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Micronutrients, metabolic complications and inflammation in Ugandan children with HIV

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Abstract

Selenium, zinc and chromium are essential micronutrients. Their alterations have been associated with HIV disease progression, metabolic complications and mortality.

This is a cross-sectional study in children with perinatally acquired HIV (PHIV, n=57), HIV exposed uninfected (HEU, n=59) and HIV unexposed uninfected (HIV-, n=56) children aged 2-10 years old, age and sex matched, enrolled in Uganda. PHIV were on stable antiretroviral therapy (ART) with undetectable viral load. We measured plasma concentrations of selenium, zinc and chromium as well as markers of systemic inflammation, monocyte activation, and gut integrity.

Among PHIV children, 93% had viral load ≤ 20 copies/mL, median CD4 was 37% and 77% were receiving a non-nucleotide reserve transcriptase regimen. Median age of all participants was 8 years and 55% were girls. Median selenium concentrations were higher in PHIV compared to the HEU and HIV- groups ($p < 0.001$), 46% of children overall had low zinc status ($p=0.18$ between groups). Higher selenium, but not chromium or zinc, was associated with lower IL6, sTNFRI and II and higher beta d glucan, a marker of fungal translocation, zonulin, a marker of gut permeability, oxidized LDL and insulin resistance ($p \leq 0.01$).

In this cohort of PHIV on ART in Uganda, there is a high prevalence of low zinc status overall. Higher plasma selenium concentrations were associated with lower systemic inflammation and higher gut integrity markers. Although our findings do not support the use of micronutrient supplementation broadly for PHIV in Uganda, further studies are warranted to assess the role of selenium supplements in attenuating heightened inflammation.

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Author Contributions:

SDF and GAM designed the research. RN, CK and VM conducted the research. LS and AS performed statistical analysis. MK, EB and NF performed the biomarker assays. SDF wrote the first draft of the manuscript. SDF and GAM had primary responsibility for final content. All authors read and approved the final manuscript.

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Keywords

micronutrients; Children with HIV; HIV-exposed uninfected infants; gut integrity; inflammation; translocation

INTRODUCTION

Nutrient deficiencies are associated with immune dysfunction and rapid disease progression in HIV(1, 2). Micronutrients are important and may have a role in HIV infection and its associated morbidities. Several cross-sectional studies have reported a significant association between low selenium levels and HIV-infection(3–6). Chromium is a nutrient that promotes the action of insulin for the use of sugars and fats, its deficiency has been reported to cause insulin resistance, hyperglycemia and hyperlipidemia(7). There are conflicting results in adults with HIV (ALHIV) as to whether chromium supplementation improves insulin resistance(8, 9). Zinc is another essential micronutrient that has been linked with HIV disease progression, independent of baseline CD4 cell count and age- and calorie-adjusted dietary intake(10).

Although HIV has transitioned to a chronic manageable disease, a number of inflammation-associated complications specifically cardiovascular and metabolic diseases are increasing. This is especially concerning for children with perinatally acquired HIV (PHIV) who face a lifetime exposure to HIV and antiretroviral therapy (ART) and are at risk of cardiometabolic complications as they age. Understanding why inflammation persists in HIV despite viral suppression and how it causes non-AIDS comorbidities, particularly in resource-limited settings, is paramount to mitigating complications associated with premature aging in HIV. Specifically, the relationship between essential micronutrients, inflammation and metabolic complications warrants further investigation in PHIVs.

Due to the success of prevention of maternal to child transmission, new HIV infections among infants have decreased significantly, while the number of HIV-exposed uninfected infants (HEU) has steadily increased(11). Numerous studies have reported adverse health outcomes in HEU children including higher mortality (12). We have previously shown that HEU infants have increased inflammation compared to unexposed infants(13).

In this study, we focused on selenium, chromium and zinc, micronutrients known to be associated with cardiometabolic complications and measured their levels in PHIVs who are virally suppressed on stable ART compared to HIV exposed uninfected (HEU) and unexposed and uninfected children (HIV-) in Uganda. Furthermore, we explored the association of these micronutrients with metabolic complications as well as with markers of inflammation, monocyte activation, and intestinal damage. Although there have been extensive investigations on the role of micronutrient in the pediatric population in lower income settings, our study is unique in that we focused on healthy children not currently admitted to a health facility, without co-infections, other than HIV, who are not viremic and well controlled on ART. In addition, we used well matched control groups both HIV exposed uninfected and HIV unexposed uninfected to further investigate the role of HIV and ART exposure on micronutrients and non-AIDS complications.

Methods

Study Design

This is an observational cohort of PHIV, HEU and HIV unexposed uninfected children prospectively enrolled at the Joint Clinical Research Center (JCRC) in Kampala, Uganda between January 2017 and May 2018. The study was approved by the Research Ethics Committee in Uganda, the Ugandan National Council of Science and Technology as well as the IRB of the University Hospitals Cleveland Medical Center, Cleveland, Ohio. Caregivers gave written informed consent; older children also gave informed assent. All participants were 2-10 years of age. PHIV participants were on stable ART for at least 6 months with HIV-1 RNA < 400 copies/mL. PHIV participants were recruited during routine clinic visits. HIV- participants were either HIV- siblings of the PHIV or recruited from the community using community liaison volunteers from the JCRC. All participants lived in Kampala or peri-urban surroundings. History of acute infections (malaria, tuberculosis, helminthiasis, pneumonia, meningitis) in the last 3 months, moderate or severe malnutrition, and diarrhea in the last 3 months were exclusionary. Known diabetes and cardiovascular diseases were also excluded.

Study Evaluations

Participants were recruited and seen at the outpatient pediatric clinic at the JCRC. Blood was drawn after an 8-hour fast. Element free tubes were used for the measurement of the micronutrients. The samples were used for measurement of glucose, insulin, lipids, micronutrients and soluble markers of monocyte activation, systemic inflammation and gut integrity. Insulin was measured by ELISA sandwich immunoassay (ALPCO, Salem, New Hampshire, USA) and the derived homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as described(14). Plasma levels of zinc, trivalent chromium and selenium levels were measured using Coupled Plasma/Mass Spectrometry (ICP-MS) at the Cleveland Heart Lab (Cleveland, OH). These specific micronutrients were selected because of their known associations with metabolic and cardiovascular disease risk in the general population(15–18). The reference ranges for zinc are 55-150 μg/dL, for chromium <5μg/L and for selenium 23-190 μg/L (ARUP Laboratories, SLC, UT).

The primary parent or caregiver were given a 12-item questionnaire that incorporated the WHO STEPS instrument (19), which is a standardized but flexible framework for countries to monitor the main non communicable diseases (NCD), and the Demographic and Health Surveys Wealth Index from USAID(20), which assesses a household's cumulative living standard including food, water and sanitation facilities access. The questionnaire measured overall food insecurity over the past 3 months. A binary variable was created to capture food insecurity (defined as frequency of hunger) compared to no food insecurity (ie: being hungry seldom or never).

Inflammation, monocyte activation and gut integrity markers

Plasma markers of monocyte activation (sCD163 and sCD14), systemic inflammation [soluble TNFα receptor I and II (sTNFRI and II), high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6)], coagulation (d-dimer), and oxidized lipids (oxidized LDL)

were measured by ELISA (R &D Systems, Minneapolis, Minnesota, USA and ALPCO, Salem, New Hampshire, USA and Mercodia, Uppsala, Sweden). The marker of fungal translocation Beta D Glucan (BDG, Mybiosource Inc. CA), lipopolysaccharide-binding protein (LBP, Hycult Biotech Inc. PA), an indirect marker of microbial translocation; zonulin (Promocell Germany), a marker of intestinal permeability and intestinal fatty acid binding protein (I-FABP, R &D Systems, Minneapolis, Minnesota, USA), a marker of intestinal integrity were measured by ELISA. The intra-assay variability ranged between 4-8% and inter-assay variability was less than 10% for all markers. All assays were performed on batched samples, never previously thawed, at Dr. Funderburg's laboratory at Ohio State University, Columbus, OH. Laboratory personnel were blinded to group assignments and clinical characteristics.11

Statistical Analyses

The primary objective of this analysis was to compare micronutrient levels between PHIV, HEU and HIV- children. The secondary objectives were to determine the association between micronutrients and inflammatory biomarkers, as well as metabolic parameters specifically body mass index (BMI), waist hip ratio, lipids and HOMA.

We hypothesized that PHIV children would have lower micronutrient levels. Second, we hypothesized that in PHIV, low micronutrient levels would be associated with higher levels of inflammation, altered intestinal integrity and metabolic complications.

We performed descriptive analyses on all of the covariates (including age, sex, race, nadir and current CD4, ART duration and type) and on the micronutrients. Kruskal-Wallis tests were used to compare continuous variables and Fisher's exact test for categorical variables, by HIV exposure/status. Spearman correlation was used to assess correlations with micronutrients and each biomarker as well as metabolic parameters combined as well as by groups. Micronutrients were analyzed as continuous variables and dichotomous variables (deficiency versus not deficient). Statistical significance was defined as $p \leq 0.05$. Regression analyses were used to determine the association between Selenium and HOMA-IR after adjusting for BMI.

All the statistical analyses were performed using Stata 15 and R 3.4.1

Results

Baseline characteristics

Overall, 172 participants were enrolled in this study and included in this analysis: 57 PHIV, 59 HEU and 56 HIV- children. Detailed patient and maternal characteristics have been previously described(21). Median [Q1, Q3] age was 7.8 years [6.39, 8.84], 55% of participants were female, median BMI was 15.2 kg/m^2 [14.38, 15.81] and 24% had food insecurity. There was no difference between baseline demographic characteristics between the groups. As shown in Table 1, HDL cholesterol, triglycerides, HOMA-IR and waist hip ratio were higher in PHIVs (<0.02).

Among PHIV, median CD4 cell count % was 37% [27, 41], viral load was 20 copies/mL. Median ART duration was 6 years [5,6], 23% were on a protease-inhibitor based regimen (lopinavir/ritonavir) and the remainder on a non-nucleotide reverse transcriptase inhibitor regimen (28% on efavirenz and 51% on nevirapine).

Micronutrient levels

As shown in Table 1, median selenium concentrations were higher in the PHIV group compared to the HEU and HIV- groups ($p < 0.001$). In addition, selenium deficiency, as defined by plasma concentrations <85 μg/L, was most prevalent in the HEU group and lowest in the PHIV group (Figure 1).

Median zinc levels were not different between the arms ($p=0.18$). In the PHIV group, 51% had zinc deficiency, as defined by plasma concentrations <75 μg/dL (Figure 1).

Median chromium concentrations were <1 μg/L; 1 PHIV child and 6 HEU children had chromium levels > 1 μg/L, ranging between 1.1-1.7 μg/L ($p<0.01$ between groups).

Micronutrients and metabolic complications

Univariable analyses were performed for each micronutrient, metabolic and anthropometric measures for all participants and then by group. Higher selenium correlated with higher levels of HOMA-IR for all participants combined ($\rho=0.22$, $p<0.01$) and for PHIVs ($\rho=0.25$, $p=0.05$).

In multivariable analyses, selenium still remained associated with HOMA-IR after adjusting for BMI ($\beta=0.007$, $p=<0.01$) for all participants but not for PHIVs ($\beta=0.013$, $p=0.09$).

Selenium, zinc and chromium did not correlate with BMI, waist hip ratio or any lipid fractionation in all participant combined or by groups ($p\geq0.1$).

We did further subgroup analyses for those participants with micronutrient deficiencies and did not find any correlation between micronutrient and metabolic measures for all participants combined or by group ($p\geq0.07$).

Micronutrients and inflammation and intestinal alteration

We performed additional univariate analyses to assess the relationship between micronutrients and biomarkers of inflammation, immune activation, intestinal integrity and microbial translocation. As shown in Figure 2, selenium levels correlated with several markers of inflammation and intestinal permeability for all participants. After excluding statistical outliers, the correlations between selenium and biomarkers remained significant for all ($p\leq0.01$) except sCD163 and D-dimer ($p\geq0.32$). Higher zinc levels correlated with lower zonulin ($\rho=-0.21$, $p<0.01$). Chromium levels did not correlate with any biomarkers (≥0.1).

Discussion

Prevalence of metabolic disorders is on the rise worldwide, and we were interested in exploring whether micronutrients are associated with any metabolic complications or ongoing inflammation and alteration in intestinal integrity in PHIV in Uganda. We observed that there was no association between low micronutrient levels and metabolic complications, however, selenium may play a role in modulating inflammation.

There is compelling evidence that micronutrient deficiencies are associated with HIV disease progression and co-morbidities(9, 22–24) and are common in children in resource limited settings(25). ART does not appear to fully resolve micronutrient deficiencies in ALHIV(26, 27).

Plasma selenium, zinc and chromium in this study were measured as an assessment of the micronutrient status in study participants. Micronutrient plasma concentrations can be affected by many factors including inflammation(28, 29), however plasma micronutrient concentrations is the most widely used method to determine micronutrient status. Other methods to assess micronutrient status also include limitations. The total selenium content of the plasma measures several components including the protein and non protein-bound selenium. The measurement of total plasma selenium captures selenium status because in non-deficient individuals, selenoproteins are maximally expressed and may not reflect selenium status in these individuals(29). Plasma zinc concentrations can also be affected by diurnal variation as well as hypoalbuminemia(30). Urinary zinc concentration could be a valuable indicator of zinc status when measured in relation to urinary creatinine, however this appears to be true only for participants with moderate zinc status at baseline(30). Lastly, chromium levels in most human samples are <1 μg/L similarly to our findings. Other techniques that have the sensitivity to detect levels below this limit of detection include neutron activation analysis and graphite furnace atomic absorption spectrometry which are not readily available(31). In order to minimize contamination, we collected our samples using element free supplies.

We found that PHIV do not have low selenium and chromium status compared to age and sex matched HEU and uninfected children who reside in a similar peri-urban area in Uganda. We found the overall prevalence of low zinc levels was high at 46% with no differences between groups. This is comparable to what has been cited for zinc deficiency in the general population of children in a similar age group in Uganda(32–34). In addition, a cross sectional study comparing zinc deficiency in PHIV in Uganda by ART status suggests that ART does not completely eliminate zinc deficiency (33). The etiologies are likely multifactorial and include food insecurity, availability and lack of food fortification (35, 36). Surprisingly, HEU children had a high prevalence of low selenium concentrations. One hypothesis is this may be secondary to the low levels of breastfeeding or early weaning and replacement with complementary feeding with low selenium content(37). This may affect the child's ability to reach and maintain an adequate selenium status.

Micronutrient deficiencies have been associated with cardiometabolic complications in the general population. Chromium, in the form of naturally occurring dinicotinic acid -

gluthatione complex, is vital for carbohydrate metabolism as it modulates the action of insulin(17). Selenium and selenoproteins play a role in the antioxidant defense system, and subsequent oxidative modification of lipids, preventing platelets from aggregating and reducing cardiovascular disease risk (18). Zinc also plays a critical role in oxidative stress and normal cellular structure and function, and its homeostasis is also associated with cardiovascular diseases and insulin resistance(15, 38). The role of micronutrients in cardiometabolic complications in HIV, however, is less clear. In ALHIV, low chromium is associated with parameters of metabolic syndrome(22) and low selenium with the development of cardiomyopathy(39). We hypothesized that low micronutrient status in PHIV could lead to oxidative stress inducing inflammation and contributing to the development of metabolic complications. We investigated the relationships among micronutrient concentrations and anthropometric measures, insulin resistance, and lipids. Higher selenium level correlated with HOMA in PHIV. We did not find any other correlation between low micronutrient status and metabolic measures. Our findings could be the result of several factors 1)our patient population: in PHIVs, well controlled on ART, micronutrients may not contribute to metabolic complications; 2)our sample size: due to the small number of participants with micronutrient deficiencies, our subgroup analyses to investigate the role of micronutrient deficiencies and metabolic complications are likely not well powered to detect a correlation 3) our study design: the cross sectional design precludes us from inferring causality and further longitudinal studies are warranted to truly investigate the role of micronutrients on the development of metabolic complications as PHIVs are exposed to a lifetime of ART and HIV.

Micronutrients may play a role in reducing mitochondrial dysfunction, oxidative stress, and may have important consequences on the chronic inflammation seen in HIV(40). Our group has found that in ALHIV with viral suppression on ART, selenium is associated with T cell activation(41) and that zinc supplementation, in a pilot study, can modulate biomarkers associated with clinical comorbidities(42). To our knowledge, only one study has assessed the role of micronutrients and inflammation on HIV in resource limited settings. The PEARLS trial is a multi-country trial in ART-naïve ALHIV and findings suggest that micronutrients and inflammations levels are associated with CD4 recovery post ART initiation(2, 17). Our findings extend this knowledge and suggests that selenium may play a role in the ongoing inflammation seen in PHIV despite ART.

Micronutrients are essential components of intestinal health and can affect the composition and function of intestinal microbiota (43, 44). Specifically, the benefits of zinc on the prophylaxis and treatment of diarrhea are well documented (45). Selenoproteins are detected in the intestine and are known to affect the intestinal microbiota(46). As such, we hypothesized that micronutrient deficiencies would be associated with altered intestinal barrier function and microbial translocation. Surprisingly, we found that high selenium status correlated with high BDG, a marker of fungal translocation, and high zonulin, a marker intestinal permeability. BDG is associated with inflammation and immune activation in ALHIV(47). Zonulin is a human protein that regulates intestinal permeability by modulating intercellular tight junctions in the gut and increases permeability and macromolecule absorption(48). Interestingly, high zonulin is associated with lower mortality in ALHIV who were virally suppressed(49). We did not measure zonulin using monoclonal

antibody and caution should be used when interpreting zonulin assays using ELISA commercial assays(50). We hypothesize that the relationship between micronutrient, intestinal health and microbiota may be complex in PHIV in resource limited settings, this may be due to other medications (all PHIVs were on cotrimoxazole which can affect intestinal microbiota), chronic helminthiasis, unsanitary water source or dietary patterns.

Our study has important limitations. First, our findings may not be generalizable as we included PHIV from a peri-urban area of Uganda who are stable on ART and virally suppressed. Second, no direct microbial translocation measures were performed, we cannot confirm whether micronutrients are associated with translocation of bacterial products. Third, we do not have detailed dietary assessments. Nevertheless, our study includes a detailed evaluation of inflammation, monocyte activation and intestinal integrity biomarkers. Additionally, the age and sex matched HEU and HIV- groups from the same peri-urban area in Uganda allows for adequate comparison and significantly adds to the literature.

Conclusion

Plasma selenium and chromium were sufficient in PHIV, however, similarly to prior studies, we found a high prevalence of low plasma zinc levels in all Ugandan children without diarrhea. In addition, our study demonstrates consistent correlations between selenium and inflammation, monocyte activation and intestinal integrity. Counter to our hypothesis, plasma micronutrient levels were not associated with metabolic measures in PHIV. Further longitudinal studies are warranted to consider the role of micronutrients in sustained inflammation in PHIV in resource-limited settings.

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Conflict of Interest

GAM served as a consultant for Gilead, GSK/Viiv, and Merck, and has received research funding from Gilead, Merck, GSK/Viiv, Roche, Astellas, Tetraphase, and BMS. NF serves as a consultant for Gilead. All other authors had no conflict of interest.

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What is known:

- Chronic inflammation is a hallmark of HIV, despite viral suppression
- Inflammation is associated with cardiometabolic complications
- Nutrient deficiencies persist in controlled HIV, however their roles in HIV-associated inflammation and non-infectious complications are unknown

What is new:

- In children with HIV, selenium may play a role in modulating inflammation and gut integrity.
- Low micronutrient levels do not appear to be associated with metabolic complications in children with controlled HIV.

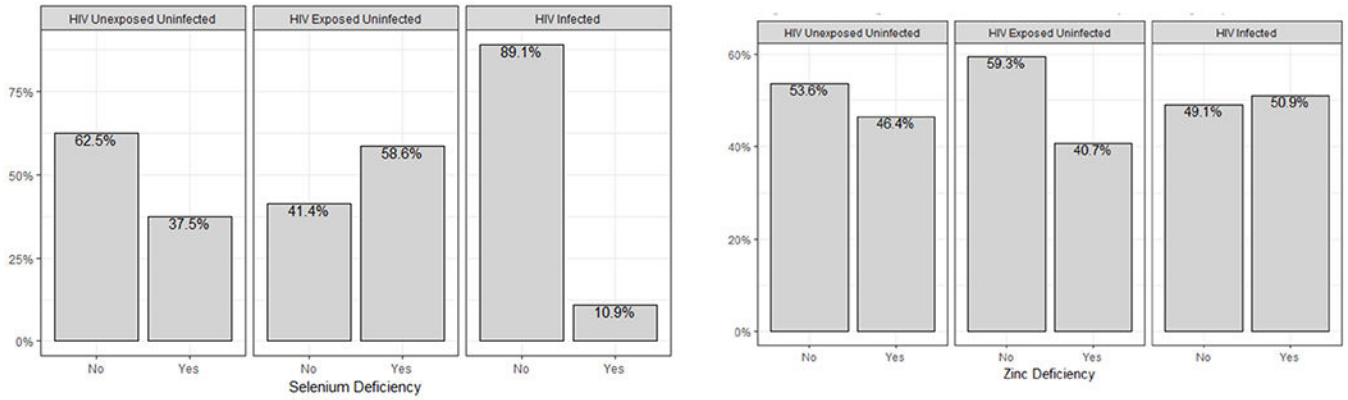

Figure 1:
Percent of participants with Selenium and Zinc Deficiency between groups

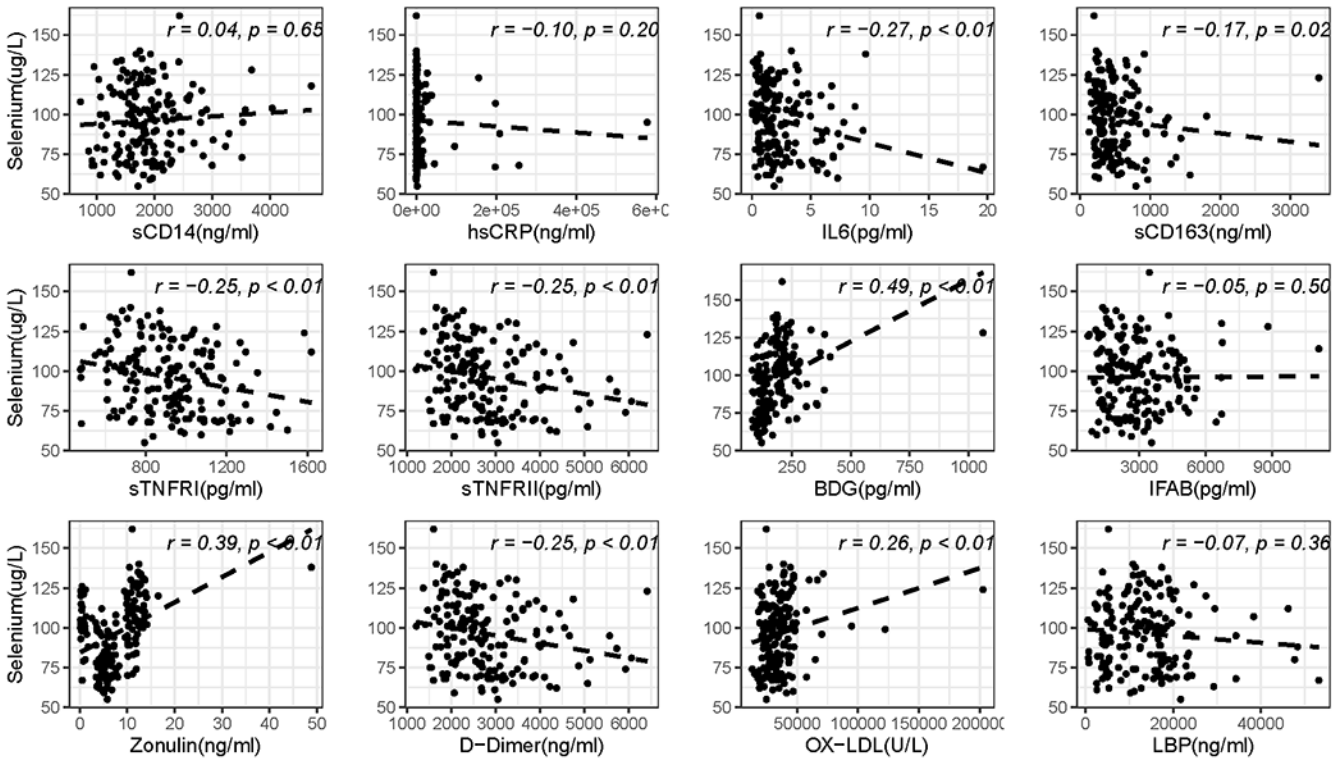

Figure 2:
Scatter plot of the correlation between Selenium and biomarkers

Table 1:

Baseline characteristics

Variables	PHIV n=57	HEU n=59	HIV- n=56	p-value
Cardiovascular and metabolic variables				
Weight- for- age- z score	−0.63 [−1.48, −0.06]	−0.46 [−0.99, 0.04]	−0.31 [−0.85, 0.10]	0.41
Height-for-age-z-score	−0.85[−1.53,0.39]	−0.22 [−1.16, 0.48]	−0.25 [−1.11, 0.14]	0.13
BMI (kg/m^2)	14.93 [14.48, 15.91]	14.92 [14.06, 15.60]	15.17 [14.57, 16.25]	0.08
Waist (cm)	57 [55, 59]	56 [53, 59]	57 [53, 58]	0.37
Hip (cm)	60 [58, 65]	62 [58, 67]	64 [61, 67]	0.05
Waist:Hip Ratio	0.92 [0.89, 0.98]	0.91 [0.87, 0.93]	0.89 [0.85, 0.92]	**<0.01**
Systolic Blood Pressure (mmHg)	98 [95, 105]	101 [93, 106]	105 [99, 109]	**0.04**
Diastolic Blood Pressure (mmHg)	63 [58, 68]	63 [58, 67]	64 [60, 67]	0.53
Cholesterol (md/dL)	152 [130, 168]	143 [129, 165]	143 [128, 160]	0.42
HDL (mg/dL)	50 [39, 57]	43 [36, 51]	42 [37, 48]	**0.01**
Non-HDL (mg/dL)	96 [83, 122]	98 [81, 118]	99 [88, 113]	0.84
Cholesterol:HDL ratio	3.00 [2.70, 3.70]	3.30 [2.85, 3.85]	3.50 [3.10, 3.80]	0.10
LDL (mg/dL)	80 [69, 102]	79 [68, 106]	86 [73, 101]	0.54
VLDL (mg/dL)	17 [13, 23]	14 [11, 22]	13 [10, 17]	**0.02**
Triglycerides (mg/dL)	83 [64, 113]	72 [56, 109]	65 [51, 86]	**0.02**
Insulin (μIU/mL)	5 [3, 7]	3 [2, 4]	3 [2, 4]	**0.00**
HOMA-IR	0.94 [0.62, 1.51]	0.57 [0.42, 1.06]	0.68 [0.41, 1.08]	**0.02**
Micronutrients				
Selenium (μg/L)	106 [94, 15]	81 [71, 97]	100 [75, 21]	**<0.001**
Zinc (μg/dL)	74 [64, 82]	78 [71, 87]	76 [68, 85]	0.18
Chromiun (μg/L)	< 1 [1, 1]	<1 [1, 1]	<1 [1, 1]	**0.01**

Median [Interquartile range]

Bold values represent p< 0.05

HDL: high density lipoprotein, HEU: Children exposed uninfected to HIV, HIV-: Children unexposed and uninfected to HIV, HOMA-IR: Homeostatic assessment insulin resistance, LDL: low-density lipoprotein, NRTI: nucleotide reverse transcriptase inhibitor, PHIV: Children with perinatally acquired HIV, PI: protease inhibitor, NNRTI: non-nucleotide reverse transcriptase inhibitor, VLDL: very low density lipoprotein.