in sera of LTNPs with strong CD8⁺ cytotoxic T-lymphocyte cells [59]. Genetic differences in human leukocyte antigen (HLA) alleles have also been shown to influence HIV disease susceptibility [60] and disease progression [61]. In particular, HLA B*5701 has been found as reported by Migueles et al. to be highly overrepresented in LTNP. Other immunological factors found include natural killer (Nk) cells in resistant Vietnam population [48] and high levels of IL-2 (interleukin-2) found in resistant infants born to HIV-positive mothers.

A mutant allele of CCR5 with a 32-base pair deletion (CCR5-delta-32) discovered in 1996 confers resistance to the highly exposed group of seronegative individuals [62,63]. It is often seen in populations of European origin (in Caucasians, 1 % are homozygous, while 15–20 % are heterozygous), which encodes a nonfunctional truncated protein. Homozygotes for the Δ-32 allele are believed to exhibit a strong and complete resistance to HIV infection, whereas heterozygotes delayed progression to AIDS as observed in LTNP [64]. This mutation is hypothesised to be absent in African origins and certain Asian populations.

6. Protective effects of antioxidants

Antioxidants are groups of substances which when present at low concentrations, in relation to oxidisable substrates, significantly inhibit or delay oxidative processes while often being oxidised themselves [65]. There exists a balance between their formation and removal (redox state). To maintain an oxido/redox balance, cells protect themselves from the toxicity of excess ROS/RNS in different ways, enzymatic and nonenzymatic antioxidants.

6.1. Relevant HIV antioxidants: Does HIV benefit from their activities?

There are many biochemical processes that oxidise reduced antioxidant molecules to neutralise free radicals and then restore the antioxidant molecules to a reduced state. In HIV infection, antioxidants serve to aid the CD4 cells in removing the virions by reducing the oxidative stress that develops during HIV infection [66]. Antioxidants are useful to the host for defence and neutralisation of free radicals.

6.1.1. Superoxide Dismutase (SOD)

Superoxide dismutase (EC 1.15.1.1) destroys the free radical superoxide by converting it to peroxide which is further destroyed by catalase or glutathione peroxidase (GHPX) reaction. It is known that SOD converts the superoxide radical to the less-reactive H_2O_2 [67]. In humans, the three forms of SOD are cytosolic Cu, Zn-SOD, mitochondria Mn-SOD and extracellular SOD (ECSOD). Generally, SOD catalyses the dismutation of $O_2^{\cdot -}$ by successive oxidation and reduction of the transition metal ion at the active site in a ping-pong-type mechanism with widely acknowledged high reaction rates [68]. Copper-zinc superoxide dismutase (Cu, Zn-SOD) is also known as SOD-I; the active site is constituted by a copper and a zinc atom bridged by a common ligand.

The HIV TAT domain is a regulatory protein of the virus that enhances the efficiency of virus transcription and has been shown to carry exogenous molecules into cells [69], thus can fuse with protein transduction domains (PTDs) for effective cellular cargo delivery [70]. TAT-PTD linked-SOD1 has been shown to be ferried across the cytoplasm and even the mitochondria where superoxide is generated, making TAT-SOD1 a source of intracellular antioxidant [72]. Currently, Qing et al. [73] in 2013 provided evidence that TAT-SOD1 has protective therapeutic activity against ionisation radiation. Conversely, cells actually infected with HIV have been reported to express less Mn-SOD and to lose their ability to induce antioxidant enzyme in response to TNF. Therefore, expression of TAT protein of HIV suppresses cellular Mn-containing superoxide dismutase (Mn-SOD) [74]. Furthermore, the protective nature of Mn-SOD has been demonstrated by several authors; its overexpression provides oxidant protection against AZT or 3TC-induced endothelial dysfunction [75] and against lung cancer radiation therapy [76].

6.1.2. Glutathione system

The glutathione system (glutathione, glutathione peroxidase, glutathione transferase and glutathione reductase) is a key defence against H_2O_2 and other peroxides. The term glutathione is typically used as a collective name to refer to the tripeptide L-gamma-glutamyl-L-cysteinyl glycine in both its reduced and dimeric forms. Glutathione is necessary for maintaining immune-mediated T-cell and phagocytosis. It inhibits HIV replication by acting at the late stages of the virus' life cycle through strong suppression of the production of p24 and gag protein as well as the viral infectivity factor (Vif) [77]. This results in a dramatic decrease in both budding and release of virus particles from chronically infected cells (either macrophages or lymphocytes). Also there is a relative decrease in the expression of gp120 (the protein component of the HIV viral coat), the major envelope glycoprotein rich in intrachain disulphide bonds. Experiments with rats showed that gp120 increases the accumulation of H_2O_2 and superoxides; thus, Brook et al. [78] demonstrated that the activity of this HIV protein increases that of the key glutathione peroxidase as a defensive mechanism against ROS. Also glutathione inhibits the reverse transcriptase (RT) process of HIV and its expression [79]. GSH further blocks in a concentration-dependent manner the (intracellular) activation of essential protein-splitting enzymes, such as HIV proteases. The glutathione redox cycle is a major source of protection against low levels of oxidant stress, whereas catalase becomes more significant in protecting against severe oxidant stress [80]. Glutathione reductase enzyme (EC 1.8.1.7), which reduces glutathione disulphide (GSSG) to the sulphhydryl form GSH, is an important cellular antioxidant.

6.1.3. Catalase (CAT)

Catalase (EC 1.11.1.6) is a tetrameric haem-enzyme consisting of 4 identical tetrahedrally arranged subunits of 60 kDa. It is highly efficient that it is difficult to be saturated by H_2O_2 at any concentration [81]. Catalase reacts with H_2O_2 to form water and molecular oxygen, a less/nontoxic product. Catalase protects cells from hydrogen peroxide generated within them. It is actively involved in the HIV disease progression and may serve as one of the marker enzymes where it augments glutathione, SOD and other antioxidants. Serum catalase is known to increase as HIV disease progresses [82, 83].

6.1.4. Vitamins A, C and E

Vitamin A plays a role in the development of both T-helper cells and B-cells. Studies have shown that vitamin A, in the form of retinol or retinoic acid, improves immunity by stimulating immunoglobulin synthesis through its action on T-cells or T-cell products. Retinoic acid inhibits the production of interleukin-6 in a dose-dependent manner by downregulating the expression of interleukin-6 mRNA [84]. Vitamin A acts as an immunostimulant by modulating the growth and function of T-cells, B-lymphocytes and natural killer cells.

Vitamin C (ascorbate, $AscH^-$) can donate a hydrogen atom to a free radical molecule (R^\cdot), thereby neutralising it while becoming an ascorbate radical itself (Asc^\cdot or $Asc^{\cdot-}$). But the free radical (Asc^\cdot) is very stable because of its resonance structure. Moreover, $AscH^-$ is

readily regenerated from the Asc^- with NADH or NADPH-dependent reductases [85]. Ascorbate can also neutralise the radical form of other antioxidants such as glutathione (GS^\cdot) and vitamin E (TOC^\cdot). Vitamin C also inhibits the replication of human immunodeficiency virus-1 (HIV-1) [86].

Tocopherols (vitamin E) interrupt free radical chain reactions by capturing the free radical; this inherent action displays the antioxidant properties of vitamin E. The free hydroxyl (OH) group on the aromatic ring of tocopherol is responsible for its antioxidant activity. The hydrogen from this group is transferred to the free radical, resulting in a relatively stable free radical form of the vitamin [87]. Vitamin E is an effective antioxidant (peroxyl radical scavenger) for terminating the chain reactions of lipid peroxidation in the cell membrane. The tocopheroxyl radical is the pro-oxidant form of vitamin E and is thought to be regenerated to the antioxidant form by a network of other antioxidants, including vitamin C and glutathione. In the mitochondria membrane, vitamin E that donates a hydrogen to neutralise a free radical can be regenerated (reduced) by coenzyme Q which has two hydrogens to donate and can avoid becoming a free radical by donating both hydrogens; this is an efficient process. Alpha-tocopherol has potent activity against HIV. The anti-HIV-1 activity may be due, in part, to their antioxidant properties. Alpha-tocopherol generally interferes with membrane integrity and fluidity. As HIV-1 is a membrane virus, any alteration of the membrane fluidity of the virus interferes with its ability to bind to cell-receptor sites, thus reducing its infectivity [88]. It stimulates CD4 T-cell and IL-2 proliferation [89]. Vitamin E inhibits CD95 (APO-1/Fas) ligand expression (part of TNF receptor which T-cell uses to undergo apoptosis) and protects T-cell from activation-induced cell death of the CD95/CD95 ligand system of T-cells [90]. Tocopherol completely inhibits and blocks DNA binding NF- κ B, resulting to complete inaction [91].

6.1.5. Flavonoids

The flavones and catechins seem to be the most powerful flavonoids for protecting the body against ROS [92]. Flavonoids may have an additive effect to the endogenous scavenging compounds; they increase their function. Flavonoids (quercetin) was reported to exhibit both anti-infective and antireplicative HIV abilities. Quercetin significantly downregulates p24 antigen production, LTR gene expression and viral infectivity in a dose-dependent manner (5–50 mM) and further downregulation of the expression of the pro-inflammatory cytokine TNF- α with concomitant upregulation of anti-inflammatory cytokine IL-13 [93]. A higher level of IL-13 is known to inhibit TNF- α production and also HIV-1 infection. Some flavonoids work on the intracellular replication of viruses, whereas others inhibit the infectious properties of the viruses. Flavonoids have inhibitory activity on reverse RT and RNA-directed DNA polymerase [94, 95]; however, it also has antiintegrase and antiprotease activities [96]. Similarly, myricetin activity was tested against HIV-RT and inhibited the enzyme by 49 % [97]

6.1.6. Metals

Zinc is a metallic divalent cation bound to proteins within cells and cell membranes. Zinc plays catalytic, structural and regulatory roles in more than 200 zinc metalloenzymes that have been identified in biological systems. Zinc fingers are exploited by transcription factors for inter-

acting with DNA and regulating the activity of genes [98]. Another structural role of zinc is in the maintenance of the integrity of biological membranes (membrane stabilisation) by its ability to stabilise thiol groups and phospholipids, resulting in their protection against oxidative injury. These properties affect signalling processes involved in cell-mediated immunity. Zinc also influences gene expression by structural stabilisation of different immunological transcription factors. It induces cytokines, including interleukin (IL)-1, IL-6 and TNF- α [99]. HIV binds to zinc ions in T-cells in order to produce proviral peptides, which form the basis of new infectious viral particles. HIV-1 protease enzyme cuts the viral chains to form new infectious viral particles, as with other proteases (collagenase, angiotensin-converting enzyme (ACE), carboxypeptidase A and neutral endopeptidases); when sufficient zinc ions are bound to the protease, it will remain inactive [100]. Zinc therefore has both an enhancing and inhibiting activity depending on its concentration in the surrounding tissues. In HIV replication, viral RNA is transformed into viral DNA via the enzyme reverse transcriptase; zinc also binds to this enzyme. Zinc influences NK cell-mediated killing and also modulates cytolytic T-cell activity and inhibition of TNF- α [101], in addition to its anti-HIV drug potentiation activity as [102].

Similarly, selenium is found in human and animal tissue as L-selenomethionine or L-selenocysteine. L-selenomethionine is incorporated randomly in proteins known as selenoproteins. The antioxidant activity of selenium is mainly accounted for by virtue of its role in the formation and function of the selenium-dependent glutathione peroxidase (GSHPx) [103]. Selenium effect on boosting cellular immunity is due to the upregulation of the expression of the lymphocyte cells' high affinity to interleukin (IL)-2 receptors, thus providing a vehicle for enhanced lymphocyte cell response as well as preventing oxidative stress to human cells [104,105]. Research has shown that the HIV virus hijacks the host supply of selenium for its own antioxidant protection, thereby inducing or exacerbating a selenium deficiency with increasing disease progression. Thus, HIV may be capable of incorporating host selenium into viral selenoprotein that has glutathione peroxidase activity [106,107].

7. A search for functional cure: Is it functional or sterilising cure?

There is currently no cure for HIV/AIDS, but recent research interest on HIV treatment tends to focus on functional cure which has renewed optimism for HIV cure. The aim of the functional cure is to get rid of all viruses from the system and remove any negative effects of HIV on the body and prevent viral rebound after discontinuation of the antiviral treatment. In other words, people who had been functionally cured would never develop AIDS or other signs of HIV disease as classified by WHO [16] and US CDC [17, 18]. Current HIV themes are now focused on this approach to solve the problem of HIV infection globally.

This type of *HIV cure* does not translate to eradicating all viruses from the body but being able to control viremia without antiviral drugs [108]. The difference between a functional cure or remission and eradication/sterilisation cure is that while the former may de-emphasise the HIV viral reservoir clearance and establish a sufficiently strong immune response with low-

level viremia at <50 copies/ml, the latter sees it as a central task to eliminate the virus from all body compartments with a plasma HIV RNA count of <1 copy/ml. In addition, the reservoir is significantly smaller in elite controllers with decreased concentration of HIV DNA. Viral reservoir is simply different areas of the body where viral copies hide quietly and undetected and are unable to be treated until they are stimulated or activated to reproduce. Anatomical reservoirs include the gastrointestinal tract (GIT), lymphoid tissue and the central nervous system (CNS). These compartments may harbour unique long-lived latently infected cells, and penetration of cART may be limited at these sites. What are the phenotypic characteristics of functional cure? First is the undetectable or very low noninfective levels of the virus (<50 copies/ml) though some authors suggested <75 copies/ml for six months [109], and second is a normal range of CD4 cell count when cART is discontinued. Although cART have tremendously improved the lives of individuals with HIV, they come with significant side effects, perhaps not the ideal functional cure which would get HIV-infected patients to the point where cART are no longer needed to keep their infections under control.

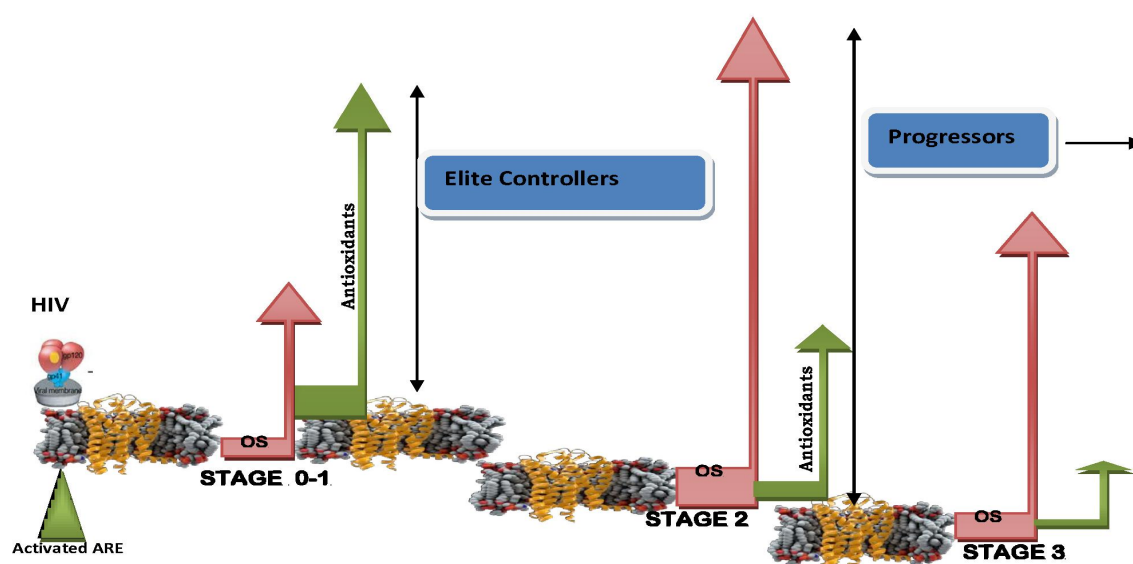


Figure 1. Schematic diagram representing a putative mechanistic model of oxidative stress (OS) activity in elite controllers and in HIV disease progression. (Consequences of oxidant/antioxidant activation in the different stages of HIV infection and interrelationship between OS and HIV control. OS= oxidative stress, ARE= antioxidant responsive element.)

8. Oxidative stress regulation of elite controllers: A reality or a hoax of functional cure

It seems certain that oxidative stress control of HIV elite controllers may contribute to the expected functional cure in HIV patients (Fig. 1). Examination of possible and established cases implicates the action of redox control instead as an approach for the cure. But is this a mis-conceived theory or a deception?

Epidemiology of elite or aviremic control of HIV infection appears to occur in approximately 1 in 300 HIV-infected persons and represents a distinct phenotype among HIV-infected individuals [110]. Through a recently established international collaboration (HIV Controller Consortium), over 300 elite controllers have been identified and recruited for study [111]. Achieving either a functional cure (long-term control of HIV in the absence of cART) or a sterilising cure (elimination of all HIV-infected cells) still remains a major challenge to scientists. As noted previously, establishment of a latent or 'silent' infection in resting CD4⁺ T-cells is a major impediment to finding HIV cure. Several randomised clinical trials have shown that treatment intensification even with additional ART has little impact on latent reservoirs. Some potential drugs used to reduce latency, including histone deacetylase inhibitors, currently used and licensed for the treatment of some cancers, methylation inhibitors, cytokines such as IL-7 or activators of NF- κ B such as prostratin, show promising activity in reversing latency in vitro when used either alone or in combination [112]. Prodrugs provoked through ferrocene-mediated oxidation currently have been developed to enhance the selectivity and specificity of anticancer drugs. Peng et al. [113] described how the strategies of ROS activation can be employed for further development of new ROS-targeting prodrugs, which must eventually lead to novel approaches and/or combined technology for more efficient and selective treatment of cancers.

The major reason why HIV cannot be cured is the persistence of HIV in a latent form in different cellular reservoirs which may be pre- or post-integration latency. Functional cure strategies tend to reduce effects of this latency. The case report of a German patient with acute myeloid leukaemia, who received a bone marrow transplant from a donor with a 32-base pair deletion in the CCR5 gene, may remain the only current example of a sterilising cure [114]. After transplantation, the patient discontinued cART for 45 months and HIV RNA remained at below 1 copy/ml with no virus found in reservoir compartments. However, a strategy of using bone marrow transplantation with a CCR5 mutant donor is not a realistic cure for HIV, given the toxicity and complexity of the treatment. Similarly, Sangamo Biosciences used zinc finger nucleases, a genome editing technique, to cut off the gene in CD4 cells that controls the expression of CCR5 coreceptor which the virus uses to enter cells, based on the coreceptor theory [115,116]. The data generated from the clinical trials with the drug SB-728-T showed control of viremia, improved CD4 cells and reduced proviral reservoirs with no safety concerns; these were sustained for 56 weeks after disruption of treatment [117,118]. How cost-effective this treatment and its availability to the large population of HIV patients remain to be answered.

There is a possibility that other cases of remission or functional cure exist in patient populations globally who may have started treatment soon after infection. But the figures are not certain on the proportion of these populations that experience functional cure, though some experts have speculated one in seven people. To date, HIV functional cure has not been 100 % successful. In 2010, the Mississippi baby (treatment started early) believed to be functionally cured of HIV after two years of treatment discontinuation now has detectable levels of the virus in her blood [119], though this paved way for rational very early treatment in perinatal HIV infection [120]. Similarly, a German patient who initiated antiretroviral therapy with AZT,

3TC and efavirenz just under three months after exposure to HIV and within one month of confirmed seroconversion, after an acute viral illness had his viral load below limit of detection with stable range of CD4 cell ($900\text{--}1,000\text{ cells/mm}^3$). He has shown no HIV RNA or associated proteins in any tissue/organ compartment after treatment interruption for nine years [121]. This case shows evidence of strong and broad CD8 T-cell responses and strong proliferative CD4 T-cell responses. What might be responsible for this? In contrast, analysis of the CCR5 coreceptor showed that the homozygous CCR5 promoter A59029G was present, but no delta 32 deletion was observed [121] and the HLA-I subtype was A 01, 02 B:44, 52. Nevertheless, HIV was recovered later from the patients using a humanised mouse model after transplantation of the patient's purified CD4 T-cells and anti-CD3/anti-CD28 stimulation. This indicated the presence of HIV capable of replication and that other factors other than CCR5 mutation may be responsible for viral control. The French VISCONTI cohort study also reported patients who started treatment early and was able to gain control of the virus replication with undetected viral load after six years of treatment interruption [122]. A period of at least four years of treatment is suggested prior to treatment interruption [123].

In most studies, preferential attention has been given to latent resting CD4⁺ T-lymphocytes as a source of HIV persistence in the cell and CCR5 coreceptor mutation as responsible for HIV control. While explanations for functional cure have proved inadequate, ROS has been demonstrated to contribute to disease progression and drug design [124]. New strategies for HIV functional cure should incorporate use of ROS-activated prodrugs [113]. Adequate data on OS condition of spontaneous controllers (natural resistance) and the posttreatment controllers (PTC)/functional cure are not available. Luc Montagner, codiscoverer of the HIV, identified oxidative stress as one of the four factors responsible for its variability [125]. Besides, recent report that P13K/Akt inhibitors can drastically sensitise HIV-infected macrophages (reservoir) to oxidative-stress-induced cell death [126] indicates possible ROS therapeutic approach to achieve HIV cure as well as the cytoprotective effect of the virus-activated P13K/Akt in human microglial cell line and macrophages against apoptotic challenge [127]. In addition, HIV infection increases the cellular levels of ROS, especially superoxide anion and peroxynitrite which accelerates HIV replication in macrophages [28]. Recently, Bhaskar et al. demonstrated that a marginal increase of about $\sim 25\text{mV}$ in EGS_H is sufficient to switch HIV-1 from latency to reaction using Grx1-roGFP2 biosensor [128], suggesting possibility of purging HIV-1 by redox modulators which shows how fluctuations in EGS_H modulate expression of antioxidant gene in infected HIV patients [129].

9. Conclusion

HIV host reservoir of latently infected cells stands as the barrier to a successful longed-for cure that would free HIV-positive patients from a lifetime of taking antiretroviral drugs. Antiretrovirals known to protect uninfected cells reduce the viral load and stave off full-blown AIDS. However, they do not eliminate the HIV reservoir in the host. Though the virus is not completely eradicated in EC, the reservoir could not replicate, so low viral load is recorded and antiretrovirals are unnecessary. OS however has been implicated in HIV replication and

disease progression; so it can be used as a surveillance tool. The chapter presents oxidative stress and redox regulation of controllers of HIV infection as a means to achieve a functional cure. Therefore, ROS should be seen as a viable strategy to achieving HIV functional cure.

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