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ORIGINAL RESEARCH

Trace element imbalance and NrF-2 expression in the modulation of Oxidative stress among HIV-infected patients

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Abstract

Background: Oxidative stress has been reported to promote HIV replication and immunodeficiency progression. However, the role of Nrf2 and certain trace elements, such as zinc, in this process remains poorly understood.

Objectives: This study investigated Nrf2 expression and oxidative stress in HIV-infected individuals and examined the relationships among selected trace elements, Nrf2 expression, and oxidative stress markers.

Methods: A case-control study was conducted among 100 adults, comprising 50 newly diagnosed HIV-infected participants and 50 apparently healthy HIV-negative controls. We measured serum iron, zinc, copper, malondialdehyde (MDA), and total antioxidant capacity (TAC) using standard biochemical methods, and assessed Nrf2 expression by real-time polymerase chain reaction. We analyzed the data using appropriate statistical methods, with significance set at $p<0.05$.

Results: MDA was significantly higher in HIV-infected participants than in controls (0.98±0.45 vs 0.68±0.34 µmol/mg), whereas TAC was significantly lower (678.25±376.92 vs 1025.59±383.61 µmol/L). Iron concentration was higher in HIV-infected participants than in controls (1.01±0.47 vs 0.66±0.80), whereas zinc was significantly lower (1.02±0.47 vs 2.13±1.38; $p<0.001$). Copper did not differ significantly between groups. Nrf2 expression was significantly higher among HIV-infected participants ($p=0.017$). Nrf2 expression correlated positively with MDA ($r=0.869$, $p<0.001$) and iron ($r=0.633$, $p=0.015$), but negatively with TAC ($r=-0.693$, $p=0.006$).

Conclusions: HIV infection was associated with increased oxidative stress, reduced antioxidant capacity, altered zinc and iron status, and increased Nrf2 expression. Nrf2 expression was associated with MDA, iron, and TAC, indicating that the Nrf2 response, trace-element status, and oxidative stress are linked in HIV infection.

Keywords: Human Immunodeficiency Virus, Nuclear Factor Erythroid 2-Related Factor 2, Oxidative Stress, Total Antioxidant Capacity, Trace Elements

Introduction

Human immunodeficiency virus (HIV), which causes Acquired immune deficiency syndrome (AIDS), is considered one of the biggest challenges of the 21st century. Although it was identified many years ago, it has been difficult to treat.[1] The impact of HIV-AIDS is particularly severe in sub-Saharan Africa, where approximately 28.5 million people, accounting for 50% of all people living with the virus worldwide, are affected. [2,3]

Reactive Oxygen Species (ROS) can cause oxidative stress, which may significantly promote HIV replication and the progression of immunodeficiency.[4] Excessive production of reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, and hydrogen peroxide, may be associated with increased activation of polymorphonuclear leukocytes during infections. Additionally, this may be influenced by the prooxidant effect of tumor necrosis factor α, which is produced by activated macrophages during the course of HIV infection.[5,6] ROS can cause significant harm, but an effective antioxidant defense system can prevent or reduce it. This system depends on trace minerals such as selenium, copper, zinc, and manganese, which are essential for enzyme function. Adequate amounts of vitamins E, A, and C, along with β-carotene in both the cytoplasm and cell membranes, also support a healthy antioxidant defense system. [7-9]

Many essential Trace Elements (TEs) play a crucial role in enzymatic reactions that alter signaling pathways. TEs mainly exert their effects by modulating redox reactions.[10] If essential trace elements such as copper, zinc, iron, and selenium are present in excess or unbound, they can act as pro-oxidants. However, when these TEs are available in specific amounts, they serve as cofactors for antioxidant and protective enzymes such as selenoproteins, glutathione peroxidases (GPX), thioredoxin reductases (TXNRD), Cu/Zn superoxide dismutase (SOD1), catalase, and metallothioneins (MT). [11,12]

Studies conducted in Nigeria have also reported alterations in trace-element and antioxidant status among individuals with HIV infection. Olaniyi and Arinola reported significant changes in plasma concentrations of selected trace elements and antioxidants among Nigerian HIV-infected patients compared with non-HIV-infected controls, with some parameters varying by disease severity.[13] Similarly, Okwara et al. reported significantly lower selenium, zinc, and

magnesium concentrations among HIV-positive adults compared with HIV-negative controls in Eastern Nigeria.[14] These findings suggest that alterations in trace-element status may accompany HIV infection and may contribute to disturbances in redox homeostasis.

Nuclear factor erythroid 2–related factor 2 (Nrf2) is a transcription factor in the Cap'n'Collar family. In its basal state, it possesses a basic leucine zipper domain.[15] In the cytoplasm, Nrf2 is bound to Kelch-like ECH-associated protein 1 (Keap1), which acts as an adapter protein for the Cullin3-based E3 ubiquitin ligase. This binding helps prevent proteasomal degradation of Nrf2.[1] Nrf2 activates genes that produce enzymes that prevent oxidative damage and metabolize harmful substances in the body, such as heme oxygenase-1, NAD(P)H quinone oxidoreductase 1, and γ-glutamylcysteine synthetase. It does this by binding to specific regions on the genes, known as antioxidant-responsive elements (AREs), located in their promoter regions. Heme oxygenase-1, in particular, helps protect cells from oxidative damage by breaking down heme into carbon monoxide, biliverdin, and iron.[16]

NRF2 was originally identified as a key factor in maintaining cellular redox balance and as a critical element in the body's defense against viral infections. However, it is now recognized as a key immune regulator, particularly during infection, making it central to the immune response.[17] Nrf2 also helps maintain cellular redox balance by coordinating antioxidant and cytoprotective responses. [15]

Although NRF2 has demonstrated antiviral properties, the specific downstream genes and mechanisms through which it exerts these effects remain under investigation. While genes like HO-1 have been implicated as potential mediators, the pathways through which they modulate viral infections remain incompletely understood. However, NRF2 plays a vital cytoprotective role by mitigating virus-induced cellular damage and regulating inflammatory responses that can cause immunopathology during infection.[11,15] Given that the activation of NRF2 and its target antioxidant genes is heavily dependent on the availability of trace elements such as selenium, zinc, copper, and iron, which serve as cofactors for various antioxidant enzymes, there is a compelling need to explore the interplay among NRF2 expression, trace element status, and oxidative stress. Therefore, this study aims to examine NRF2's role in maintaining oxidative balance in people with HIV and assess how selected trace elements relate to this regulatory pathway, thereby improving

understanding of the mechanisms underlying oxidative stress in HIV infection.

Methods

Study Design: We employed a case-control, cross-sectional, analytical study design.

Study Location: We conducted this study at Babcock University Teaching Hospital in Ilishan-Remo, Ogun State, Nigeria. The hospital is a major regional healthcare provider and offers a broad range of specialized medical services. Researchers purposively recruited HIV-positive participants from the Antiretroviral Therapy (ART) Clinic within the Department of Community Medicine. The clinic provides ongoing treatment, monitoring, and counseling services to individuals living with HIV/AIDS. We chose this setting for its steady patient flow, structured treatment programs, and reliable access to medical records, making it ideal for recruiting participants and collecting relevant clinical and laboratory data.

Study Duration: The study was conducted from March 2024 to February 2025.

Study Participants: A total of 100 individuals, aged 18 to 60 years, participated in this study. The study population comprised two groups: 50 newly diagnosed HIV-positive patients and 50 HIV-negative individuals who served as the control group. The HIV-positive participants were recruited from the Antiretroviral Therapy (ART) Clinic of the Department of Community Medicine at Babcock University Teaching Hospital, Ilishan-Remo, Ogun State, Nigeria. The control group consisted of 50 apparently healthy individuals who had tested negative for HIV on multiple occasions over a six-month period. These participants were selected from the general community and hospital visitors after careful screening to confirm their HIV-negative status. Both the case and control groups included adults, with a mix of male and female participants. To reduce potential confounding by age, we age-matched participants in both groups.

Sample Size Calculation: We calculated the minimum sample size using the formula for comparing two independent means at a 5% level of significance and 80% statistical power. The calculation yielded a minimum sample size of 28 participants per group, giving a total of 56 participants. To increase statistical power and the reliability of the study findings, we recruited a larger sample. A total of 100 participants were therefore recruited, comprising 50 HIV-infected participants and 50 HIV-negative controls.

Inclusion and Exclusion Criteria: HIV infection status defined case and control classification. Participants were eligible for inclusion in the case group if they were adults aged 18 to 60 years, had confirmed HIV infection, were recruited from the Antiretroviral Therapy clinic at Babcock University Teaching Hospital, and provided written informed consent. Participants were eligible for inclusion in the control group if they were adults who tested HIV-negative, were apparently healthy, were recruited from the hospital or surrounding community, and provided written informed consent. Participants were excluded if they had a history of chronic disease, were smokers, consumed alcohol, used nutritional supplements, or were taking medications that could influence oxidative stress or trace-element status.

Recruitment and Consent of Participants: Researchers purposively recruited HIV-infected participants from the Antiretroviral Therapy Clinic of Babcock University Teaching Hospital, Ilishan-Remo, Ogun State, based on predefined eligibility criteria. The HIV-negative control participants were recruited from apparently healthy individuals presenting at the hospital and from the surrounding community who met the control eligibility criteria. We approached potential participants and screened them for eligibility before enrolment. We explained the study's purpose, procedures, and requirements to eligible participants and obtained written informed consent from each participant before participation and blood sample collection.

Study Protocol and Data Collection: After enrolment and completion of the consent process, we obtained relevant demographic and clinical information from each participant. We aseptically collected approximately 10 mL of venous blood from each participant into appropriately labeled sterile blood collection tubes. We collected blood for serum biochemical analyses into plain tubes, allowed it to clot at room temperature, and centrifuged it at approximately 3,000 rpm for 10 minutes. We carefully transferred the separated serum into labeled, sterile plain cryovials and stored it at −20 °C until analysis. We collected blood samples in EDTA-containing tubes for molecular analysis of Nrf2 expression, then processed and stored them at −20 °C until analysis. We used serum samples to determine iron, zinc, copper, total antioxidant capacity (TAC), and malondialdehyde (MDA). We measured trace elements by atomic absorption spectrophotometry and TAC and MDA by spectrophotometric methods. We assessed Nrf2 expression by reverse transcription polymerase chain reaction (RT-PCR). We assigned unique study codes to samples to

maintain participant confidentiality and ensure accurate linkage between laboratory results and participant information. We then collated the laboratory results and participant data for statistical analysis.

Ethical considerations: The Babcock University Health Research Ethics Committee approved this study (Approval ID: BUHREC 471/23) before the research commenced. Participation was voluntary, and we obtained consent forms from each participant before the study. We included all participants who gave written consent. We conducted the study in accordance with the Declaration of Helsinki.

Biochemical analysis: We determined serum iron, copper, and zinc concentrations by atomic absorption spectrophotometry (AAS), based on the absorption of element-specific wavelengths by ground-state atoms. Analysis was performed using an Agilent 240FS AA Atomic Absorption Spectrophotometer (Agilent Technologies, USA). We determined total antioxidant capacity (TAC) using the ferric reducing ability of plasma (FRAP) method, based on antioxidants reducing ferric ions to ferrous ions in the sample, as described by Benzie and Strain.[18] We determined malondialdehyde (MDA) spectrophotometrically as an index of lipid peroxidation using the method described by Adam-Vizi and Seregi.[19] We performed spectrophotometric measurements using a Jenway 7315 UV/Visible Spectrophotometer (Cole-Parmer, UK). We determined Nrf2 expression by reverse transcription polymerase chain reaction (RT-PCR). We extracted RNA, reverse-transcribed it to complementary DNA, and amplified it with Nrf2-specific primers; we normalized expression to a reference gene. We amplified the products using a Bio-Rad CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories, USA) according to the manufacturer's instructions.

Statistical analysis: We performed statistical analyses using SPSS software (version 28.0). We used Student’s t-test to compare group means and Pearson's correlation to assess relationships between parameters. *We considered P-values* < 0.05 statistically significant.

Table I: Socio-demographic characteristics of study participants

Characteristic	Case (n=50)	Control (n=50)	Test statistic	*p*-value
Age (years), (mean ± SD)	39.6 ± 8.7	38.9 ± 8.4	0.41[a]	0.682
Age group (years), [n (%)]				
18–29	7 (14.0)	8 (16.0)	0.34[b]	0.844
30–44	29 (58.0)	28 (56.0)		
≥45	14 (28.0)	14 (28.0)		
Sex, [n (%)]				
Male	21 (42.0)	23 (46.0)	0.16[b]	0.687
Female	29 (58.0)	27 (54.0)		

[a]**Independent *t*-test;** [b]**Chi-square test;** ***Statistical significance was set at p < 0.05.***

Results

Table I shows the socio-demographic characteristics of the study participants. The HIV-infected group had a mean age of 39.6 ± 8.7 years, compared with 38.9 ± 8.4 years among the HIV-negative group, with no statistically significant difference between the groups (p = 0.682). Participants aged 30–44 years constituted the largest proportion in both the HIV-infected and HIV-negative groups, accounting for 58.0% and 56.0%, respectively. Females constituted 58.0% of the HIV-infected group and 54.0% of the HIV-negative group, while males accounted for 42.0% and 46.0%, respectively. Sex distribution did not differ significantly between the groups (p = 0.687).

Table II compares oxidative stress markers and selected trace elements between HIV-infected and HIV-negative participants. MDA was significantly higher in HIV-infected participants than in HIV-negative participants (0.98 ± 0.45 vs 0.68 ± 0.34 µmol/mg; p < 0.001), whereas TAC was significantly lower in HIV-infected participants (678.25 ± 376.92 vs 1025.59 ± 383.61 µmol/L; p < 0.001). Zinc concentration was significantly lower in the HIV-infected group than in the HIV-negative group (1.02 ± 0.47 vs 2.13 ± 1.38 mg/L; p < 0.001), whereas iron concentration was significantly higher in the HIV-infected group (1.01 ± 0.47 vs 0.66 ± 0.80 mg/L; p = 0.010). Copper concentration did not differ

significantly between the two groups (0.77 ± 0.23 vs 0.89 ± 0.56 mg/L; p = 0.186).

Table II: Comparison of oxidative stress markers and selected trace elements between HIV-infected (Case) and HIV-negative (Control) participant

Parameter	Case Mean ± SD	Control Mean ± SD	*t*-value	*p*-value
MDA (µmol/mg)	0.98 ± 0.45	0.68 ± 0.34	3.666	<0.001*
TAC (µmol/L)	678.25 ± 376.92	1025.59 ± 383.61	4.497	<0.001*
Zinc (mg/L)	1.02 ± 0.47	2.13 ± 1.38	5.386	<0.001*
Copper (mg/L)	0.77 ± 0.23	0.89 ± 0.56	1.337	0.186
Iron (mg/L)	1.01 ± 0.47	0.66 ± 0.80	2.647	0.010*

***Statistically significant at p < 0.05. MDA, malondialdehyde; TAC, total antioxidant capacity; SD, standard deviation.**

Figure 1 compares the mean fold change in Nrf-2 levels between case and control participants. NRF-2 in the HIV-positive group was 1.52±1.35, which was significantly higher (p = 0.017) than the findings in the non-HIV-infected group (0.165±0.10).

Table III showed a significant negative correlation between MDA and TAC (r = -0.246, p = 0.016). The table also revealed a nearly significant positive correlation between TAC and zinc (r = 0.194, p = 0.057). The table further showed a significant direct relationship between Nrf-2 and iron levels (p = 0.015).

Figure 2 shows a strong positive correlation between MDA and Nrf-2 (r = 0.869, p < 0.001).

Figure 3 shows an inverse correlation between TAC and Nrf-2 (r = -0.693, p = 0.006).

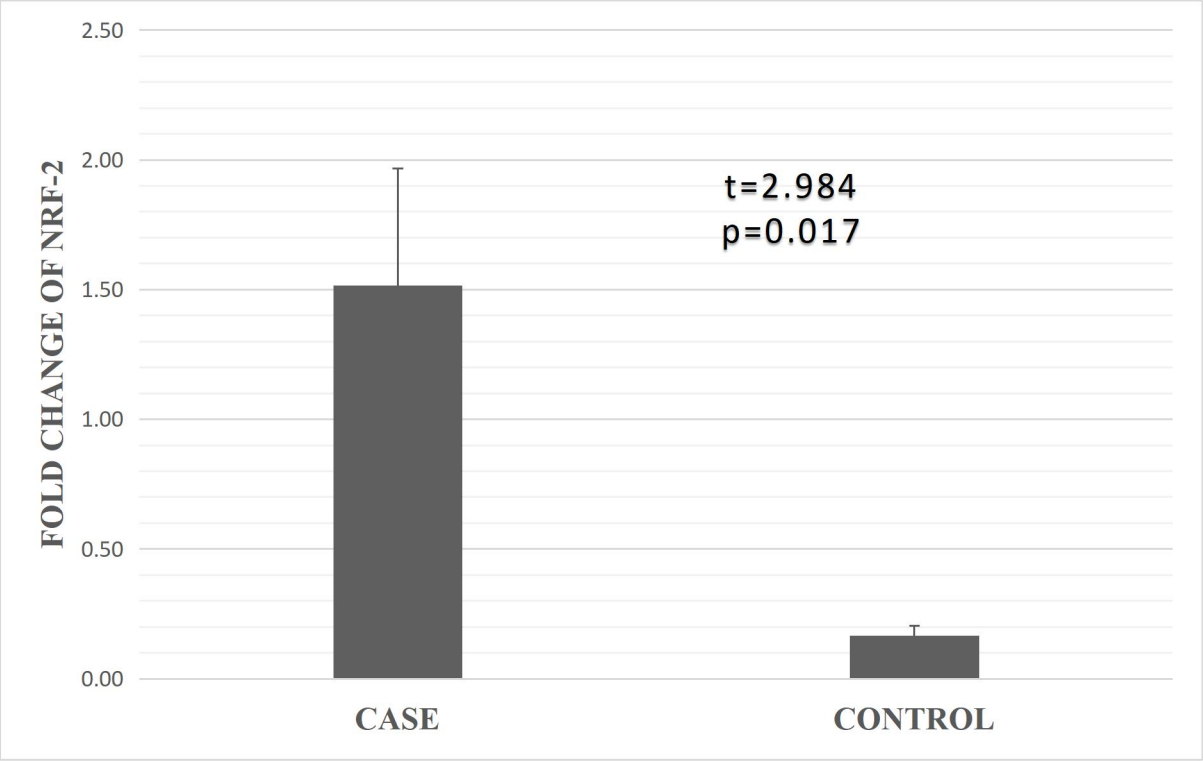

Figure 1. Comparison of NRF-2 between case and control

Table III: Relationship between NrF-2, oxidative stress markers and selected trace elements using Pearson's correlation

Parameters	Parameters	r-value	p-value
MDA	TAC	-0.246	0.016
	ZINC	-0.129	0.203
	COPPER	-0.121	0.232
	IRON	0.039	0.701
TAC	MDA	-0.246	0.016
	ZINC	0.194	0.057
	COPPER	-0.077	0.455
	IRON	0.084	0.416
ZINC	MDA	-0.129	0.203
	TAC	0.194	0.057
	COPPER	0.012	0.908
	IRON	-0.023	0.820
COPPER	MDA	-0.121	0.232
	TAC	-0.77	0.455
	ZINC	0.012	0.908
	IRON	0.076	0.450
NRF-2	ZINC	-0.483	0.177
	COPPER	0.131	0.656
	IRON	0.633	0.015

***Statistically significant at P <0.05**

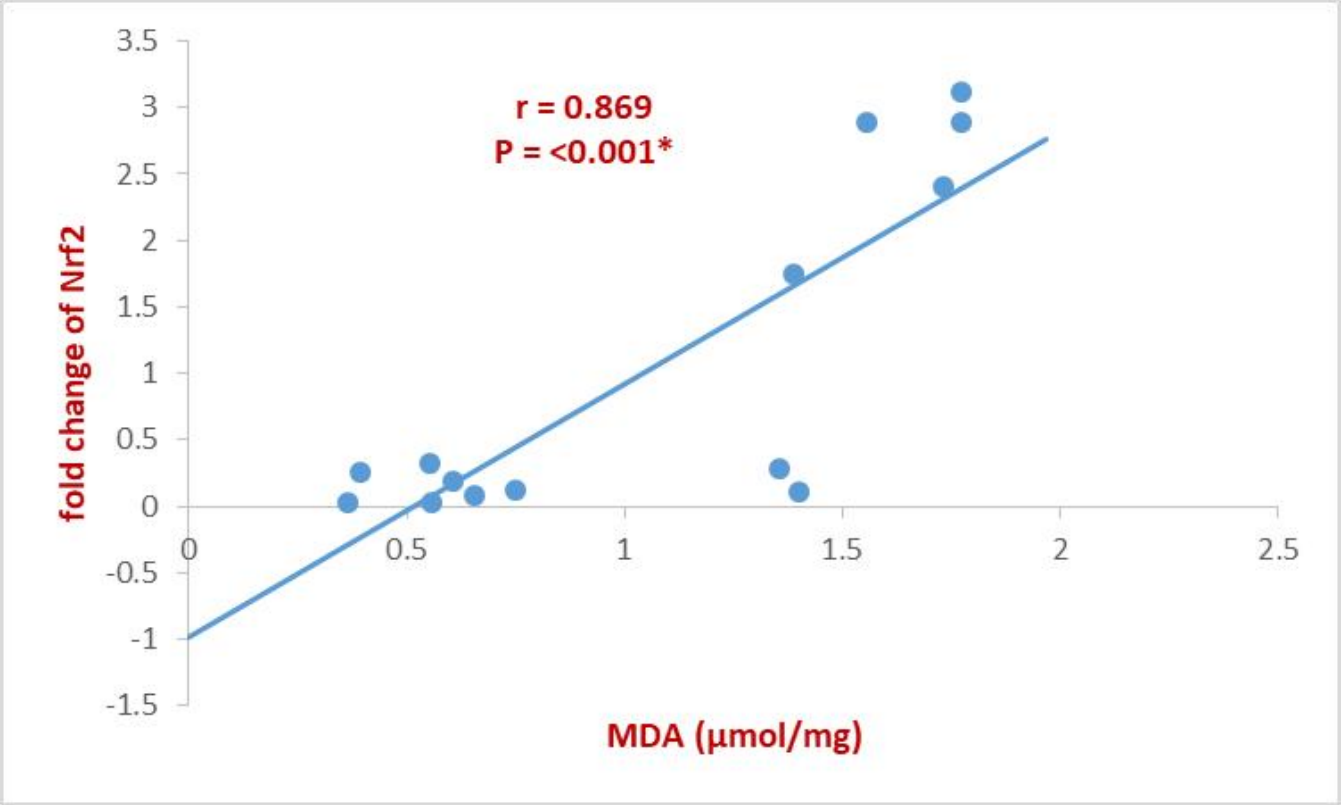

Figure 2. Relationship between MDA and NRF-2 using Pearson's correlation

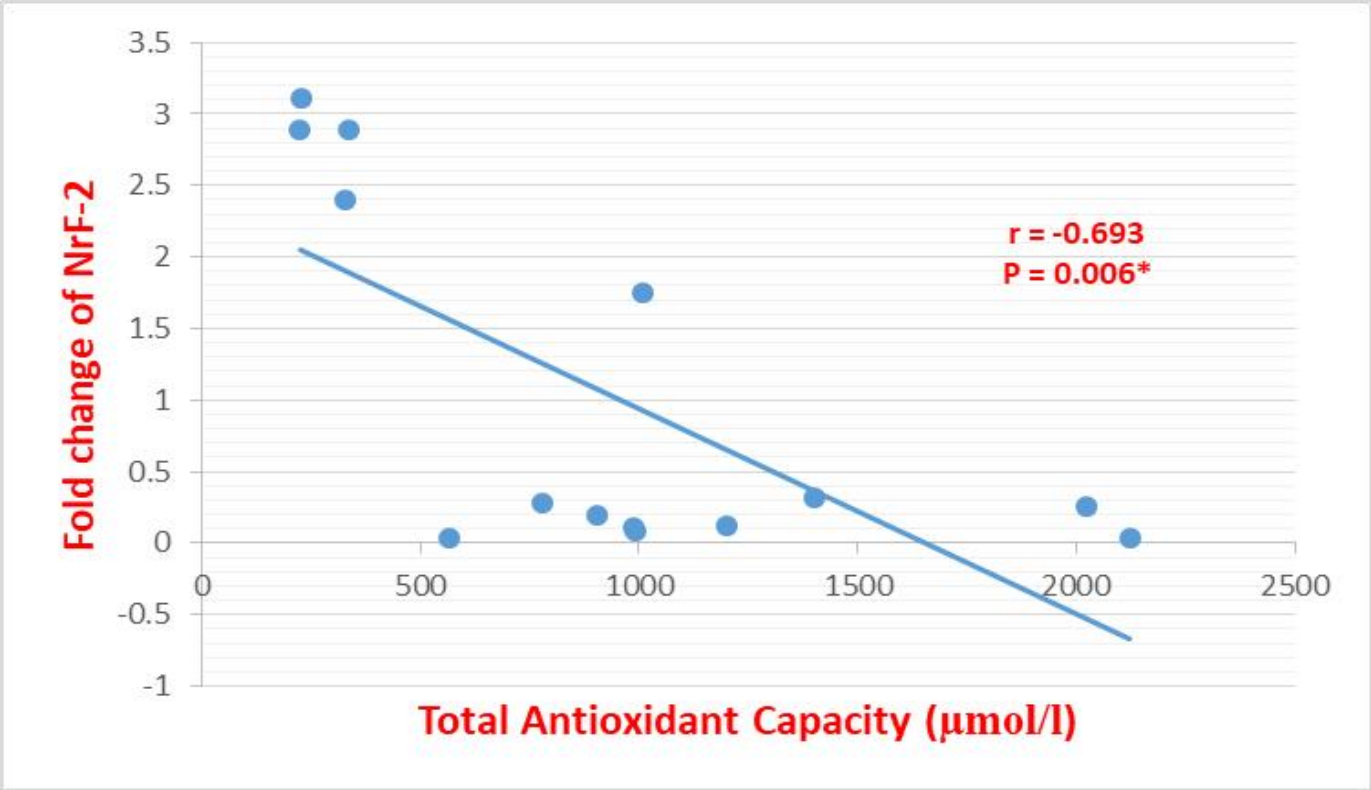

Figure 3. Relationship between TAC and NRF-2 using Pearson's correlation

Discussion

Human immunodeficiency virus (HIV) infection is linked to chronic inflammation, oxidative stress, and immune dysregulation.[20] This study investigated the relationship between oxidative stress markers, trace elements, and nuclear factor erythroid 2–related factor 2 (Nrf2) expression in HIV-positive patients compared with HIV-negative controls in Nigeria. The findings indicated significant alterations in oxidative stress parameters among HIV-positive patients, evidenced by markedly elevated malondialdehyde (MDA) levels and significantly reduced total antioxidant capacity (TAC) compared with HIV-negative controls. MDA is a stable end-product of lipid peroxidation and is often used as a biomarker of oxidative damage to cell membranes. Its elevation in HIV-positive individuals points to increased peroxidative damage induced by overproduction of reactive oxygen species (ROS). In contrast, reduced TAC reflects a compromised antioxidant defense system in these patients. TAC measures the cumulative effect of all antioxidants present in plasma, including enzymatic antioxidants (such as

superoxide dismutase and catalase) and non-enzymatic molecules (like glutathione, vitamins C and E). A low TAC therefore signals an inadequate response to oxidative stress, leaving cells vulnerable to damage. [21,22]

A 2023 cross-sectional study conducted in Indonesia similarly reported significantly lower serum TAOC levels in HIV-infected individuals compared to healthy controls ($P < 0.05$), mirroring our observation of reduced TAC among HIV-positive patients.[23] Although the study found a weak correlation between TAOC and CD4 count or viral load, its core finding, significantly reduced total antioxidant capacity in HIV patients, aligns directly with our results.

Mechanistically, HIV infection leads to sustained immune activation and chronic inflammation, both of which are key sources of ROS. HIV-infected cells, particularly macrophages and CD4+ T lymphocytes, produce large amounts of ROS either directly via viral replication or indirectly through inflammatory mediators like TNF-α and IL-6.[20,24] These ROS disrupt cellular redox homeostasis by overwhelming the body's antioxidant defenses, causing oxidative stress. Additionally, HIV proteins such as Tat and gp120 have been implicated in mitochondrial dysfunction and increased ROS generation, further exacerbating oxidative injury.[25] Mitochondrial damage reduces ATP production and increases electron leakage, enabling electrons to react with oxygen and form superoxide radicals. These radicals initiate chain reactions that damage lipids, proteins, and DNA. The accumulation of MDA and the depletion of TAC observed in this study reflect these underlying biochemical processes and highlight the oxidative burden faced by HIV-infected individuals. [21,26]

Trace element analysis revealed significant differences between the case and control groups. Zinc levels were substantially reduced in HIV-positive patients, which is consistent with previous findings that serum zinc concentrations tend to decrease with disease progression. This decline is partly due to the virus's reliance on zinc-dependent enzymes such as integrase for replication.[27] Additionally, the immune system's increased demand for zinc to maintain immune function during chronic infection may further deplete systemic zinc levels.[7] Zinc deficiency has been associated with impaired immune responses, increased oxidative stress, and worsened clinical outcomes in HIV-infected individuals.

In contrast, iron levels were significantly higher in HIV-positive patients. Iron can

promote viral replication and oxidative stress via the Fenton reaction, which generates reactive oxygen species (ROS) that contribute to cellular damage and inflammation. Excess iron may also facilitate pathogen growth, including HIV, and modulate host immunity.[28] Meanwhile, copper levels did not differ significantly between the two groups, suggesting that copper homeostasis may be less affected in early or stable stages of HIV infection, or regulated differently than zinc and iron in the context of HIV.

Nuclear factor erythroid 2–related factor 2 (NrF-2) was significantly elevated in HIV-positive individuals compared with the control group. NrF-2 plays a crucial role in sensing oxidative stress and mediating adaptive responses by translocating to the nucleus, where it binds to antioxidant response elements (AREs) and upregulates the expression of various cytoprotective genes, including those encoding glutathione synthesis enzymes, heme oxygenase-1 (HO-1), and NAD(P)H quinone dehydrogenase 1 (NQO1).[26] The observed elevation in NrF-2 levels in HIV-positive patients may represent a compensatory mechanism triggered by excessive oxidative stress, a common consequence of chronic HIV infection.

This cellular response appears to correlate with elevated malondialdehyde (MDA) levels, a marker of lipid peroxidation, further suggesting a heightened oxidative burden in HIV-infected individuals. The concurrent increase in MDA and NrF2 supports the hypothesis that HIV-induced oxidative stress activates the NrF2 pathway as a protective measure.[25] However, while Nrf2 upregulation may enhance antioxidant defenses, persistent activation may not fully counteract oxidative imbalance amid ongoing viral replication and immune dysregulation.

Additionally, this study found a significant positive correlation between NRF2 expression and iron levels in HIV-positive patients, indicating that elevated iron levels were associated with increased NRF2 activity. This relationship suggests an adaptive cellular response to oxidative stress induced by iron. Iron, particularly in its free ferrous form (Fe^{2+}), participates in the Fenton reaction, generating highly reactive hydroxyl radicals that contribute to oxidative damage. This oxidative stress activates the NRF2 pathway by promoting dissociation of NRF2 from its cytoplasmic repressor, KEAP1, allowing NRF2 to translocate to the nucleus and initiate transcription of antioxidant and cytoprotective genes. These include genes that regulate iron homeostasis, such as ferritin (which stores

excess iron) and ferroportin (which facilitates iron export), thereby minimizing further ROS generation. This finding aligns with recent studies, such as Lim et al. (2019) [29], which showed that increased iron levels activate NRF2 and increase hepcidin expression via the BMP6 pathway, contributing to systemic iron regulation. Similarly, Pan-de la Rosa et al. (2020) [30] confirmed that prolonged iron exposure induces oxidative stress and NRF2 activation, increasing expression of downstream protective genes such as NQO1 and ferritin. These findings suggest that the positive correlation observed between NRF2 and iron levels reflects NRF2's essential role in defending against iron-mediated oxidative stress in people with HIV.

This study has limitations to consider when interpreting the findings. The case-control design compares HIV-infected and HIV-negative participants but does not establish temporal or causal relationships among HIV infection, trace-element alterations, oxidative stress, and Nrf2 expression. The study assessed only a limited number of trace elements and oxidative stress markers, so it did not account for other factors that may affect Nrf2 expression and redox status. This limits the results' generalizability.

Conclusion

HIV-infected participants had increased oxidative stress, with higher MDA levels and lower TAC than HIV-negative controls. Nrf2 expression was significantly higher and positively correlated with MDA and iron levels. Zinc and iron levels were significantly altered in HIV-infected participants, whereas copper showed no significant difference. Overall, HIV infection was associated with altered trace-element status, oxidative stress, and Nrf2 expression.

Recommendations: Consider assessing oxidative stress and selected trace-element status in the biochemical monitoring of HIV-infected individuals, particularly zinc and iron status. Further studies should investigate the relationship between trace-element alterations, Nrf2 expression, and oxidative stress using larger sample sizes and longitudinal study designs. Future research should also evaluate whether changes in trace-element status and Nrf2 expression are associated with HIV disease progression, treatment status, and other relevant clinical outcomes.

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Authors' Contributions: TOO conceived and designed the study. TOO, FEE, and OTB contributed to the literature review and data collection. TOO and FEE analyzed the data, while TOO and OTB contributed to

data interpretation. TOO and FEE drafted the manuscript, and TOO, FEE, and OTB revised it and approved the final version.

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Conflicts of Interest: The authors declare no conflicts of interest associated with this study.

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