The role of antioxidant enzymes and micronutrients in mitigating HIV-associated oxidative stress in Sub-Saharan African populations

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Abstract

HIV/AIDS poses a major public health burden in sub-Saharan Africa, a region disproportionately affected by both chronic infections and malnutrition. While antiretroviral therapy (ART) has markedly improved survival and viral suppression, emerging evidence highlights the persistent role of oxidative stress in immune dysfunction, disease progression, and comorbidity development in people living with HIV. This review examines the mechanisms of HIV-associated oxidative stress and evaluates the role of antioxidant enzymes and micronutrients in its modulation. It further explores the prevalence and causes of regional micronutrient deficiencies in sub-Saharan Africa and synthesizes findings from intervention studies to guide evidence-based nutrition and policy strategies in HIV care. The review reveals that HIV and ART disrupt antioxidant systems while also depleting essential micronutrients due to poor dietary diversity, soil nutrient depletion, and socioeconomic constraints. Evidence from multiple clinical trials in sub-Saharan Africa and beyond demonstrates that targeted micronutrient supplementation can enhance antioxidant capacity, improve CD4+ counts, reduce opportunistic infections, and support

ART efficacy, particularly in nutrient-deficient individuals. Mitigating HIV-associated oxidative stress through antioxidant and micronutrient support offers a critical but underutilized strategy in HIV care. Integrating nutritional screening, targeted supplementation, and food fortification into HIV management frameworks could substantially improve immune recovery and long-term well-being among people living with HIV.

Keywords: HIV, Oxidative stress, Antioxidant enzymes, Micronutrient deficiency, Sub-Saharan Africa, Antiretroviral therapy

Introduction

Human Immunodeficiency Virus (HIV) infection is a major public health challenge, particularly in sub-Saharan Africa, which accounts for approximately two-thirds of the global HIV burden [1]. Although significant advances in antiretroviral therapy (ART), including the rollout of potent regimens such as Tenofovir-Lamivudine-Dolutegravir (TLD), have transformed the management of HIV, people living with HIV (PLWH) continue to experience systemic complications that may undermine immune recovery [2]. One such complication, and frequently underrecognized in clinical settings, is oxidative stress. Oxidative stress results from an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defense systems [3]. In the context of HIV, both the virus itself and ART can promote excessive ROS generation, which leads to lipid peroxidation, DNA damage, protein dysfunction, and the activation of pro-inflammatory pathways [4,5]. Consequently, these oxidative events are implicated in immune dysregulation, accelerated aging, and non-AIDS comorbidities such as cardiovascular disease and neurocognitive impairment [6].

To counteract oxidative stress, the body relies on its antioxidant defense systems, which comprise enzymatic mechanisms, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), and non-enzymatic micronutrients including vitamin C, vitamin E, selenium, zinc, and magnesium [7,8]. However, several studies have reported reduced activity of these enzymes and depletion of micronutrients in HIV-infected individuals, particularly among untreated patients or those with advanced disease [9,10]. Even though ART can partially restore antioxidant capacity, persistent oxidative imbalance has been observed in

virologically suppressed individuals, raising concerns about potential long-term effects [11]. Importantly, in sub-Saharan Africa, this biochemical challenge is further compounded by high rates of micronutrient deficiencies due to food insecurity, poor dietary diversity, and coexisting infections [12, 13]. Despite these challenges, antioxidant-based adjunct therapies remain underutilized in HIV management protocols across the region. Furthermore, the existing literature on antioxidant enzyme dynamics and micronutrient interactions with HIV pathology is fragmented, with few region-specific syntheses available to guide nutritional or pharmacological interventions.

In light of this gap, this review aims to synthesize current evidence on the role of antioxidant enzymes and micronutrients in modulating oxidative stress among HIV-infected populations in sub-Saharan Africa. Specifically, it highlights the mechanisms linking oxidative stress to HIV pathogenesis, assesses the status of antioxidant defenses in the region, and explores the therapeutic potential of micronutrient supplementation. Therefore, this review seeks to inform future research directions and support integrated HIV care strategies tailored to the nutritional and biochemical realities of African populations.

Materials and method

Search strategy and data sources

This review was conducted using a structured, integrative literature search approach. Relevant peer-reviewed articles were sourced from multiple electronic databases and academic repositories including PubMed**,** Google Scholar**,** Scopus**,** ScienceDirect**,** and Web of Science. Keywords used in combination and with Boolean operators included: *HIV*, *oxidative stress*, *antioxidant enzymes*, *micronutrients*, *glutathione*, *selenium*, *zinc*, *HIV and ART toxicity*, *mitochondrial dysfunction*, and *sub-Saharan Africa*. The search was restricted to articles published in English between 2000 and 2025. Reference lists of key articles and systematic reviews were also hand-searched to identify additional studies that met inclusion criteria.

Eligibility criteria

To ensure scientific relevance and contextual specificity, studies were included based on the following criteria:

1. Study population: Human subjects living with HIV, particularly in sub-Saharan Africa.
2. Focus: Studies that investigated oxidative stress, antioxidant systems, micronutrient status, or ART-associated mitochondrial dysfunction.
3. Study design: Clinical trials, observational studies, mechanistic studies, systematic reviews, and meta-analyses.
4. Outcome measures: At least one outcome related to oxidative stress biomarkers, antioxidant enzyme activity, micronutrient levels, or ART-induced redox imbalance.

Studies were excluded if they:

1. Focused solely on non-HIV populations.
2. Lacked primary data or were editorial/opinion pieces without empirical support.
3. Were duplicates or preclinical animal studies without human data relevance.

Data extraction

The articles were screened by title and abstract, followed by full-text review. Key data extracted included study location, sample size, ART regimen, oxidative stress markers measured, micronutrient profiles, and clinical results. Findings were organized thematically into the following categories:

1. Mechanisms of oxidative stress in HIV infection.
2. ART-associated mitochondrial and oxidative effects.
3. Micronutrient deficiencies in sub-Saharan Africa.
4. Evidence for antioxidant enzyme and micronutrient interventions.
5. Policy implications and nutrition-integration strategies.

A narrative synthesis approach was used to consolidate the literature, highlighting trends, gaps, and context-specific insights.

Mechanisms of oxidative stress in HIV infection

Oxidative stress is a pathological state arising from an imbalance between the production of reactive oxygen species (ROS) and the capacity of the body's antioxidant defenses to neutralize them [3, 14]. In the setting of HIV infection, oxidative stress is not merely a secondary complication, it plays an integral role in immune dysregulation and the

development of non-AIDS comorbidities [15]. Importantly, multiple interlinked mechanisms contribute to oxidative stress in HIV-infected individuals, involving both viral and host-derived factors.

To begin with, several HIV-encoded proteins, most notably *Tat*, *gp120*, *Nef*, and *Vpr*, have been shown to directly stimulate ROS production in host cells. *Tat* protein, for example, enhances the activity of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase in immune cells and promotes mitochondrial dysfunction, both of which elevate intracellular ROS levels [16]. Similarly, *gp120*, the viral envelope glycoprotein, induces calcium influx and depolarization of mitochondrial membranes in neurons and endothelial cells, leading to increased superoxide production [17]. *Nef* has also been implicated in the disruption of antioxidant enzyme expression and can impair mitochondrial function in macrophages and T-cells [18]. Together, these viral proteins are not only cytotoxic but also modulate host cell signaling in ways that favor viral replication, inflammation, and apoptosis [19,20].

In addition to viral protein effects, mitochondria themselves are a major source of intracellular ROS, primarily through electron leakage from respiratory chain complexes I and III [21]. In HIV-infected cells, mitochondrial dysfunction is a consistent feature, driven by a combination of direct viral effects, inflammatory cytokines, and antiretroviral therapy (ART)-related mitochondrial toxicity, particularly with older nucleoside reverse transcriptase inhibitors such as zidovudine and stavudine [22,23,24]. This mitochondrial dysfunction leads to impaired ATP production and elevated ROS generation, thereby initiating a self-perpetuating cycle of mitochondrial damage and oxidative stress. Moreover, damage to mitochondrial DNA (mtDNA) further compromises mitochondrial function, exacerbating oxidative injury [25].

Compounding these effects, HIV infection is characterized by persistent immune activation, even in individuals receiving effective ART. Activated immune cells, particularly macrophages and neutrophils, produce large quantities of ROS and reactive nitrogen species (RNS) as part of their antimicrobial defense [26]. However, in the context of chronic HIV infection, this ROS production becomes dysregulated and contributes to bystander tissue damage [27]. Furthermore, increased levels of pro-

inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) amplify oxidative stress by both stimulating ROS-generating pathways and downregulating antioxidant enzyme expression [28].

Another critical component of the antioxidant system is glutathione (GSH), the most abundant intracellular non-enzymatic antioxidant, essential for detoxifying ROS and maintaining redox homeostasis [29]. Unfortunately, HIV-infected individuals often exhibit significantly reduced levels of total and reduced GSH, especially in CD4+ T cells. This depletion is attributed to several factors, including increased GSH utilization due to elevated ROS levels, impaired synthesis caused by cysteine and methionine deficiency, and inhibition of glutathione-regenerating enzymes such as glutathione reductase [30,31]. As a result, low GSH levels not only increase susceptibility to oxidative damage but also impair T-cell proliferation, phagocyte function, and overall antiviral immune responses [32].

Moreover, in many sub-Saharan African populations, HIV infection coexists with malnutrition and widespread micronutrient deficiencies, particularly of zinc, selenium, vitamin C, and vitamin E, which are vital cofactors for antioxidant enzymes [33]. Poor dietary intake, intestinal malabsorption, and the increased metabolic demands during infection all contribute to these deficiencies [34]. In addition, environmental exposures such as biomass smoke, coinfections like tuberculosis, and lifestyle factors including alcohol or substance use further increase oxidative burden in HIV-infected individuals [35].

While ART remains the cornerstone of HIV management, it is important to note that certain antiretroviral drugs, especially early-generation nucleoside analogues, have been implicated in mitochondrial toxicity and oxidative stress [36]. Mechanistically, these drugs inhibit DNA polymerase-γ (responsible for mtDNA replication), induce mitochondrial membrane permeability transition, and promote mtDNA mutations [37]. Although newer ART regimens such as TLD (Tenofovir-Lamivudine-Dolutegravir) exhibit improved safety profiles, emerging evidence suggests that even dolutegravir may alter redox balance through off-target effects on mitochondrial function [38]. Table 1 shows the mechanisms of oxidative stress in HIV infection.

Table 1: Summary of Mechanisms of Oxidative Stress in HIV Infection

Mechanism	Key Features	Impact
1. Viral Protein-Induced ROS	HIV proteins (Tat, gp120, Nef, Vpr) stimulate ROS via mitochondrial and NADPH oxidase activation	Promotes oxidative damage and viral replication [5,39]
2. Mitochondrial Dysfunction	Mitochondrial injury from HIV/ART leads to impaired respiration and increased ROS generation	Cell apoptosis and chronic oxidative stress [40]
3. Chronic Immune Activation	Persistent inflammation elevates ROS through activated macrophages, neutrophils, and cytokine signaling	Persistent inflammation, elevating ROS [29,41]
4. GSH Depletion	Reduced synthesis and increased usage of GSH in HIV-infected individuals	Impaired detoxification of ROS, weakened immune response [5,42]
5. Nutritional Deficiencies	Low intake/absorption of antioxidants, common in HIV-affected populations	Compromised antioxidant defense, worsened oxidative burden [32,43]
6. ART-Induced Oxidative Effects	Some ART drugs impair mitochondrial DNA replication and function	Mitochondrial toxicity, sustained ROS generation [44]

Impact of ART regimens on antioxidant systems

Antiretroviral therapy (ART) has transformed HIV from a fatal illness into a manageable chronic condition. It has significantly reduced HIV-associated morbidity and mortality by suppressing viral replication and restoring immune function [45]. However, emerging evidence indicates

that ART, particularly certain drug classes and regimens, can contribute to oxidative stress and impair the host's antioxidant defense systems. This paradox where ART promotes immune restoration while simultaneously introducing metabolic complications has gained increasing attention in recent years, especially in regions like sub-Saharan Africa, where ART use intersects with nutritional deficiencies and a high burden of infectious diseases [46,47].

One of the most well-documented manifestations of this paradox is mitochondrial toxicity, particularly with early-generation nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine (AZT), stavudine (d4T), and didanosine (ddI) [48]. These agents inhibit mitochondrial DNA polymerase-γ, an enzyme essential for the replication of mitochondrial DNA (mtDNA). As a result, inhibition leads to mtDNA depletion, mitochondrial dysfunction, and increased production of ROS [49]. This sequence of events compromises oxidative phosphorylation, increases electron leakage from the electron transport chain, and triggers apoptotic pathways in both immune and non-immune cells [50]. Clinically, this is associated with a range of mitochondrial-related complications, including lipodystrophy, neuropathy, myopathy, lactic acidosis, and hepatic steatosis, which are especially prevalent in sub-Saharan populations on long-term ART [51].

In addition to mitochondrial toxicity, several studies have shown that ART can directly or indirectly reduce the activity of key antioxidant enzymes [52,53,54]. For instance, decreased activity of glutathione peroxidase (GPx) has been reported among ART-experienced patients, especially those on older regimens. This reduction compromises the enzymatic breakdown of hydrogen peroxide (H_2O_2), thereby increasing the risk of cellular oxidative damage [52]. Similarly, ART-induced mitochondrial stress may overwhelm superoxide dismutase (SOD), resulting in the accumulation of harmful superoxide radicals (O_2^-) [53]. Moreover, evidence suggests that catalase activity may also be downregulated in ART-treated individuals, although outcomes vary depending on the specific regimen and duration of therapy [54]. Supporting this, a study conducted in Nigeria found that HIV-infected individuals on first-line ART regimens exhibited significantly lower SOD and catalase levels compared to HIV-negative controls, indicating a persistent

redox imbalance despite virologic suppression [55].

Complementing these findings, glutathione (GSH), a tripeptide composed of glutamate, cysteine, and glycine, plays a central role in detoxifying ROS and maintaining redox homeostasis [56]. Unfortunately, ART, particularly NRTIs, has been shown to impair GSH metabolism in multiple ways: by depleting precursor amino acids required for synthesis, increasing GSH utilization due to oxidative stress, and suppressing the expression of glutathione reductase, the enzyme essential for regenerating reduced GSH from its oxidized form glutathione disulfide (GSSG) [57]. These disruptions lead to reduced GSH levels in various tissues, including peripheral blood mononuclear cells (PBMCs) and the central nervous system. Consequently, the diminished antioxidant capacity results in compromised immune function, impaired detoxification, and heightened vulnerability to oxidative damage [58].

Furthermore, antioxidant micronutrients such as zinc, selenium, vitamin C, and vitamin E act as cofactors for enzymatic antioxidants or serve as direct ROS scavengers [59]. ART may influence the metabolism and bioavailability of these micronutrients. For example, zidovudine has been associated with decreased serum concentrations of selenium and zinc, possibly due to increased oxidative utilization [60]. Similarly, protease inhibitors (PIs) have been linked to lipid abnormalities that may interfere with the transport and storage of fat-soluble vitamins such as A and E [61]. Additionally, drug-induced gastrointestinal side effects can impair micronutrient absorption, particularly in malnourished individuals or those suffering from coinfections such as tuberculosis or chronic diarrhea [62]. When combined with widespread food insecurity in many African settings, these factors contribute to compounded micronutrient depletion and further elevate oxidative vulnerability.

In response to the toxicity concerns associated with older ART agents, the introduction of integrase strand transfer inhibitors (INSTIs) like dolutegravir (DTG), a key component of the WHO-recommended TLD regimen (tenofovir + lamivudine + dolutegravir), has been met with optimism due to its more favorable safety profile [63]. These newer agents generally exhibit fewer overt mitochondrial toxicities compared to older NRTIs or PIs. Nevertheless, emerging in vitro and clinical data suggest that DTG

may still exert subtle mitochondrial effects, including alterations in mitochondrial membrane potential and modest increases in ROS generation [64]. Over time, chronic exposure may disrupt redox balance, especially in individuals with pre-existing nutritional deficiencies or metabolic disorders. Thus, even modern ART regimens may contribute to a persistent, low-grade oxidative state that could predispose patients to long-term comorbidities such as cardiovascular disease, insulin resistance, and neurocognitive decline [65]. Table 2 summarizes ART effects on antioxidant system.

Table 2: Summary of ART Effects on Antioxidant Systems

Mechanism	Description	Effect on Antioxidant System
Mitochondrial Toxicity	NRTIs (e.g., zidovudine, stavudine) inhibit mtDNA polymerase-γ	ROS production, oxidative stress [66]
Enzyme Suppression	ART reduces activity of SOD, catalase, and GPx	Weakened enzymatic antioxidant defense [67]
Glutathione Depletion	ART increases GSH use and reduces its synthesis/regeneration	Poor ROS neutralization [68]
Micronutrient Interference	ART affects absorption and metabolism of zinc, selenium, vitamins C & E	Reduced non-enzymatic antioxidant protection [69]

Regional dietary deficiencies and micronutrient status

Sub-Saharan Africa continues to bear a disproportionate burden of malnutrition and infectious diseases, particularly HIV. The region's dietary landscape is shaped by food insecurity, reliance on nutrient-poor staple crops, and limited access to animal-source foods, fruits, and vegetables [70]. Consequently, deficiencies in critical micronutrients such as zinc, selenium, vitamins A, C, and E, and magnesium are widespread [71]. These deficiencies are

especially concerning among PLWH, whose metabolic demands are heightened due to chronic immune activation and oxidative stress [72]. Furthermore, parasitic infections, environmental exposures, and ART-related gastrointestinal side effects exacerbate nutrient depletion and impair absorption, which has worsened nutritional vulnerability in this population [73].

Zinc and selenium deficiencies are particularly notable, given their roles in immune regulation and antioxidant defense. Zinc deficiency, driven by poor intake and impaired absorption, is linked to faster HIV progression and reduced ART efficacy [74]. Similarly, selenium deficiency, common in regions with selenium-poor soils like Nigeria and Malawi, weakens glutathione peroxidase activity and correlates with lower CD4+ counts and increased viral replication [75]. Vitamins C and E, as non-enzymatic antioxidants, are also frequently lacking due to poor fruit, vegetable, and oil consumption. These deficiencies collectively contribute to elevated oxidative stress, immune suppression, and poor treatment [76]. Notably, dietary surveys and serum biomarker studies across countries such as Nigeria, Kenya, and South Africa consistently show suboptimal intake of these micronutrients, even among ART-treated individuals [77].

In response to these challenges, numerous studies have explored the benefits of micronutrient supplementation as an adjunct to HIV care. Evidence from randomized controlled trials in Tanzania, Zimbabwe, and Botswana suggests that multivitamins (B, C, E), selenium, and zinc supplementation can improve CD4+ counts, reduce viral load, enhance antioxidant capacity, and shorten recovery time from opportunistic infections [78,79,80]. For instance, daily selenium supplementation was shown to stabilize immune function and lower inflammation, while zinc reduced diarrheal morbidity in HIV-positive children. Despite these promising findings, supplementation benefits are most evident in individuals with baseline deficiencies, which highlights the need for targeted interventions based on local nutritional profiles [81].

Nevertheless, challenges remain in translating this evidence into broad policy recommendations. The heterogeneity of study designs, variations in baseline nutritional status, and the presence of confounding factors such as co-infections complicate interpretation [82]. Furthermore, risks associated with high-dose

supplementation, particularly with fat-soluble vitamins and trace minerals, underscore the importance of clinical monitoring [83]. While supplementation cannot replace ART, it plays a vital supportive role, particularly in resource-limited settings where malnutrition is endemic. Therefore, integrating nutritional screening, education, and supplementation into HIV programs may significantly enhance treatment outcomes and overall well-being in sub-Saharan African populations. Table 3 shows the clinical considerations of important vitamins in HIV management.

Table 3: Summary of Vitamins A, C, and E in HIV Management

Vitamin	Biological Role	Key Findings from Studies	Clinical Considerations
Vitamin A	Supports mucosal immunity	High-dose supplementation may increase risk of mother-to-child transmission during pregnancy	Use cautiously in pregnancy [84]
Vitamin C	Supports immune cell activation	Enhances immune cell function, especially in ART-naïve individuals	Often deficient due to low fruit/vegetable intake [85]
Vitamin E	Supports T-cell function	- Works synergistically with vitamin C to enhance antioxidant defense	Risk of accumulation with excessive supplementation [85]

Implications for policy in low-resource settings

In sub-Saharan Africa regions, the clinical management of HIV is frequently complicated by food insecurity, poor dietary diversity, and high rates of co-infection. Moreover, limited access to healthcare infrastructure exacerbates these issues [86]. Given the growing evidence on the role of antioxidant and micronutrient support in improving HIV outcomes, it is increasingly important to translate research findings into practical, context-sensitive public health policies [87]. Integrating nutrition into HIV

care can no longer be treated as optional but must become a core component of comprehensive HIV management.

To achieve this integration, several strategies have been proposed. First, nutrition should be prioritized as part of routine HIV care through systematic nutritional assessments and micronutrient screening at both the community and facility levels. Food-based interventions, such as school feeding programs and household gardens, can help strengthen long-term nutritional resilience [88]. Second, while universal supplementation may not be feasible, targeted micronutrient interventions for high-risk groups, such as children, pregnant women, and malnourished adults, should be implemented using standardized protocols [89]. This approach ensures that essential vitamins and minerals, including zinc, selenium, and vitamins A, C, and E, are effectively incorporated into HIV care guidelines. Importantly, monitoring systems should be established to track safety, compliance, and clinical impact [32,90].

In addition, existing public health infrastructure can be leveraged to expand the reach of micronutrient interventions. Programs designed for maternal-child health, tuberculosis control, or immunization can serve as delivery platforms for micronutrient supplements and integrated health messaging [91]. Training healthcare workers to understand the link between nutrition and HIV treatment is equally vital. Moreover, longer-term strategies should address systemic drivers of deficiencies through food fortification and agricultural policies. These include mandating fortification of staple foods, promoting biofortified crops, and improving soil nutrient content [92]. Finally, ensuring the sustainability and equity of these interventions is crucial. Micronutrient programs must be cost-effective, supported by reliable economic data, and tailored to benefit vulnerable populations such as orphans, rural communities, and women [93]. Innovative financing models and public-private partnerships can support affordable supplement distribution. Furthermore, governments must invest in research, surveillance, and adaptive policy feedback systems to ensure interventions remain evidence-based and responsive to evolving needs.

Conclusion

Oxidative stress remains a central yet under-addressed complication in the clinical course of HIV, particularly in sub-Saharan Africa where both the prevalence of HIV and the

burden of malnutrition are high. The synergistic role of antioxidant enzymes and micronutrients is vital for mitigating oxidative stress and supporting immune recovery. However, persistent regional dietary deficiencies and limited access to nutritional resources continue to undermine the therapeutic gains of ART, especially in vulnerable populations. Given the compelling evidence from mechanistic studies and clinical interventions, integrating antioxidant and micronutrient strategies into HIV care protocols is no longer optional, it is essential. Policy frameworks must prioritize nutrition as a core component of HIV management, supported by routine screening, targeted supplementation, food fortification, and cross-sectoral collaboration.

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