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Interaction of Occupational Toxic Metal Burden with HIV Status and Increased Cancer Risk

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Authors' contributions

This work was carried out in collaboration among all authors. Authors UDC, BAS, AGO, AOG and AJI, designed the study. Authors UDC, UZC, AKS and AGO recruited the participants and collected the data. Authors UDC, BAS, UZC, AKS, AOG and AJI conducted laboratory analysis. Authors OM and UDC analysed the data. Authors AJI, AOG, UDC, BAS, AGO and OM interpreted the data. Authors AJI, AOG, UDC, BAS and AGO drafted the report. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This study aimed to investigate the effects of HIV infection and occupational exposure on the concentrations of selected toxic metals and essential trace elements such as zinc in relation to the carcinogenic process.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Participants were recruited from two local government areas (Calabar municipal and Calabar south) and one secondary health facility in Calabar, Nigeria from April 2017 to February 2018.

Methodology: Study participants comprising 248 adults (191 males, 57 females, aged 18-65 years) were divided into four groups based on HIV status and occupational exposure to toxic metals: HIV-positive exposed (HPE; n=62), HIV-positive unexposed (HPU; n=66), HIV-negative exposed (HNE; n=60), and HIV-negative unexposed (HNU; n=60). The HIV-positive and HIV-negative groups had similar occupations, ages, and other characteristics. Blood cadmium (Cd), lead (Pb), mercury (Hg) and selenium (Se) were measured by inductively coupled plasma optical emission spectrometry (ICP-OES), while serum zinc (Zn) and copper (Cu) were determined using atomic absorption spectrometry.

Results: Lead, cadmium, and mercury were significantly elevated in HPE (14.92 ± 0.54 µg/dl, 0.25 ± 0.01 µg/L, 1.93 ± 0.08 µg/L respectively) compared with the HNU (11.07 ± 0.48 µg/dl, 0.17 ± 0.01 µg/L, 0.76 ± 0.05 µg/L), $p<0.01$, respectively. Zinc, a well-known antioxidant, p53 activator, and cell cycle regulator, was significantly lower in the HPE than in HPU, HNE, and HNU ($p=0.02$, $p<0.01$, $p<0.01$ respectively). Toxic metal exposure and HIV-positive status were associated with increased Pb and Hg levels as well as decreased Zn, suggesting additive effects.

Conclusion: Occupationally exposed HIV-positive individuals exhibited a higher toxic metal burden and a lower zinc level, both of which are important determinants of genome instability and may exacerbate DNA damage as well as impair DNA repair, raising cancer risk. Further studies with a larger sample size may fully elucidate the mechanisms underlying the interaction between HIV infection and occupational toxic metal exposure.

Keywords: Human immunodeficiency virus; occupational exposure; toxic metal; cancer risk.

1. INTRODUCTION

Over 14 million new cancer cases and 8.2 million cancer deaths are estimated to occur globally each year, with low- and middle-income countries accounting for 57% of new cancer cases and 66% of cancer deaths [1]. Infectious agents are major contributors to the global cancer burden, with an estimated 2.2 million infection-attributable cancer cases reported worldwide in 2018 [2]. Infectious agents such as Helicobacter pylori, hepatitis B virus (HBV), hepatitis C virus (HCV), human herpesvirus type 8 (HHV8), human immunodeficiency virus (HIV), and human papillomavirus (HPV) are considered potentially modifiable risk factors of cancer [3]. According to Odutola *et al.* [4], infections play a significant role in the etiology of a wide variety of malignancies in the Nigerian population, with 22% of incident cancer cases related to infectious agents. Indeed, 23.2% of cancer cases reported in Nigeria in the Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) 2018 database were caused by infections [2].

Occupational exposure to toxic metals occurs as a result of their use in a variety of industrial processes, including grinding, painting, soldering, welding, and working near engines, colour pigments, alloys, coal combustion, resuspended dust, vehicle emissions, construction dust, and industrial emissions [5,6]. Toxic metals are considered occupational pollutants because metal mixtures containing lead, cadmium, mercury, and other hazardous metals are present in the workplace and can exert adverse effects on biochemical and physiological processes with attendant health problem, key among which is cancer [7–9]. Current malignancies can be attributed to occupational exposures in the past, and a considerable proportion of future cancers could be attributed to occupational exposures if historical trends and current exposure patterns persist [10]. Toxic metals have been shown to have genotoxic and carcinogenic potential via a variety of mechanisms. Epigenetic modifications, activation of hypoxia signalling pathways, and the production of reactive oxygen species, resulting in oxidative damage are widely recognized as the

major mechanisms underlying metal-induced toxicity, including carcinogenesis [11].

Each year, workers are occupationally exposed to a mixture of chemicals, some of which may be carcinogenic, but the ingredients are kept as a trade secret [12]. The impact of environmental and occupational exposures to toxic metals has not been adequately investigated as contributors to the rising cancer incidence among the HIV population in small and medium-sized industries [13]. Previous studies have either focused on occupationally exposed workers or on HIV-infected patients as their subjects of investigation, providing evidence that HIV-infection or occupational toxic metal exposure independently increases the risk of cancer through a variety of mechanisms. However, the possible synergistic effects of these factors on cancer risk have received little attention. This study was, therefore, designed to examine the joint effects of occupational toxic metals and HIV infection on the carcinogenic process, while taking into account demographic and lifestyles factors.

2. MATERIALS AND METHODS

2.1 Study Participants

The study population comprised one hundred and twenty-eight HIV positive and one hundred and twenty HIV negative Nigerian adults (191 men, 57 women, mean age of 38.35 ± 0.72 years), who were age and sex matched and had similar environmental and occupational characteristics. They were all adjudged to be clinically healthy following the administration of a medical and social questionnaire. Participants for this study was recruited in Calabar, Cross River state, Nigeria.

In this comparative cross-sectional study, participants were selected using a convenience sampling strategy. Participants who reported regular use of a supplement at the time of the study or in the preceding month were excluded. Exposure characterization in the study was based on HIV test results and the occupations of study participants. Interviews were conducted using a structured questionnaire to elicit relevant information, including occupational exposure data. Hence, the occupational exposed group of the study population were all drawn from various occupations associated with toxic metal exposure, such as cement factory workers, electricians, bars & night-clubs workers, auto-mechanics, painters & printing press workers, weed sprayers and pesticide workers, welders, and petrol station dispensers. Additionally, the unexposed group of the study population consisted of occupational groups considered low risk for toxic metal exposure, such as teachers, students, and admin staff in both the private and public sectors (data entry clerks, customer service clerks, receptionists). Thus, the total study population (N = 248) was stratified into 4 primary subgroups based on HIV status and occupational exposure to toxic metals (Fig. 1).

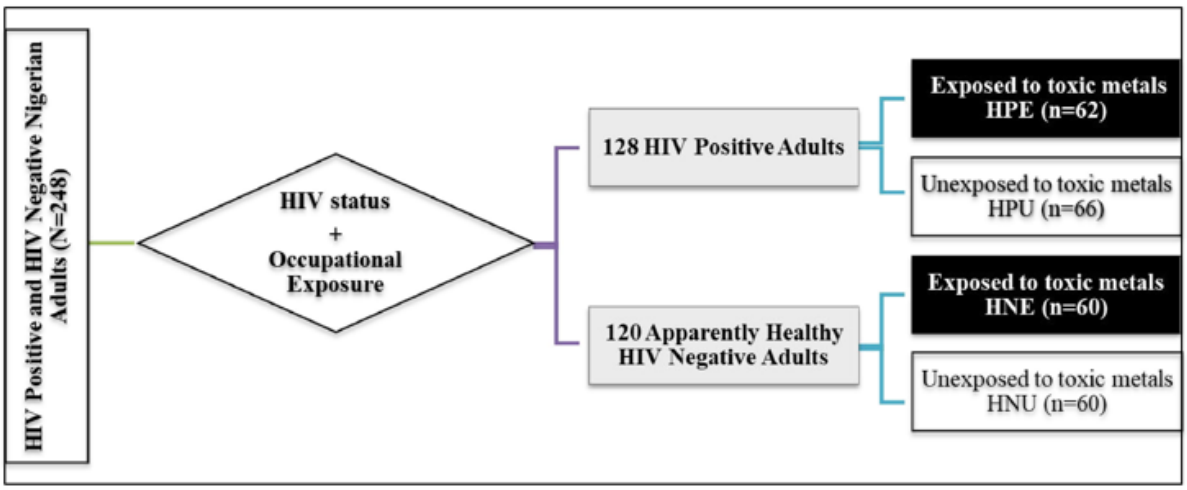

Fig. 1. Schematic of subgroups in the study population
HPE: HIV Positive Exposed; HPU: HIV Positive Unexposed; HNE: HIV Negative Exposed; HNU: HIV Negative Unexposed

2.2 Elemental Analysis of Metals in Blood Sample Using ICP-OES

Blood cadmium (Cd), lead (Pb), mercury (Hg) and selenium (Se) concentrations were determined by inductively coupled plasma optical emission spectrometry (ICP-OES) using the PerkinElmer Optima 3300 DV ICP-OES instrument (Manufacturer: Perkin Elmer; Model: Optima), based on the method by Jones [14]. This method directly measures Pb, Cd, Hg and Se content of whole blood specimens after a simple dilution sample preparation step.

Prior to sample analysis, interference corrections were established, and an initial demonstration of instrument performance was documented. Additionally, the plasma was given 30 to 60 minutes to equilibrate. The plasma power and nebulizer flow were optimised. During optimization, a standard solution containing known amounts of various metals was pumped through the torch. Adjusting the plasma power between 1300 and 1400 W while observing the element's signal strength in the continuous graphics window constitutes optimization. The wattage that produces the best signal was determined and utilised during analysis. In addition, the nebulizer flow was incrementally varied between 0.90 and 0.60 L/min for radial and axial plasmas, respectively, and the optimal flow was determined and applied to the analyses.

It is generally accepted that use of serum in measurements, which is usually produce after coagulation process usually leads to nonuniform distribution of materials especially those that are more located inside the red cells such as Pb. For this reason, EDTA tubes were collected using the phlebotomy protocols outlined in our laboratory manual. After whole blood collection and proper vertexing, a fraction of the original volume was diluted and mixed properly to ensure a uniform distribution of cellular materials that would accurately reflect the average metal concentration of all fractions of the larger specimen. Before analysis, dilution of blood was performed by adding 1 part sample + 50 parts diluent consisting of a solution of 1% HNO3 and 0.01% Triton® X-100.

Blood samples were introduced into the ICP-OES instrument as a liquid sample stream and forced through an argon-gas nebulizer, which converts the bulk liquid into an aerosol of small droplets. A flowing argon stream selectively passes the smaller droplets in the aerosol through the spray chamber into the 6000-8000K plasma of the ICP, where they are dried, vaporised, atomized, excited, and/or ionised by the plasma. The high energy of the plasma results in the excitation and/or ionization of the atoms of lead, cadmium, mercury, and selenium. When excited atoms and ions return to their ground states, photons of a specific wavelength are emitted, which are collected by a device that sorts the emission by wavelength. The emitted energy is detected and converted into electronic signals, which are then converted into concentration data.

2.3 Zinc and Roles in Biologic Processes

Many Zn-dependent enzymes and proteins make Zn an important micronutrient for many adaptive functions or physiological processes, such as DNA repair, cell cycle regulation, antioxidant defense systems, adaptive and acquired immune functions associated with cancer prevention. Due to the known involvement of Zn in many biologic processes, we studied Zn levels in HIV positive and HIV negative individuals who were occupationally exposed and unexposed to understand the role of either lower or higher levels in the complex interactions of toxic metals and HIV infection in promoting cancer disease risk. Zn levels in each group were measured and compared.

2.4 Determination of Serum Zn and Cu Levels

Serum zinc (Zn) and copper (Cu) concentrations were determined using the methods of Smith *et al.* [15] and Osheim [16] with a 210/211 VGP atomic absorption spectrophotometer (Buck Scientific, USA) at 213.9 nm and 324.7 nm, respectively. The AAS is a sensitive and accurate technique for measuring trace metal concentrations in biological samples. Quality control checks were performed to ensure that the results were accurate and precise. This entailed repeating analyses with certified reference materials. Furthermore, the AAS instrument was regularly maintained and calibrated using standard solutions, in accordance with the manufacturer's instructions for instrument operation.

2.5 Statistical Analysis

The Statistical Package for Social Scientists (SPSS) version 25.0 software was used to conduct statistical analyses, including descriptive statistics (SPSS Inc., USA). All values were expressed as the mean standard error of the

mean. Levels of toxic metals and trace elements in the 4 subgroups of the study population were compared using ANOVA. The Scheffe or Games-Howell significant difference post hoc test was used to determine the differences when the null hypothesis of ANOVA was rejected. The Chisquare test and Fisher's exact test were used for qualitative variables. Pearson correlations were used to establish the correlation between the different parameters. Two-way ANOVA was used to examine associations between markers of cancer risk (outcome variables) and the independent variables, HIV status and toxic metal exposure. A significance level of <0.05 was considered statistically significant.

3. RESULTS

The proportions of consenting HIV positive and HIV negative individuals were comparable when grouped by occupations that predispose workers to toxic metal exposure and those that do not (Table 1). Duration spent on occupations associated with toxic metal exposure in the HPE (9.94 ± 1.14 years) was comparable to that of the HNE (9.73 ± 1.06 years), p = 0.90. Descriptive statistics of primary outcome measures studied in relation to the two independent variables, HIV status and Occupational exposure is represented in Table 2.

Table 1. Occupations of study participants categorized into exposed and unexposed groups

Occupations	HIV Positive	HIV Negative	X^2	*P*-value
Occupationally Exposed			[a]8.94	.25
Cement factory worker	2(3.2%)	1(1.7%)		
Electrician	5(8.1%)	6(10%)		
Bars & Night club worker	14(22.6%)	6(10%)		
Mechanic	14(22.6%)	19(31.7%)		
Painter & Printing press worker	6(9.7%)	3(5%)		
Weed sprayer &Pesticides worker	7(11.3%)	3(5%)		
Welder	7(11.3%)	13(21.7%)		
Petrol Station Dispenser	7(11.3%)	9(15%)		
Total	**62(100%)**	**60(100%)**		
Occupationally Unexposed			0.14	.99
Admin Staff (Private sector)	23(34.8%)	21(35%)		
Civil Servants (Admin Public Sector)	16(24.2%)	13(21.7%)		
Teachers & Students	7(10.6%)	7(11.7%)		
Unemployed & unexposed	20(30.3%)	19(31.7%)		
Total	**66(100%)**	**60(100%)**		

[a]Fisher's Exact Test
$\chi 2$ = Chisquare

Table 2. Descriptive statistics of primary outcome measures studied in relation to the two independent variables, HIV status and occupational exposure

Dependent Variable	Independent Variable		Mean	Std. Error	95% Confidence Interval	
	HIV Status	Occupational Exposure			Lower Bound	Upper Bound
[Pb] µg/dl	Positive	Exposed	14.92	0.54	13.83	16.01
		Not Exposed	13.66	0.43	12.80	14.53
	Negative	Exposed	13.10	0.44	12.21	13.98
		Not Exposed	11.07	0.48	10.11	12.02
[Cd] µg/L	Positive	Exposed	0.25	0.01	0.23	0.28
		Not Exposed	0.34	0.01	0.32	0.36
	Negative	Exposed	0.18	0.01	0.16	0.19
		Not Exposed	0.17	0.01	0.15	0.19
[Hg] µg/L	Positive	Exposed	1.93	0.08	1.76	2.10
		Not Exposed	0.88	0.05	0.78	0.97
	Negative	Exposed	0.67	0.05	0.57	0.76
		Not Exposed	0.76	0.05	0.67	0.86

Table 2. Continued

Dependent Variable	Independent Variable		Mean	Std. Error	95% Confidence Interval	
	HIV Status	Occupational Exposure			Lower Bound	Upper Bound
[Se] µg/L	Positive	Exposed	73.72	1.74	70.24	77.19
		Not Exposed	60.26	2.63	55.01	65.51
	Negative	Exposed	79.97	4.73	70.49	89.44
		Not Exposed	84.94	4.74	75.45	94.42
[Cu] µg/dl	Positive	Exposed	127.76	6.57	114.63	140.89
		Not Exposed	124.06	6.15	111.78	136.34
	Negative	Exposed	118.66	7.82	103.00	134.31
		Not Exposed	115.88	4.92	106.02	125.73
[Zn] µg/dl	Positive	Exposed	96.75	2.25	92.26	101.25
		Not Exposed	108.12	3.00	102.13	114.10
	Negative	Exposed	120.80	4.84	111.10	130.48
		Not Exposed	125.18	5.12	114.93	135.43
Cu/Zn ratio	Positive	Exposed	1.35	0.08	1.20	1.50
		Not Exposed	1.17	0.05	1.06	1.28
	Negative	Exposed	1.02	0.08	0.86	1.19
		Not Exposed	0.92	0.05	0.83	1.02

Pb = Lead; Cd = Cadmium; Hg = Mercury; Se = Selenium; Zn = Zinc; Cu = Copper

Blood Pb, Cd, and Hg concentrations were significantly higher in occupationally exposed HIV positive individuals than in HIV negative unexposed individuals ($p < 0.001$) (Fig. 2). While the occupationally exposed HIV positive individuals had higher blood Pb levels than HIV positive individuals who were occupationally unexposed and HIV negative exposed individuals, the difference was not significant ($p = 0.31$ and $p = 0.07$ respectively). Interestingly, blood Cd and Hg levels were significantly higher in occupationally exposed HIV positive individuals than in HIV negative exposed individuals ($p < 0.001$) (Fig.e 2). In addition, the occupationally exposed HIV positive individuals had higher blood Hg levels than HIV positive individuals who were occupationally unexposed ($p < 0.001$) (Fig. 2). Zinc level was significantly lower in the HIV positive exposed individuals when compared with the other three groups (HPU, HNE, HNU) ($p = 0.02$, $p < 0.001$, $p < 0.001$ respectively) (Fig. 2). In contrast, serum Cu levels were higher in HIV positive exposed individuals than in the other three groups (HPU, HNE, and HNU), but the difference was not statistically significant ($p > 0.05$). There was also a significant positive correlation between serum Zn and Cu levels ($r = 0.27$, $p < 0.001$).

The effects of occupational exposure and HIV infection on selected toxic metals and trace elements were studied using a two-way ANOVA model. While occupational exposure and HIV infection increased blood Pb level in an additive and independent manner ($p < 0.001$) (Fig. 3A) both factors act interactively to elicit changes on Cd level ($p < 0.001$) (Fig. 3B). HIV infection independently increased blood Cd levels in both the occupationally exposed and unexposed study groups ($p < 0.001$). Interestingly, HIV infection and occupational exposure increased blood Hg levels synergistically ($p < 0.001$) (Fig. 3C).

HIV infection had an independent influence on selenium levels ($p < 0.001$), but it also interacted with Occupational toxic metal exposure to cause alterations in selenium levels ($p = 0.01$) (Fig. 3D). Furthermore, both occupational exposure and HIV infection decreased serum Zn levels independently, and the effects were additive (Fig. 3E). On the other hand, both factors tended to raise serum Cu levels independently, but the effects were not significant ($p = 0.62$ and $p = 0.18$, respectively) (Fig. 3F).

4. DISCUSSION

There are indications that infection with HIV and occupational toxic metal exposure might predispose to cancer risk. An increased risk of cancer was found in HIV-positive people who were exposed to toxic metals at work. Indeed, this study highlighted the combined effects of occupational chemical exposure and HIV infection on cancer biomarkers, with

some of these effects being additive or interactive in relation to the carcinogenic process. The current study demonstrates that HIV infection exacerbates pre-existing cancer risks associated with occupational exposures and vice versa.

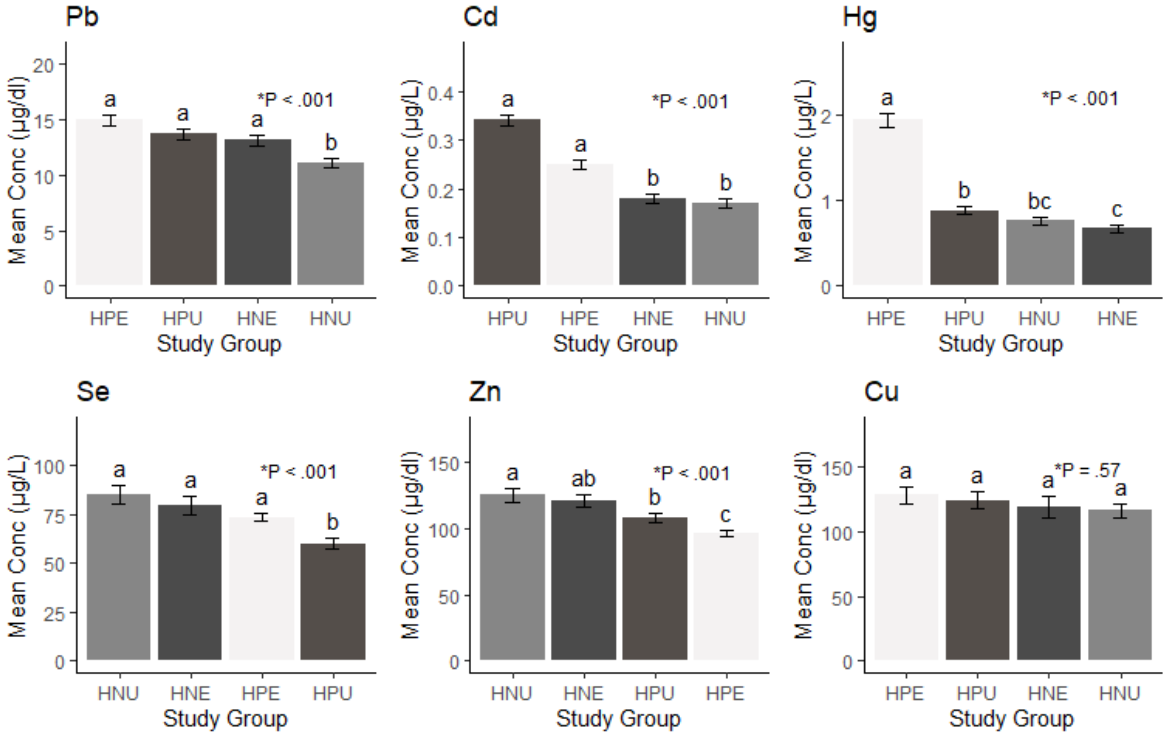

Fig. 2 Selected toxic metals and essential trace elements in occupationally exposed and unexposed groups of HIV positive and negative participants

** Overall p-value across the study group*

Pb = Lead; Cd = Cadmium; Hg = Mercury;

Se = Selenium; Zn = Zinc; Cu = Copper

➲*Mean levels of toxic metals (Pb, Cd, Hg) and trace elements (Se, Zn, Cu) in HIV positives exposed occupationally to toxic metals (HPE, n=62), HIV positives unexposed occupationally to toxic metals (HPU, n=66), HIV negatives exposed occupationally to toxic metals (HNE, n=60), and HIV negatives unexposed occupationally to toxic metals (HNU, n=60)*

➲*Mean values with no superscript in common differ significantly (p < 0.05). The error bars show the standard error of the mean; values are mean ± Standard Error*

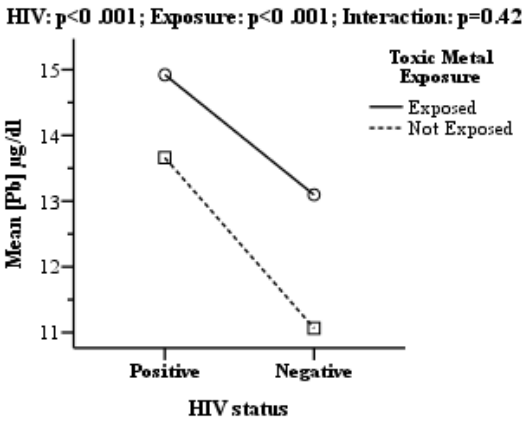

Fig. 3A. Effect of independent factors on Pb

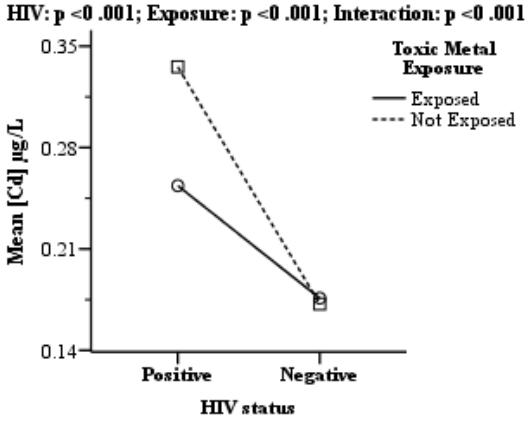

Fig. 3B. Effect of independent factors on Cd

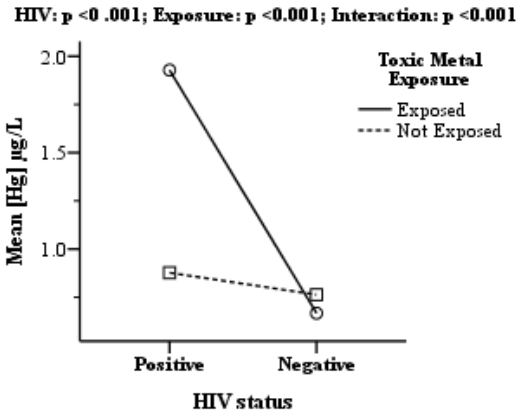

Fig. 3C. Effect of independent factors on Hg

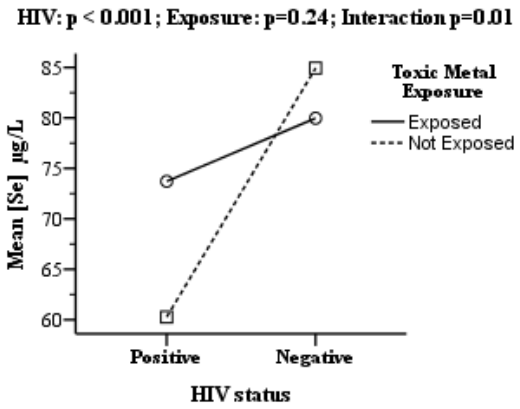

Fig. 3D. Effect of independent factors on Se

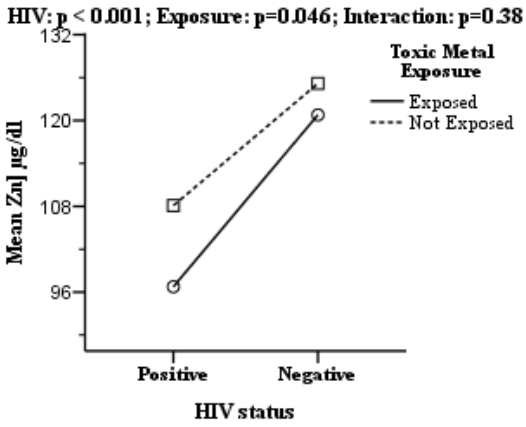

Fig. 3E. Effect of independent factors on Zn

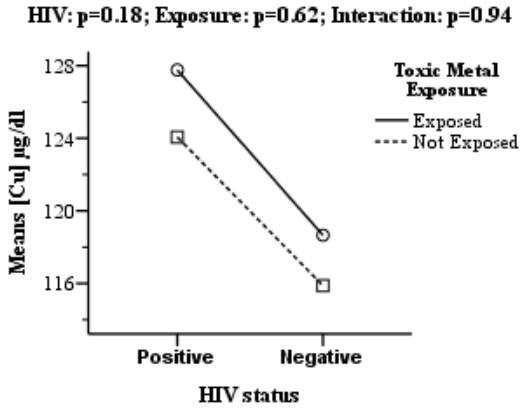

Fig. 3F. Effect of independent factors on Cu

Fig. 3. Effects of HIV status & occupational exposure on toxic metal and essential trace elements levels

Toxic Metals and Essential Trace Elements: (A) Blood Lead level [Pb]; (B) Blood Cadmium level [Cd]; (C) Mercury [Hg]. (D) Selenium [Se]; (E) Zinc [Zn]; Copper [Cu]

Independent Factors: HIV = HIV Status; Exposure = Occupational exposure to toxic metals.

A significant effect(s) of the two factors at $p < 0.05$

Mean concentrations of toxic metals and essential trace elements in the occupationally exposed groups (circles) stratified by HIV status were compared with the occupationally unexposed groups (squares) stratified by HIV status. The effects of occupational toxic metal exposure and HIV infection were considered additive and independent of each other in a two-way ANOVA model if the main effects were significant ($p < 0.05$) and the interaction was not significant ($p > 0.05$). The effects of occupational toxic metal exposure and HIV infection, on the other hand, were considered interactive (i.e., the factors interact to create a synergistic effect) if the interaction effect is significant ($p < 0.05$), regardless of the p-values of the main effects. Visually (based on the profile plots), no intersection of the lines connecting the occupationally exposed and occupationally unexposed groups indicates that the effects of each factor on toxic metal and essential trace element levels were additive and independent of each other if $p < 0.05$ for the main effects, whereas intersection of the lines indicates that factors interacted (Figs. 3A-F). Synergism occurs when two factors interact to influence a biological response rather than acting independently

It is apparent from the results that the combination of toxic metal exposure and HIV infection considerably lead to higher blood Pb, Cd, Hg, and decreased Zn levels, which together suggest a trend towards increased risk of cancer and other health related conditions associated with repression of antioxidant function. The significantly elevated Pb, Cd, and Hg blood

levels observed in the occupationally exposed HIV positive individuals are consistent with previous reports by Xu *et al.* [17], Emokpae & Mbonu [18], and Folorunso *et al.* [19]. These studies, however, examined a single cancer risk factor in isolation, rather than in combination with other risk factors. To our knowledge, no previous studies have evaluated toxic metal and essential trace element levels in HIV-positive individuals who are occupationally exposed, as the majority of research has focused on occupationally exposed workers or HIV-infected patients.

The effect of occupational exposure and HIV infection on blood mercury level was assessed. Blood Hg level was significantly higher in the occupationally exposed HIV positive group compared with the occupationally unexposed HIV positive, and the occupationally exposed and unexposed HIV negative groups, which is a finding that aligns with past studies [17,18,20–22]. The occupationally exposed HIV positive individuals are likely to have been further exposed to mercury through their diet, with fish being a major source of methyl mercury exposure, but this was not assessed. In a synoptic review, Eisler [23] reported that mercury levels in the hair, urine, blood, and other tissues of occupationally exposed gold miners exceeded all safety thresholds recommended by many national and international regulatory authorities responsible for human health protection. Previous studies have linked mercury to the development of cancer [24,25]. The genotoxic effect of mercury could be elicited by either the production of oxygen free radicals, damage to microtubules and DNA repair mechanisms, or direct damage to DNA.

Furthermore, our findings indicate that occupational chemical exposure and HIV infection exhibited positive cooperativity, resulting in elevated blood levels of Cd and Hg, which may disrupt cell cycle regulation and control mechanisms and thus pose a significant cancer risk to humans. Wei *et al.* [26] and Kolluru *et al.* [27] earlier demonstrated that Cd promotes carcinogenesis via aberrant cell cycle regulation, whereas Marima *et al.* [28] reported that the components of highly active antiretroviral therapy (HAART) [efavirenz (EFV) and lopinavir/ritonavir (LPV/r)] alter cell cycle progression, with a significant S-phase arrest, indicating cellular stress, cytotoxicity, and DNA damage within the cell. The International Agency for Cancer Research (IARC) has established a strong link between cadmium exposure and cancer risk, concluding that occupational Cd exposure increases cancer risk [29]. However, this author did not evaluate the effect of concomitant infection with HIV and exposure to toxic metals. Based on our investigation, it is suggested that simultaneous occupational exposure to Cd, Hg, and Pb, along with HIV infection, may potentially interact to suppress the levels of Zn. Therefore, occupational exposure to toxic metals in HIV positive individuals may worsen decreased Zn levels and dysregulation of the anti-oxidative pathway.

The precise molecular mechanism by which HIV infection may exert a positive cooperativity effect in the presence of elevated Cd and Hg levels, thereby promoting a synergy for increased cancer risk, is not fully understood. Rezapour *et al.* [30] clearly showed that cadmium levels in nasopharyngeal cancer patients were significantly higher than in controls and concluded that exposure to cadmium was likely to cause nasopharyngeal and pharyngeal cancer. In contrast to that report, we did not determine organ specific cancer risks, however the molecular biology that underpin their finding was not clearly understood. To investigate a possible mechanism for cancer risk in HIV-infected patients who are also exposed to toxic metals, we hypothesized that toxic metal exposure, especially Cd, might promote cancer risk by increasing the sensitivity of cells to the effects of certain HIV-associated viral proteins that repress the ability of cells to repair oxidative DNA damage via a zinc dependent pathway.

Conversely, HIV-associated viral proteins may increase the vulnerability of cells to oxidative DNA damage, exacerbating the pre-existing risk of developing cancer in occupationally exposed individuals via a zinc dependent mechanism. This is consistent with the observation that HIV-1 proteins, particularly the envelope glycoprotein gp120 and the HIV-1 trans-acting protein Tat, generate reactive oxygen species (ROS) and cause oxidative stress, as well as deplete the protective antioxidant enzymes copper/zinc superoxide dismutase (SOD) [31]. Zinc-binding proteins, like those found in DNA repair proteins like XPA and poly (ADP-ribose) polymerase 1 (PARP-1), as well as the tumor suppressor protein p53, appear to be the most vulnerable to oxidative attack [32]. We therefore suggest that the significantly lower Zn levels found in occupationally exposed HIV-positive individuals may reflect the consequence of susceptibility to

reactive oxygen species and depleted copper/zinc superoxide dismutase (Cu++/Zn++ SOD) activity, allowing for increased oxidative DNA damage, thereby causing genomic instability and cancer risk.

The observed decrease in zinc, potentially resulting from the combined impact of HIV infection and exposure to toxic metals, can be partially attributed to the metabolic antagonism between zinc and cadmium. Anetor [33] reported that a high Cd/Zn ratio causes a high error rate and defective DNA repair processes, which increases the risk of cancer. Additionally, our results are in line with prior studies [34,35]. Osuna-Padilla *et al.* [36] reported a high prevalence of suboptimal serum zinc levels in a cohort of antiretroviral-experienced HIV-infected individuals. Decreased zinc level has been linked to elevated levels of multiple inflammatory cytokines [37,38], a possible predictor of an increased cancer risk. Our result suggests that chronic Zn insufficiency combined with occupational toxic metal exposure may predispose HIV-infected people to even greater risk of cancer via oxidative stress. Thus, highlighting the need for health promotion interventions among HIV positive workers in order to minimize probable workplace exposure to toxic metals and the associated risks of cancer in HIV positive populations.

5. CONCLUSION

Our study revealed that the combination of occupational toxic metal exposure and HIV infection considerably increased the risk of cancer over and above the risk associated with either factor alone. While the two explanatory variables, HIV-infection and toxic metal exposure, together raise Pb, Cd, and Hg levels, they simultaneously lower the protective micronutrient Zn. Increased levels of toxic metals in the body, as well as micronutrient imbalances, may result in oxidative stress, DNA damage, impaired DNA repair mechanisms, and altered angiogenesis, among other consequences. These pathophysiological effects may combine to pose a significant cancer risk in occupationally exposed HIV-infected individuals. However, further studies are required to better understand the mechanisms underlying the interaction of HIV infection and occupational toxic metal exposure, as well as to develop effective strategies for reducing cancer risk in people with these risk factors.

ETHICAL APPROVAL AND CONSENT

This study involves human participants and was approved by the University of Ibadan/University College Hospital Health Research Ethics Committees (UI/EC/0226). Before taking part in the study, participants provided informed consent. All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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