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Oxidative Stress in People Living With HIV: Are Diverse Supplement Sources the Solution?

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ABSTRACT

Background and Aim: Antiretroviral therapy (ART) has reduced human immunodeficiency virus (HIV)/AIDS to a manageable chronic condition even though no cure exists. Despite ART control, latent HIV infection results in failed memory CD4 T-cell responses, immune overactivation, inflammation, oxidative stress, genomic instability, deoxyribonucleic acid (DNA) damage, and premature CD4 T-cell ageing. Overproduction of reactive oxygen species during oxidative stress can cause mitochondrial DNA damage, cancer, neurodegenerative and cardiovascular diseases, and premature aging in people living with HIV (PLWH). This review outlines current knowledge in oxidative stress among PLWH.

Methods: Google Scholar, Scopus, PubMed, and Science Direct were searched for literature conforming with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines from studies published from January 2013 to December 2023. A total of 75 studies from 22 countries were identified, with 52 studies carried out in human participants, 17 studies in cell lines, and 6 studies in animal models to assess oxidative stress levels.

Results: An increased oxidative stress with no changes in antioxidant levels was reported in HIV-positive smokers, and those on substance abuse. Long-term ART usage showed high levels of oxidative protein products and low levels of antioxidants when compared to short-term ART usage. The use of supplements such as N-acetylcysteine, selenium, and silibinin in animal models and cell lines showed increased cell viability, reduced reactive oxygen species, and increased antioxidant levels, which are promising therapeutic interventions that should be studied in PLWH to further help improve their disease outcomes.

Conclusions: Identifying extracts from natural and synthetic products with antioxidant effects will improve the general well-being of PLWH.

1 | Introduction

Human immunodeficiency virus (HIV) remains a significant global health issue, with millions of new infections occurring annually. Out of 38 million HIV-positive individuals worldwide, 67% receive treatment, with 1 in 7 being unaware of the infection [1]. Antiretroviral therapy (ART) has transformed HIV/AIDS from a progressive disease to a manageable chronic

condition. However, no scalable cure exists, necessitating long-term treatment for people living with HIV (PLWH); even short interruptions can cause viral load rebound [2].

Failed memory CD4 T-cell responses, immune overactivation, inflammation, genomic instability, DNA damage, premature CD4 T-cell aging, and oxidative stress have been demonstrated in PLWH [3–5]. Also, overproduction of reactive oxygen species (ROS) during oxidative phosphorylation, which causes mitochondrion DNA damage, cancer, neurodegenerative and cardiovascular diseases (CVD), and premature aging has been shown in PLWH [6, 7]. The increased ROS lead to elevated 8-oxoG and malondialdehyde (MDA) levels, which are independent predictors of disease progression and mortality [8, 9]. HIV-infected individuals experience a decrease in the activity of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione oxidase [10, 11], and various metabolic events resulting from the infection have a direct impact on the consumption of antioxidant components, leading to an increase in oxidative stress (OxS) [12–14].

Oxidative stress has been implicated in dyspnea, mitochondrial dysfunction, insulin resistance, genomic damage and cognitive effects, endothelial vascular dysfunction, reduced muscle strength, and longer hospitalization [15], and efforts to improve these conditions have been made with the use of supplements such as GlyNAC, a supplement that is made from glycine and N-acetylcysteine, to correct glutathione deficiency in HIV-infected patients (Horowitz et al., 2020; Assimakopoulos et al., 2021). Supplements such as N-acetylcysteine, selenium, and silibinin have been explored in animal models and cell lines and shown increased cell viability, reduced ROS, and increased antioxidant levels [15, 16], thereby serving as promising therapeutic interventions that should be further studied in PLWH to help improve the disease outcomes of these people.

This article seeks to outline the current knowledge of oxidative stress in HIV infection under various conditions such as ART usage and co-morbidities with other disease conditions and explore the usage of supplements from diverse sources as therapeutic interventions to help solve the problem of oxidative stress and improve the health of PLWH.

2 | Methods

2.1 | Eligibility Criteria

Eligibility criteria that were considered for selecting the studies used in the review included:

2.1.1 | Inclusion Criteria

Human subjects in cross-sectional studies, observational studies, cohort studies, case reports, clinical trials, case-control studies, randomized phase II and randomized controlled trials, and cell lines experimental and animal model studies that discussed oxidative stress in PLWH were included in the review. All original research that satisfied the requirements and were written in English and published between January 2013 and December 2023 was included.

2.1.2 | Exclusion Criteria

The evaluation criteria excluded editorials, commentaries, systematic and literature reviews, brief reports, books, abstracts without primary data and/or explicit descriptions of methods, and studies that were written in languages other than English language.

2.2 | Data Sources and Search Strategy

Relevant terms searches using terms like “Oxidative Stress,” “HIV,” or “Human Immunodeficiency virus,” or “PLWH,” or “People Living With HIV,” in PubMed, Google Scholar, Scopus, and Science Direct. We then used additional criteria to retrieve papers about “antioxidants,” “ART,” “smoking,” “narcotics,” “exercise,” “supplements,” and “co-morbidities” were conducted. Additionally, appropriate studies were found by manually searching through references. A hand search was performed from the reference lists of the identified studies.

2.3 | Study Choice

For each search, titles were imported into Endnotes, and duplicates were removed. Two researchers independently checked records for eligibility using titles and abstracts. The full texts of any papers that were deemed to be potentially relevant were then located, assessed, and decided upon by consensus to be incorporated into the research. A third investigator arbitrated disputes or reached a compromise to settle them.

2.4 | Risk of Bias Assessment

The JBI critical appraisal tool and risk of bias (ROB) assessment for systematic review was adopted for this study with the purpose of assessing the methodological quality of the studies used, and to determine the extent to which the studies have addressed the possibility of bias with respect to design, conduct, and analysis. All the papers that were selected for inclusion in the current review were evaluated by two reviewers using the JBI critical appraisal checklist for systematic review, and finetuned to include study subject description, assay, assessment of outcomes, statistical analysis and treatments/intervention. Both reviewers made judgements regarding the ROB independent of each other, and areas of differences were resolved by discussion and reflection, or in consultation with a third reviewer. Supporting Information Table S1 shows the risk of bias (ROB) assessment of publications on oxidative stress that were included in the study.

2.5 | Data Extraction and Synthesis

Data extraction was done, and three tables were created and was written in English language. The first table has headings

on year of publication, study place, study participants, sample size, study design, assay type, clinical findings, and authors. The second table summarized findings from cell lines, which had headings on year of publication, study place, cell line type, assay type, clinical findings, and authors. The third table also summarized findings from animal models, which had headings on year of publication, study place, animal model type, sample size, assay type, clinical findings, and author.

3 | Results

PRISMA standards were used to select the studies (Figure 1), and a total of 32314 results were found via database searches (Google Scholar: 23800, Scopus: 1164, ScienceDirect: 7296, PubMed: 54). Following the screening process, seventy-five (75) research studies satisfied the qualifying requirements (Figure 1). Duplicate entries were eliminated using EndNote software. Also, 32198 studies were excluded from further screening because they did not match the eligibility requirements. The exclusion of fifty-seven (57) studies was justified by the following: Abstract (1), systematic review, literature review, meta-analysis (39), brief report (1), editorial (1), commentary (1), other languages (2), and books (12). Eighteen more reports were produced because of manually scanning the references. This analysis contained seventy-five studies (Figure 1).

In this review, studies were identified in 22 countries, with the United State of America contributing 22 of the included studies. Other countries where studies were carried out included Brazil (11), Nigeria (8), India (7), and Cameroon (4). Two (2) studies each was carried out in Ghana, Spain, France, South Africa, Italy, Mexico, and Germany. Only one study was identified in the following countries (Zambia, Cuba, Uganda, Malaysia, United Kingdom, Iran, Cuba, Ethiopia, China, and Canada). Study participants included HIV patients, HIV naïve groups, HIV-negative participants, animal models, and cell lines.

Fifty-two studies were carried out in human subjects (Table 1), 17 studies in cell lines (Table 2), and 6 in animal models (Table 3) to assess oxidative stress levels. The various studies looked at the effect of supplements, ART, antioxidants, HIV single and co-infections, mechanisms, exercise, and aging on oxidative stress in HIV infection.

HIV-infected women have higher GSH and WBC levels than men [62], and lower zinc and copper levels were observed in HIV-infected children [63]. Cytochrome P2A6 induces increased OxS stress and viral load in smokers, HIV+ only, and HIV-positive smokers compared to HIV-negative non-smokers [17], and exercise was found to decrease inflammatory markers and oxidative stress in people with PLWH [19] while also enhancing physical fitness and reducing GSSG/GSH and TBARS levels [18].

ART-naïve patients showed reduced superoxidase dismutase (SOD) activity compared to ART experienced and control groups, and manganese had a strong negative correlation with SOD activity and a positive correlation with $CD4^+$ count [64]. Co-morbidities like tuberculosis increase GSH levels and reduce

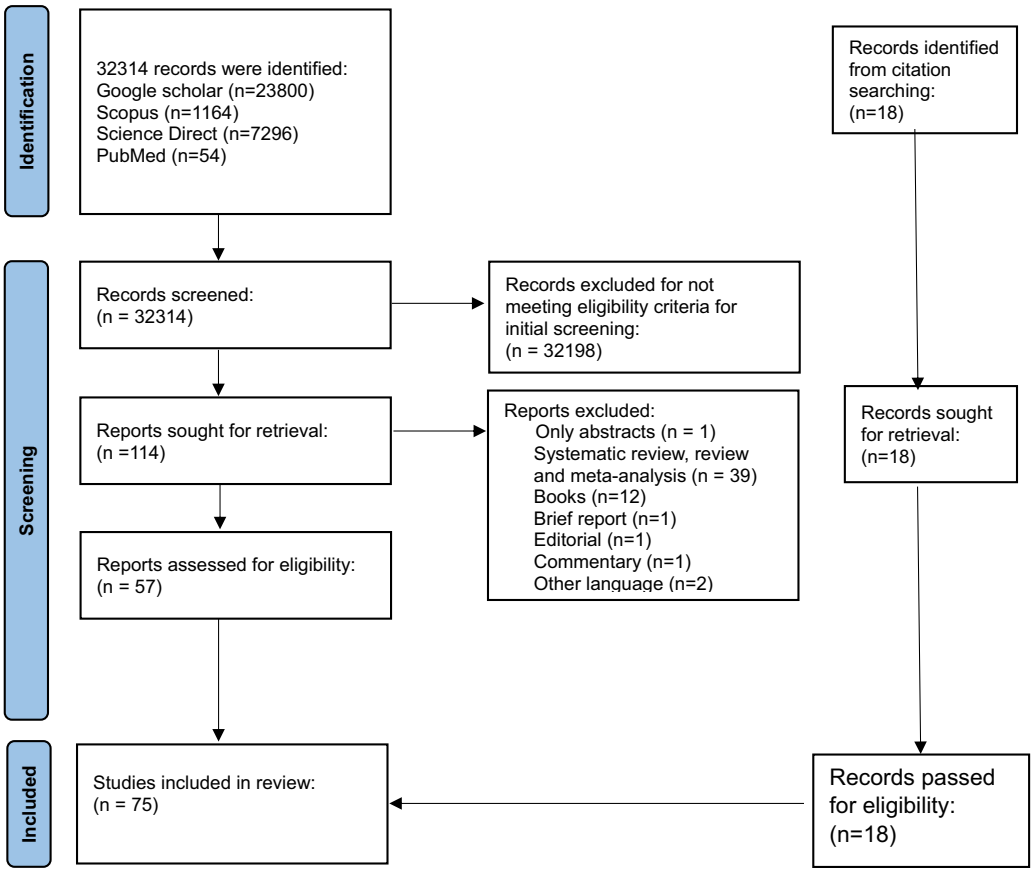

FIGURE 1 | PRISMA flow diagram showing the selection criteria of studies.

TABLE 1 | Summary of studies carried out on oxidative stress among people living with HIV.

Year of publication	Study place	Study participants	Sample size	Study design	Findings	Authors
April 2015	Cameroon	HIV-negative non-smokers, HIV-positive non-smokers, HIV-negative mild to moderate smokers, HIV-positive mild to moderate smokers	32	Prospective cohort	Most antioxidants remain unaltered, indicating their inability to counter oxidative stress. CYP2A6 and CYP3A4 are induced in smokers and HIV positives, respectively.	Ande [17]
October 2018	Brazil	HIV participants	416	Clinical trial	Exercise training enhanced physical fitness in PLWH by decreasing GSSG/GSH and TBARS levels and improving redox status.	Deresz et al., [18]
2023	Brazil	HIV women	10, 8 years and above	Quasi experimental	The study found high levels of GSSG, but no changes in GSH levels or GSH/GSSG ratio, indicating an increase in oxidative stress.	Nunhes et al., [19]
September 2018-June 2019	Zambia	HIV patients on ART HIV-negative participants	54 HIV patients 57 HIV-negative participants	Cross-sectional	PLWH experience higher levels of oxidative stress and endothelial activation, which may result in increased arterial stiffness and higher CVD prevalence.	Chikopela et al., [20]
2019	Cuba	HIV patients HIV-negative participants	330 participants: 110-healthy individuals 110-mono-infected HIV patients 110-HIV/HCV coinfected patients	Case-control with convenient sampling	HCV-HIV patients exhibited reduced lipid-serum antioxidant capacity compared to healthy individuals, as evidenced by higher total hydroperoxide and advanced oxidation protein products.	Gravier-Hernández et al., [21]
2018	Uganda	HIV adult patients (> 18)	Four groups: HIV infected, ART-naïve HIV infected, ART-treated HIV/PTB coinfected, ART-naïve HIV/PTB coinfected, ART treated.	Cross-sectional with convenient sampling	HIV patients have lower levels of Vitamin C and albumin compared to controls, with ART associated with higher albumin, higher GGT, and lower vitamin C.	Musisi et al., [22]
2021	Brazil	People living with HIV	HIV/TB coinfected and above 18 years	Single center, randomized, phase II trial	Patients undergoing NAC showed a significant increase in	Safe et al., [23]

(Continues)

TABLE 1 | (Continued)

Year of publication	Study place	Study participants	Sample size	Study design	Findings	Authors
					GSH levels and total antioxidant status, while reducing lipid peroxidation compared to the control group.	
2020	USA	HIV participants on ART HIV-negative participants	24 subjects (12 HIV subjects, 12 HIV-negative subjects) for testing 16 subjects (8 HIV subjects, 8 HIV-negative subjects for validation	Prospective cohort	HIV+ individuals on ART exhibit increased circulating EVs with miRNAs linked to inflammation and oxidative stress, suggesting potential biomarkers for disease pathogenesis.	Chettimada et al., [24]
2021	USA	Cells from HIV Cells from negative subjects HIV-positive subjects	Blood donors > 18 years HIV-positive patients on ART	Prospective cohort	Targeting the acute oxidative stress response through mini-MAVS can induce HIV-1 transcription, adding to the arsenal of 'shock-and-kill' strategies for reactivating latent HIV-1.	Sarabia et al., [25]
2020	Spain	HIV-positive individuals	117 elderly HIV-positive participants > 56 years	Cross-sectional	HIV-1 persons showed higher plasma levels of sCD14 and MDA, indicating an association between frailty, immune activation markers, and oxidative stress.	Alvarez et al., [26]
2015	USA	282 participants enrolled. 123 participants consented	34-HIV-positive patients—narcotic use disorders 23-HIV-positive patients—meth use disorders 41-HIV seronegative subjects—no history of substance use disorders 25-HIV seronegative subjects—meth use disorders Participants > 18 years	Prospective	HIV and Meth use interact with depressive symptoms, but not oxidative stress. Different mechanisms mediate these symptoms, not always related to oxidative stress.	Panee et al., [27]
2021	Cameroon	HIV-positive participants on ART	87 HIV-positive participants on	Cross-sectional	The study found a weak positive correlation between	Voufo et al., [28]

(Continues)

TABLE 1 | (Continued)

Year of publication	Study place	Study participants	Sample size	Study design	Findings	Authors
			ART of both sexes from 26–72 years		IL-6 and MDA, a strong negative correlation between FRAP and MDA, and a strong positive correlation between MDA and GSH.	
2015	Mexico	35 HIV participants in each group. 20–55 years	35 HIV+ on omega 3 fatty acids 35 HIV+ on placebo,	Randomized double blind, parallel controlled clinical trial	Treatment with omega 3 fatty acids as compared with placebo decreased triglycerides but oxidative stress markers were not different between groups.	Amador-Licona et al., [29]
2013	USA	85 HIV-positive patients	216 HIV-positive men, 69 HIV-positive women. Ages between 30 and 47 years	Cross-sectional	Women have higher F2-IsoP levels than men, but men show a relationship with circulating F2-IsoP and iron levels, while women with HIV infection do not.	Crist et al., [30]
2020	Brazil	20 HIV-positive participants	20 HIV-positive patients, above 18 years, on cART for at least 18 months	Double blind, crossover, randomized clinical trial	Curcumin supplementation in HIV-infected individuals receiving antiretroviral therapy and training did not enhance their glycaemic, inflammatory, or oxidative stress profiles.	da Silva et al., [31]
2013	India	50 HIV-positive participants 50 non-HIV participants	HIV positives matched for age and sex with non-HIV participants (30 men and 20 women), 21–50 years	Matching method	HIV seropositive cases showed decreased mean plasma zinc and TAC compared to controls, while copper and MDA increased, both statistically significant.	Doddigarla et al., [32]
2014	Brazil	HIV-positive children Non-HIV-positive children	10 HIV-positive children on ART, 14 non-HIV-positive children, 2–8 years old	Prospective	HIV-positive individuals showed higher TBARS and NN values before supplementation, but decreased DPPH values post-supplementation,	Figueira et al., [33]
2021	Cameroon	297 HIV-positive patients	297 HIV-positive patients' group into 3:	Prospective	*Azadirachta indica* and *Senna siamea* decoction stimulates CD4+ production without toxicity,	Goni Hamadama et al., [34]

(Continues)

TABLE 1 | (Continued)

Year of publication	Study place	Study participants	Sample size	Study design	Findings	Authors
			97 HIV patients on decoction only 100 patients on ART only 100 patients on both ART and decoction		reducing toxicity caused by ARTs intake.	
2016	USA	24 HIV-positive patients	24 HIV patients > 50 years were grouped into 3: 9 HIV patients on PharmaNAC 900 mg twice daily, 8 HIV patients on 800 mg twice daily 7 patients on placebo	Randomized placebo-controlled	PharmaNAC, well-tolerated for 8 weeks, increased reduced glutathione levels in red blood cells while decreasing oxidized glutathione levels, suggesting it may enhance cells' ability to neutralize higher ROS levels.	Gupta et al., [35]
2020	Iran	180 positive HIV patients	180 patients from 18 to 60 years grouped into 3: 60 patients on Zinc 60 patients on Selenium 60 patients on placebo	Randomized double-blind placebo-controlled trial	Zinc supplementation significantly reduced the risk of opportunistic infections, but no significant improvement in CD4 count was observed in this group.	Hadadi et al., [36]
2013	Brazil	HIV-positive adults	182 HIV adults from 20–59 years Stable on ART for 6 month or more	Cross-sectional	Vitamin A and Beta-carotene concentration in patients under the different HAART regimen.	Kaio et al., [37]
2021	Ghana	HIV-positive adults	103 HIV adults: 77 females and 26 males, 18 years and above	Cross-sectional	Increased MPO and CAT activities in HIV-positive subjects on HAART were linked to CD4 cell counts, suggesting potential benefits from antioxidant supplementation in treatment.	Kpewou et al., [38]
2020	USA	HIV-positive adults Non-HIV participants	8 PLWH (6 men and 2 women) Age, gender and BMI-matched uninfected controls, 45–65 years, stable on ART, not hospitalized for 6 months	Prospective	GlyNAC nutritional supplementation enhances comorbidities indicative of premature aging in PLWH, including functional and cognitive decline.	Kumar et al., [39]

(Continues)

TABLE 1 | (Continued)

Year of publication	Study place	Study participants	Sample size	Study design	Findings	Authors
2017	USA	HIV-positive adults	487 HIV mono-infected, HIV/HCV coinfected, 18–60 years, BMI > 18 but < 40	Observational	Lower plasma zinc concentrations were linked to liver fibrosis progression and mitochondrial oxidative stress in HIV and HIV/HCV groups, suggesting zinc may impact liver disease outcomes.	Martinez et al., [40]
2019	Mexico	HIV-positive men	124 HIV men, on ART for more than 6 months, with low viral loads	Retrospective	HIV-positive individuals often experience deficiencies in zinc and selenium intake and serum concentration, which are linked to body composition, bone mineral density, and inflammation.	Osuna-Padilla et al., [41]
2019	Brazil	HIV-positive adults	20 HIV adults: 12 males and 8 females,	Double blind, crossover, randomized clinical trial	No significant differences in substrate oxidation or body composition between groups, but increased serum triglyceride levels after curcumin supplementation.	Silva et al., [42]
2018	Malaysia	HIV-positive adults	26 patients: low dose honey 20 g one daily for 6 mths 24 patients: intermediate dose honey 20 g twice daily 22 patients: high dose honey 20 g once daily 23 patients: no honey	Randomized, controlled, open-labeled	Tualang honey administration reduced viral load in asymptomatic HIV subjects, indicating its potential role in boosting the immune system and reducing viral load in HIV-positive individuals.	Yusuf et al., [43]
2018	USA, Boston	HIV Male (White and nonwhite), 35–65 yrs	43 HIV-positive males on ART 34 HIV-negative participants	Cross-sectional	cART increases metabolic oxidative markers in HIV patients.	Chettimada et al., [44]
2017	Nigeria, Benin City	African Male and Female HIV patients, 20–52 yrs	126 HIV-positive patients on ART, 50 HIV-positive naïve patients 40 HIV-negative participants	Case-control	Inflammation, immune activation and microbial infections in HIV naive subjects decrease activity of oxidative burst enzymes.	Emokpae, Mrakpor [45]
2014	Cuba, Havana	30 HIV-positive Adults, 30–50 yrs	160 HIV-positive patients, 40 HIV-negative participants	Cross-sectional	Individuals with delayed HIV diagnosis experienced higher damage and lower	González-Blanco et al., [46]

(Continues)

TABLE 1 | (Continued)

Year of publication	Study place	Study participants	Sample size	Study design	Findings	Authors
					antioxidant status compared to the control, HIV asymptomatic, and AIDS groups.	
2021	Nigeria, Ogun State	HIV PREGNANT Women	20 HIV/Malaria patients, 21 HIV patients only, 51 malaria patients only, 158 negative participants	Random Sampling	8% of HIV pregnant women coinfected with malaria have CD4 + < 200 μl, elevated MDA concentration in HIV pregnant women coinfected with malaria.	Idowu et al., [47]
2021	USA, New Orleans	HIV-positive and HIV-negative participants	439 HIV-positive patients 350 HIV-negative patients	Case-control	Oxidative markers elevate cardiovascular biomarkers (IL-6, hs-CRP) in CVD with concomitant reduction in cardioprotective gases (H_2S, NO)	Islam et al., [48]
2013	USA, Cleveland	HIV-positive and HIV-negative participants, 37–45 yrs	38 HIV-positive patients, 26 on ART 15 HIV-negative participants	Cross-sectional cohort	Other factors and oxidative stress markers decrease IL-7 responsiveness in HIV-patients	Kalinowska et al., [49]
2017	India, Mumbai	HIV-positive and HIV-negative participants, 20–60 yrs	300 HIV-positive patients on ART 300 HIV-negative participants	Case-control	Plasma 8-hydroxy-2-deoxyguanosine, an oxidative marker of metabolic syndrome causes more DNA damage in HIV patients on ART	Kolgiri et al., [50]
2016	Brazil	HIV-positive and HIV-negative participants	54 HIV-positive patients on ART 93 HIV-negative participants	Prospective multicentre cohort	oxidative stress influences mortality in HIV individuals through DNA damage	Masiá et al., [51]
2021	Nigeria, Ogun State	HIV-positive and HIV-negative participants	58 HIV-positive patients 26 HIV-negative participants	Cohort	BMI in HIV seropositive patients decrease with correlated decrease in weight, but negatively correlates with MDA, PCO, AOPP	Odewabi et al., [52]
2017	Brazil, Sao Paulo	HIV-positive male patients 20–49 yrs	30 asymptomatic HIV-positive	Longitudinal	HIV patients with CD4 + > 500 cells/ml showed more DNA damage, and 8-isoprostane levels increased after cART initiation.	Tasca et al., [53]
2013	Cameroon, Yaoundé	285 participants	151 HIV ART Naïve 134 HIV-negative participants	Case-control	HIV seronegative naïve patients showed increase in LPI and MDA levels and	Teto et al., [54]

(Continues)

TABLE 1 | (Continued)

Year of publication	Study place	Study participants	Sample size	Study design	Findings	Authors
					decrease in TC, HDLC, LDLC, TAA which are linked to reduction in CD4 cell counts	
2019	USA, Boston	HIV-positive patients, adults	20 HIV-positive patients, Virally suppressed, on ART for > 6 months	Parallel Switch	A switch from efavirenz to integrase inhibitors in HIV patients improves mood, cognition, and neurological oxidative stress	Asundi et al., [55]
2016	Spain, Barcelona	HIV-positive individuals	96 HIV participants on EFV 48 HIV participants on ATV	Multicentre, prospective cohort	Elevated Bilirubin reduces Lp-PLA2 and Ox-LDL significantly in HIV patients on ATV with an increase in MPO.	Estrada et al., [56]
2017	Ethiopia, Addis Ababa	HIV-positive children HIV-negative children, 3–15 yrs	50 HIV-positive HAART 50 HIV-positive HAART naive 50 HIV-negative participants	Cross-sectional	Increase in MDA in HAART-treated. Decrease in MDA in HAART-naïve. Increase in Vitamin C and Zinc in HAART-Treated. Decrease in Vitamin C and Zinc content in HAART Naïve.	Mebrat et al., [57]
2023	USA, Johnson City	HIV-positive and negative participants	77 HIV-positive participants 46 HIV-negative participants	Case-control	Increased cellular and mitochondria ROS during HIV latency in PLWH	Schank et al., [58]
2014	India	HIV-positive ART naïve Infected adults	270 HIV ART Naïve, 30 participants from nine countries.	Sub-cohort, Randomized clinical trail	ART naïve HIV-infected individuals experience deficiencies in one or multiple micronutrients.	Shivakoti et al., [59]
2019	South Africa, Johannesburg		72 HIV ART Treated, 13 HIV ART Naïve 13, 21 HIV Neg	Stratified random sampling	Amino acid metabolites decrease in concentration in ART HIV-positive people	Sitole et al., [60]
2016	Brazil, Sao Paulo	120 HIV-positive adults of both sexes	40 HIV on ART < 5 years 40 HIV on ART > 5 years 40 HIV-negative participants	Prospective, Observational, cross-sectional	Increase in Plasma selenium and decrease in seleno-methionine in ART treated HIV patients compared to healthy individuals. GSH and GPX decreases in ART patients while MDA significantly increases.	Watanabe et al., [8]
2019	Nigeria	96 participants	**Group 1**: 24 HIV seronegative	Prospective cross-sectional	Long-term treatment group had significantly high levels of MDA,	Ikekpeazu et al., [61]

(Continues)

TABLE 1 | (Continued)

Year of publication	Study place	Study participants	Sample size	Study design	Findings	Authors
			age-matched individuals as controls. **Group 2**: 24 sero-positive patients not on ART, also called the **Group 3**: 24 sero-positive patients on ART < 1 year. **Group 4**: 24 seropositive patients on ART for > 1 year.		and diminished TAS compared to the Short-term treatment and No HIV groups ($p < 0.05$). In addition, there was significantly elevated variation in the copy number of mitochondrial genes.	
2019	Nigeria	180 participants	60-HIV infected patients on ART 40-HIV infected patients, ART naïve 80- Healthy HIV-negative individuals	Prospective cross-sectional	Antioxidants; GSH and GPX were found to be significantly reduced in HIV.	Coco-Bassey et al., [62]
2014	Brazil	83 participants	51- HIV infected children. 32-healthy HIV-negative siblings	Cross-sectional	HIV-infected children may experience a delay in the progression to AIDS due to their inadequate nutritional status in selenium and copper.	Pugliese et al., [63]
2019	Ghana	242 participants	105 HIV infected patients on ART. 77 HIV infected ART naïve. 60 HIV-negative individuals.	Cross-sectional	ART-naïve patients showed reduced SOD activity compared to ART and control groups, with manganese showing a strong negative correlation with SOD activity and a positive correlation with CD4+ count.	Quaye et al., [64]
2019	Canada	People living with HIV	91 HIV-positive individuals. 35 years and above	Cross-sectional	Age, systolic blood pressure, and atherosclerosis may be linked to higher serum gamma-tocopherol levels, but CIMT showed no significant association with RBC n-3 PUFA or n-6 PUFA ratio.	Schwenger et al., [65]
2017	USA	30 HIV-positive participants	15 HIV-positive participant with CD4+ cell < 200 cells/mm^3	Double-blinded clinical trial	Liposomal glutathione supplementation in HIV-infected individuals with	Valdivia et al., [66]

(Continues)

TABLE 1 | (Continued)

Year of publication	Study place	Study participants	Sample size	Study design	Findings	Authors
		17 healthy HIV-negative participants	15 HIV-positive participants with CD4+ cells between 200–350 cells/mm3 17 healthy participants Ages – 30–65 years		CD4 + T cell counts below 350 cells/mm3 can restore redox homeostasis and cytokine balance, aiding the immune system in controlling opportunistic infections.	
2019	USA	130 participants Age: 22–78 years	34 participants: HIV- & COPD - 36 participants: HIV + & COPD – 34 participants: HIV - & COPD + 28 participants: HIV + & COPD +	Cross-sectional	Systemic oxidation in COPD and HIV patients may contribute to decreased lung function and CD4 counts, suggesting new mechanisms underlying increased COPD prevalence.	Watson et al., [67]

Abbreviations: CIMT, carotid intima-media thickness; COPD, chronic obstructive pulmonary disease; crASI, arterial stiffness index; CRP, C-reactive protein; crPWV, carotid-radial pulse wave velocity; Cys, cysteine; CySS, cystine; ELISA, enzyme-linked immunosorbent assay; GSH, reduced glutathione; GSSG, oxidized glutathione; HIV, human immunodeficiency virus; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography-tandem mass spectrometry; Lp-PLA2, lipoprotein-associated phospholipase; MDA, malondialdehyde; MPO, myeloperoxidase; MSM, men who have sex with men; OxLDL, oxidized low-density lipoprotein; PUFA, polyunsaturated fatty acids; RT PCR, real-time polymerase chain reaction; RT-qPCR, reverse transcriptase quantitative polymerase chain reaction; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; VL, viral load.

lipid peroxidation [23], while 72% of HIV/HCV group exhibited higher total hydroperoxide and advanced oxidation protein products compared to a control group [21]. A study found higher levels of GGT in HIV infected individuals, and infected methamphetamine (meth) users had higher levels of GSH and GPx activity, with the meth usage influencing depression symptoms but did not affect oxidative stress [27].

Randomized studies examined the impact of various supplements on oxidative stress in PLWH and observed that omega-3 fatty acids resulted in low triglyceride levels, but there was no significant difference in OxS markers [29]. Curcumin supplements and exercise do not also improve inflammatory or OxS profiles in HIV patients [31], but *Agaricus sylvaticus*, an antioxidant mushroom, reduced thiobarbituric acid reactive substance (TBARS) and increased DPPH in HIV-positive children on ART after treatment but not before treatment [33]. A study comprising three cohorts (one on decoction only, the second on ART only, and the third on both decoction and ART) reported that the cohort on ART only had hepatic toxicity and high levels of OxS, whereas no sign of toxicity was observed in the decoction only, and decoction and ART cohorts [34].

Knockdown of SOD1 or APE1 was suggested to maintain mitochondrial respiration [89]. Sitole and colleagues used metabonomic strategies to identify metabolic markers in HIV-infected individuals, revealing increased levels of aspartic acid, phenylalanine, and glutamic acid while tyrosine and cystine levels are downregulated and thus serve as essential metabolic markers for predicting HIV/cART-induced oxidative stress and therefore contribute to HIV management and treatment [60].

For studies on cell lines, a study reported no impact of HIV-1 protein production or infectivity and reduction in infected cells in a Jurkat cell line and isolated primary $CD4^+$ T cells when infected with selenium and seleno-proteins [16], and another study used N-acetyl cysteine as a supplement to investigate the role of polyamine catabolism in Tat-induced oxidative stress in human neuroblastoma cells [73]. Tat-induced ROS production and spermine oxidase (SMO) activation were prevented by the NMDAR antagonist MK 801. Pretreatment with N-acetylcysteine and MK 801 restored cell viability.

Samikkannu and colleagues found that oxidative stress-induced glutathione synthases, superoxide dismutase, and GPx affect cell cycle-regulated proteins, influencing neuronal dysfunction in HIV-1 gp120 co-morbidity with morphine in human microglial cell lines [68].

Rao and Kumar [78] found that chronic exposure to ethanol and ART significantly impacts cytochrome P450 enzymes, antioxidant enzymes, ROS, and cytotoxicity in U937 cells [78], and alcohol, anti-HIV drugs, and lopinavir significantly altered ER stress markers in another study, leading to increased cell death in primary mouse hepatocytes compared to control cells [69].

In an animal model study, Mg-supplementation increased HIV-1-Tg expression in transgenic rats, leading to increased oxidized glutathione and triglyceride levels [83]. Anti-Koch and HAART drugs impair hepatic and renal functions, decrease glutathione, increase lipid peroxidation, and DNA fragmentation in rats, thereby causing oxidative stress [85], and silibinin, a natural extract from *Silybum marianum*, also mitigated liver injury and

TABLE 2 | Summary on studies carried on oxidative stress in cell lines.

Year of publication	Study place	Cell line type	Findings	Authors
2015	USA	Microglial cells	HIV morphine users experience elevated oxidative stress and cell cycle machinery impact, causing the progression of the HIV infection.	Samikkannu et al., [68]
2015	USA	Primary mouse hepatocytes	Hepatocytes and nonparenchymal cells exhibit distinct responses to alcohol and anti-HIV drugs in vitro, with Nrf2-mediated oxidative stress contributing to alcohol and drug-induced toxicity.	Hu et al., [69]
2013	USA	Primary cortical neuroglial cells	Oxidative stress is linked to ARV-induced neurotoxicity, suggesting the potential for adjunctive therapies to complement ARV therapy and reduce neurotoxicity in this patient population.	Akay et al., [70]
2014	USA	Murine neuronal cell lines SweAPP N2a cells	Efavirenz influences the Ab promoting effects of this cART regimen by increasing Ab peptide production and decreasing clearance.	Brown et al., [71]
2020	India	Human monocytic cell line U937, murine macrophage cell lines RAW 2547, chronically HIV-1 infected U1, J1.1 T lymphocytic cell lines, J-Lat 10.6 cells	The study found that treatment with N-acetyl cysteine (NAC) or inhibitors of host factors, galectins and Hsp90, effectively reduced HIV-1 reactivation by M. tuberculosis-specific exosomes.	Tyagi et al., [72]
2013	Italy	ARP697-HIV tat B protein, ARP235 plasmid p(63.4.1) tat, ARP5010/IG5/LTR-luciferase cells	Cells treated with N-acetylcysteine and MK80 inhibited reactive oxygen species formation and restored viability, suggesting polyamine metabolism-derived H2O2 plays a role in neurotoxicity induced by Tat-stimulated NMDAR.	Capone et al., [73]
2020	France	HEK293, HEK. Env and HEK/CD4.403/CXCR4 cells	Env exposure leads to a decrease in the expression of peroxisomal proteins, CAT and PEX14, through autophagy, but downregulation of BECN1 or SQSTM1/p62 restores their expression levels.	Daussy et al., [74]
2019	USA	Primary human monocyte derived macrophages	Chronic ethanol exposure can increase HIV-1 replication in MDM through CYP2E1-mediated oxidative stress, potentially paving the way for effective treatment strategies for alcohol users infected with HIV.	Gong et al., [75]
2021	China	Human brain monovascular endothelial cell lines hCMEC/D3	Oxidative stress inhibition reduced TRPM2 channel activation and protein expression, while 8-Br-ADPR attenuated METH and HIV-Tat effects on TJ protein expression and increased BBB permeability to Evans blue and NaF.	Huang et al., [76]

(Continues)

TABLE 2 | (Continued)

Year of publication	Study place	Cell line type	Findings	Authors
2021	USA	2D10 cells, J-lat 10.6, J-lat 6.3, J-lat 5A8 cells	Mini MAVS, a response to antioxidative stress, can induce HIV-1 transcription, enhancing the arsenal of'shock-and-kill' strategies for reactivating latent HIV-1.	Sarabia et al., [25]
2022	France	Jurkat, SupTI and HEK2Bt cell lines	Selenium did not affect HIV-1 protein production or infectivity, but it slightly reduced infected cells in Jurkat cells and isolated primary CD4 T cells, and slightly altered the seleno-proteome.	Guillin et al., [16]
2023	Italy	Human glioblastoma astrocytoma (U373-MG) and human neuroblastoma cells (SH-SYSY)	Astrocytic antioxidant response, specifically Holo-bLf, exacerbates Tat-induced excitotoxicity on human neuronal SH-SY5Y cells, highlighting the role of iron in Tat's biological activities.	Ianiro et al., [77]
2016	India,	U937 Monocytic Cells	EtOH and ART-treated cell lines showed high CYP2E1 transcription and protein levels, decreased Superoxide dismutase 1 mRNA levels, and increased ROS production compared to control group.	Rao, Kumar [78]
2016	Germany, Munich	Human umbilical vein endothelial cells; Immortalized E.A hy926 Cells (control)	Efavirenz inhibits endothelial meshwork formation, increases oxidative stress in ER and further elevates autophagy. N-acetylcysteine and quercetin ameliorates pro-oxidant activity.	Weiß et al., [79]
2022	United Kingdom	Rat insulinoma INS-1E cell line	Tenofovir disoproxil fumarate and emtricitabine did not impact cell viability or apoptosis/necrosis levels in INS-1E cells, while beta-cell exposure to efavirenz or rilpivirine partially mediated oxidative stress and mitochondrial toxicity.	Maandi et al., [80]
2020	Germany	The T lymphocyte cell lines J-Lat 9.2 and 15.4, Jurkat E6.1 (ATCC), Jurkat-Tag cells	Antioxidant and iron import pathways are determinants of HIV-1 latency and support their pharmacologic inhibition as tools to regulate PML stability and impair latency establishment.	Shytaj et al., [81]
2014	India	The Grx1-roGFP2-containing vector. We grew human embryonic kidney 293 T cells (ATCC, Manassas, VA), the human monocytic U937 and T-lymphocytic Jurkat cells (ATCC, Manassas, VA), and the chronically infected U1and J1.1 cells	Measurement of glutathione-redox potential (*E*GSH) revealed higher capacity of latently infected cells to resist oxidative stress and apoptosis, whereas HIV-1 replication perturbed glutathione homeostasis.	Bhaskar et al., [82]

Abbreviations: DNA FISH, deoxyribonucleic acid fluorescence in situ hybridization; ELISA, enzyme-linked immunosorbent assay; GSH, reduced glutathione; GSSG, oxidized glutathione; MTT assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; PBMC, peripheral blood mononuclear cells; RT-qPCR, quantitative reverse transcriptase polymerase chain reaction

TABLE 3 | Summary of studies on animal models on oxidative stress in HIV.

Year of publication	Study place	Animal model type	Sample size	Findings	Authors
2019	USA	Male 5-week-old Hsd: HIV-1 (F344) transgenic rats and the background wild type control (Fischer 344/NHsd) rats	At 3 months old, the control and HIV-1 Tg rats were divided into 8 groups	The downregulation of Nrf2 in Tg+cART rats significantly compromised their antioxidant response, which was effectively mitigated by Mg-supplementation at the genomic level.	ElZohary et al., [83]
2017	USA	Sprague Dawley Embryonic Rats	Primary cortices from the brain	Elvitegravir and Lopinavir cause neurotoxicity in vitro by decreasing MAP2 and increasing ROS in cortical neuroglial cells at high dosage concentration.	Stern et al., [84]
2021	Nigeria, Osun State	24 Wistar Rats (twelve weeks Old)	G1 = HAART-Treated only; G2= Anti-Koch Treated Only; G3= Anti-koch+ HAART treated; G4= Distilled water	HAART and Anti-Koch treatment boosts MDA, NO, and MPO levels, but decreases renal SOD, GPx, and GST, while significantly reducing total renal protein, albumin, and Globulin.	Hamed et al., [85]
2016	India, Tamilnadu	Wistar albino rats (2-3 months old)	G1=Saline + Propylene glycol treated (control), G2 = AZT alone; G3 = INH alone, G4 = AZT + INH, G5= silibinin	AZT, INH and AZT + INH increase the activity of AST, ALT, ASAL and bilirubin in Serum. silibinin elevates the activity of NA + /K + , Mg2 + , and ca2+ ATPase in the liver.	Raghu, Karthikeyan [86]
2015	South Africa, Durban	Wistar Rats (8-weeks old)	Treated AZT = G1, G2, G3 Treated D4T = G4, G5, G6 Treated Naringin=G2, G5 Treated Vitamin E = G3, G4(Positive control) Treated Distilled Water= G7	AZT and d4T treated with Naringin or Vitamin E increase body weight, and glutathione peroxidase but decrease abdominal fat mass, liver index and MDA.	Adebiyi et al., [87]
2021	Nigeria	32 inbred adult male rats	4 groups: 8 for control, 8 for anti-koch-treated, 8 for HAART-treated, 8 for anti-koch & HAART-treated.	Animals treated with a combination of antikoch and HAART showed significant increases in malondialdehyde, nitric oxide, C-reactive protein, and myeloperoxidase activity.	Akhigbe, Hamed [88]

Abbreviations: CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; GPx, glutathione peroxidase; GST, glutathione S transferase; HAART, highly active antiretroviral therapy; MDA, malonaldehyde; MPO, myeloperoxidase; NO, nitrite oxide; OxS, oxidative stress; ROS, reactive oxygen species; RT-qPCR, quantitative reverse transcriptase polymerase chain reaction; TBARS, thiobarbituric acid reactive substances.

cholestasis in rats by decreasing enzyme activities, indicating its hepatoprotective and antioxidant potential [86].

4 | Discussion

We conducted a review to assess oxidative stress levels in HIV infection. Our review showed varied reports on antioxidant use in HIV, mechanisms involved in oxidative stress in HIV infection, supplement effects on oxidative stress, oxidative effects on ageing, oxidative stress levels among PLWH on ART, and oxidative stress in HIV comorbidities.

HIV-1 infection or anti-HIV-1 treatment can affect human redox status [90]. Viruses disrupt cell function, leading to an imbalance in ROS systems as they depend on host cell biosynthetic mechanisms. Host mechanisms such as ROS and cytokines also contribute to viral infections [91]. Free radicals significantly impact viral diseases, affecting host cell metabolism and replication, causing inflammation, and decreasing immune cell proliferation [91]. Oxidative stress may contribute to various stages of the viral life cycle [90], and ROS produced excessively by immune response, impact viral pathogenesis and mutation. Their toxicity and reactivity may explain tissue injury in viral diseases involving immunological interactions [91].

4.1 | Mechanisms of Oxidative Stress in HIV Infection

HIV-1 increases ROS production and causes mitochondrial dysfunction [92], and this is influenced by proteins like Gp120 [93], Tat [94], Nef [95], Vpr [96], and reverse transcriptase [97]. Gp120 has been shown to increase ROS production in various cell lines [98, 99], but no such increase was observed in HIV-1-infected monocytes [100]. The Tat protein triggers ROS production through NADPH oxidases [101], SMO [94], and mitochondrial dysfunction [102], with no significant increase in H_2O_2 content in the cytoplasm or mitochondria [103]. HIV-1 Nef protein exhibits prooxidant activity in microglial cells and neutrophils due to interaction with Vav protein [104]. Viral protein R (Vpr) is a key regulator of ROS production in yeast [105], causing oxidative stress and mitochondrial dysfunction [106], and this stress leads to decreased levels of superoxide anion, hydroxyl radical, glutathione, and antioxidant enzyme activities [105]. Binding of Vpr to adenine nucleotide translocase also promotes mitochondrial dysfunction, which exacerbates oxidative stress and contributes to HIV-1 pathology [106].

4.2 | Alcohol Effect on Oxidative Stress in HIV Infection

Alcohol in the bloodstream causes increased vascular cell admission and metabolism, compromising blood-brain barrier integrity. The liver converts alcohol into acetaldehyde, CYP2E1, catalase, and hydrogen peroxide (H_2O_2) including ADH from the cytosol, CYP2E1 from microsomes, and catalase from peroxisomes [107]. The brain's CYP2E1 and catalase enzymes help metabolize alcohol [108, 109], altering HAART treatment and making the liver a silent reservoir for HIV-1 infections [110], as HAARTs are designed for CD4-dependent infections [111].

Alcohol or HIV-1 regulatory proteins, like Tat and gp120, can destabilize BBB integrity by causing stress fiber formation and ROS redistribution [112, 113]. Tight junction proteins and ethanol metabolites like acetaldehyde can directly affect the BBB, compromising its permeability and allowing acetaldehyde to enter the brain microvasculature [114]. HAART metabolism is controlled by CYP450, the primary pathway for alcohol metabolism in the brain, and certain drugs like nelfinavir can produce active metabolites with antiviral properties [115]. Some treatment regimens may require drug boosting, potentially increasing toxicity and side effects, though alcohol consumption has not been proven to affect the pharmacokinetics of HAART drugs [116].

4.3 | The Use of Supplements in Reducing Oxidative Stress in HIV Infection

The HIV virus triggers a robust immune response, releasing inflammatory cytokines and ROS, which increase viral replication in infected cells via NF-kB and activator protein-1 [117]. Selenium is essential for the GPx enzyme, which reduces hydrogen peroxide and organic hydroperoxides, protecting cells from oxidative stress [118]. GPx, along with other antioxidant enzymes, decreases viral activation with selenium supplementation, thereby reducing NF-kB activation, increasing GPx activity, and reducing TNF-α-mediated HIV activation [117]. Chronic HIV infection may increase TNF levels activating NF-kB and continuing the viral activation cycle [119]. Studies show that selenium added before TNF-α can partially inhibit viral replication in chronically infected lymphocytes and monocytes during acute HIV infection [120].

Seleno-proteins are abundant in immune cells and are upregulated during activation as they are necessary for Ca^{2+} flux in T cells, neutrophils, and macrophages [121, 122]. T cells and macrophages have the highest levels of seleno-proteins in the immune system, which can be compromised when selenium deficiency exists [122]. Seleno-proteins are antioxidants crucial for protein folding and cell signaling, and deficiency leads to loss of non-essential seleno-proteins, affecting immune response and antibody production in lymphocytes [122, 123].

N-acetyl cysteine (NAC) is a natural and synthetic compound that acts as a safe antidote against free-radical species, including Cys/GSH deficiency and four major redox couples regulating cellular redox environment [90]. NAC supplementation increased cysteine (Cys) plasma levels, slowing trans-sulfuration, sparing homocysteine and serine [124], diverting the serine to glycine pathway, and normalizing GSH levels by consuming spared Cys [125]. GSH increase and normalization in glutamine (Gln) may be achieved by generating glycine from glutamic acid and sparing serine to form Cys from homocysteine, with all three together generating GSH [124, 125].

Curcumin, a polyphenol in turmeric, has been reported to reduce oxidative stress, inflammation, and insulin resistance [126], protecting against various diseases like neurological

[127], metabolic [128], renal [129], and cancer [130]. Curcumin reverses alterations in rats with 5/6 nephrectomy through enhanced nuclear factor (erythroid-derived 2)–like 2 (Nrf2) translocation, oxidant stress reduction, and antioxidant enzyme preservation [131] and partially prevents prostate cancer through nuclear factor erythroid 2-related factor 2 (Nrf2) [132]. Curcumin has been found to have a neuroprotective effect in rats with neurodegeneration and focal cerebral ischemia, activating Nrf2 and increasing superoxide dismutase and glutathione peroxidase activity [127].

4.4 | Effect of Oxidative Stress in Ageing

Cellular events involved in aging are characteristic of many chronic degenerative diseases, including neurodegeneration, CVD, and chronic obstructive pulmonary disease [133].

Frailty phenotype, including CVD, hypertension, diabetes, renal failure, and bone fracture, is associated with aging and can be a potential marker of disability and increased mortality [134]. Frailty is characterized by involuntary weight loss, weakness, poor endurance, exhaustion, and low physical activity [135]. Observational studies indicate that frailty is linked to proinflammatory biomarkers like IL-6, C-reactive protein, and TNF-α [136].

HIV-positive patients exhibit a premature aging phenotype, with earlier onset of co-morbidities and higher risk of non-AIDS-related morbidity and mortality despite ART, resulting in a higher risk of mortality [12].

4.5 | Lifestyle and Co-Morbidities on OxS

Lifestyle factors like alcohol and illicit drug consumption, smoking, and HBV/HCV co-infections in HIV-positive patients worsen their frailty [137, 138] as high ethanol consumption increases MDA, reduces GSH, and partially nullifies red wine's antioxidant capacity [139].

Methamphetamine users experience higher OxS levels due to dopaminergic system dysregulation, hyperthermia, apoptosis, neuroinflammation, increased viral replication, Tat-mediated neurotoxicity, neurocognitive impairment, and increased inflammatory response [140].

Chronic hepatitis caused by the Hepatitis C virus (HCV) leads to reduced GSH levels, increased ROS production by mitochondria, and interference with the NrF/ARE pathway, highlighting the importance of ROS in HCV-associated pathogenesis [141]. Different outcomes of results for comorbidities may be because many studies were carried out at one time point, but longitudinal studies would have been more helpful in identifying trends in oxidative stress and antioxidant levels.

4.6 | ART Effect on Oxidative Stress in HIV

Oxidative stress is a critical mechanism in the progression of AIDS. It has been observed that perturbations in antioxidant defense systems and redox imbalance are present in many tissues of HIV-infected patients [90]. The impact of ART on oxidative stress parameters has been the subject of limited and conflicting studies. HAART administration improved glutathione redox status in HIV-infected subjects, suppressing tumor necrotic factor-alpha (TNF-α) release and increasing cell proliferation in vitro, though without full normalization [142]. Another study found a significant reduction in glutathione peroxidase in HIV-infected individuals with CD4 + T-cell count below 200 cells/mm^3 [143], contradicting previous reports of increased GPx in ART-infected individuals [144]. HIV-infected males have lower GSH levels compared to females, suggesting sex-specific differences in antioxidant capacities [62] with female mitochondria displaying higher GSH and GPx activities, potentially protecting against ROS-mediated damage [145].

ART toxicity activates frailty mechanisms, with elevated F2-isoprostanes (F2-IsoP) levels linked to antiretroviral agent use and suppressed viral replication [146]. Nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) increase intracellular concentrations, causing cellular senescence and mitochondrial dysfunction [147]. PIs alone induce prelamin A accumulation, leading to genomic instability and cellular senescence [147]. Long-term use of PIs, which trigger the production of ROS, is linked to metabolic perturbations like lipodystrophy and insulin resistance, which can inhibit respiratory chain complexes and increase systemic inflammation [148]. PIs decrease electron transporter chain activity, generating reactive species and increasing superoxide production. ART is linked to immune senescence and chronic inflammation by altering the phenotype of senescent cells and secreting proinflammatory cytokines [149].

4.7 | Antioxidants in HIV/AIDS

Few studies explore the link between serum antioxidant micronutrients, red blood cell polyunsaturated fatty acids (RBC PUFA), and CVD in PLWH, a concern due to micronutrient deficiencies causing disease progression and treatment failure [150]. Studies explored the role of n-3 PUFA in PLWH, but fish oil supplementation has been proven beneficial for hypertriglyceridemia and PLWH [29, 151]. High n-3 PUFA intake reduces CVD mortality [151] and inhibits proinflammatory pathways but does not improve endothelial function in HIV-infected men [152].

HIV-infected patients show reduced antioxidant enzyme activities, while ART-naïve individuals show reduced blood SOD, GPx, and catalase activities and elevated malondialdehyde levels compared to healthy controls [64, 153]. Increased antioxidant enzyme activity improves HIV-positive health, decreases lipid peroxidation, and improves CD4+ counts in ART-naïve patients [154]. Low glutathione reductase (GR) activity leads to elevated oxidized glutathione (GSSG) levels, oxidative stress, and viral replication [154].

Manganese (Mn) is a crucial trace element for HIV disease management, strongly associated with CD4+ count, while other trace elements like Fe, Se, and Cu show weak correlations. Elevated manganese concentrations inhibit reverse transcription [155]. Other studies found a negative correlation between manganese level and

total SOD activity in HIV-infected patients with high viral loads [156, 157], with an established inhibition of Mn SOD by HIV Tat protein, resulting in a significant reduction in trace element levels.

4.8 | Magnitude of Oxidative Stress Among Different Study Groups

A study of oxidative burst enzymes in HIV-positive HAART-naïve, HIV-positive on HAART, and HIV-negative control subjects observed a significantly higher levels of CD4+ cells, catalase (CAT) and myeloperoxidase (MPO) activities compared to HIV-positive HAART-naïve subjects and negative control, but no significant difference was observed in the activity of superoxidase dismutase (SOD) among all the groups [45]. The observed results corroborated an earlier study that showed significantly higher MPO activity in HIV infected individuals on HAART compared to negative control subjects (Syed et al., 2013).

In another study, total antioxidant capacity (TAC) was determined in four groups, HIV infected and on HAART for < 1 year, HIV infected and on HAART for > 1 year, HIV infected HAART-naïve, and negative controls in both male and female participants [61]. The study observed that TAC in patients on HAART for less than a year was the highest, followed by the negative controls, patients on HAART for more than a year, and then patients who were HAART-naïve, in that order. The observation was suggested to be probably due to increased antioxidant consumption lifestyle in the new treatment-initiated group. In the same study, elevated MDA and decreased TAC were observed in HIV-naïve patients followed by those receiving therapy for more than a year, patients on HAART for more than 1 year, and negative control, and suggested that oxidative stress was significantly higher in the HAART-naïve group than the others [61].

4.9 | Limitations and Critical Gaps

Most of the studies that were used in the current review were carried out in high-income settings, and the majority of the studies were non-interventional [27, 44]. Some of the studies had no information about risks factors such as lifestyle habits, and small sample sizes, differences in baseline characteristics, and variability in cART usage duration among participants could be confounding factors that limits extrapolation of study outcomes to the general populations of PLWH [46, 61, 67, 158]. Study designs of some of the studies do not allow for a causal relationship between specific parameters [19, 31]. Cardinal makers of oxidative stress, such as glutathione, superoxide dismutase, and catalase, were not assessed in some studies [60, 65, 73], and the effect of some supplements, such as curcumin, were not investigated for long term and its associated risk factors [31], which could have resulted in oxidative stress reduction and led to improved disease outcomes.

5 | Conclusions

This study highlights oxidative stress response in HIV individuals. Contradictory reports on oxidative stress response necessitate further studies to ascertain its authenticity. The use of supplements such as selenium, seleno-proteins, and N-acetylcysteine in cell lines, and magnesium and silibinin extract in animal models, has been shown to improve glutathione levels and thereby reduce oxidative stress response and aging. There is therefore the need to replicate the usage of these supplements in PLWH to ascertain their efficacy in humans. Further studies should also investigate other supplements usage and identify other extracts from natural and synthetic products that can be used in improving the antioxidant status of HIV-infected persons.

Author Contributions

Esimebia Adjovi Amegashie: conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, writing – original draft, writing – review and editing. **Ruth Oyawole Sikeola:** data curation, formal analysis, investigation, methodology, writing – original draft. **Emmanuel Ayitey Tagoe:** conceptualization, formal analysis, project administration, supervision, validation, visualization, writing – review and editing. **Elijah Paintsil:** conceptualization, formal analysis, funding acquisition, project administration, resources, supervision, validation, visualization, writing – review and editing. **Kwasi Torpey:** conceptualization, formal analysis, funding acquisition, project administration, resources, supervision, validation, visualization, writing – review and editing. **Osbourne Quaye:** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review and editing.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Transparency Statement

The lead author Osbourne Quaye affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.