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The Role of Selenium in HIV Infection Cosby A Stone, Kosuke Kawai, Roland Kupka, Wafaie W Fawzi Harvard School of Public Health

Cosby A Stone,
School of Public Health and School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

Kosuke Kawai,
Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

Roland Kupka, and
Department of Nutrition, Harvard School of Public Health, Boston, MA, USA and United Nations Children's Fund, Regional Office for West and Central Africa, Dakar, Senegal

Wafaie W. Fawzi
Departments of Nutrition, Epidemiology, and Global Health and Population, Harvard School of Public Health, Boston, MA, USA

Abstract

HIV infection is a global disease that disproportionately burdens populations with nutritional vulnerabilities. Laboratory experiments have shown that selenium has an inhibitory effect on HIV *in vitro* through antioxidant effects of glutathione peroxidase and other selenoproteins. Numerous studies have reported low selenium status in HIV-infected individuals, and serum selenium concentration declines with disease progression. Some cohort studies have shown an association between selenium deficiency and progression to AIDS or mortality. In several randomized controlled trials, selenium supplementation has reduced hospitalizations, diarrheal morbidity, and improved CD4 cell counts, but the evidence remains mixed. Additional trials are recommended to study the effect of selenium supplementation on opportunistic infections, and other HIV disease related comorbidities in the context of highly active antiretroviral therapy in both developing and developed countries.

Keywords

Selenium; HIV; trace minerals; dietary supplements; micronutrients

Introduction

The HIV pandemic has placed a great demand upon the scientific community to develop effective prevention and treatment methods. Since the beginning of the pandemic, over 25 million people are estimated to have died from the disease.[1] It is a leading cause of death in many parts of the world, and a disease that disproportionately affects the marginalized and socially disadvantaged. Many of the affected also suffer from chronic food insecurity and malnutrition, and so therapies that could potentially target both HIV disease and

Corresponding author: Cosby A Stone, 724 34th St. South, #4, Birmingham, AL 35205, 205-356-7820, cstonejr@gmail.com.

malnutrition such as multivitamins have been extensively researched for potential benefits.[2] Among such therapies, the antioxidant micronutrients, theorized to have potential benefits in HIV disease apart from correcting deficiencies have frequently been examined.[3,4,5,6,7]

Selenium is an essential micronutrient found in the soil. First discovered by Berzelius in 1817, it has been found to serve functions in DNA oxidative damage repair, DNA synthesis, and cellular signalling via thioredoxin reductase conversion of circulating thyroxine into its active form via iodothyronine deiodonases, and antioxidant defense and leukocyte adherence in the form of glutathione peroxidases.[8,9,10] These three major classes of enzymes have in common the biological form of selenium contained within selenocysteine residues, a transformation of the amino acid serine that is synthesized on a specialized $tRNA^{sec}$. [11] Selenium deficiency has also been found to be involved in Keshan's disease, a cardiomyopathy first described in China occurring subsequent to infection with a coxsackie B virus.[12] The mechanism is believed to be due to the accumulation of oxidative damage related mutations in the viral genome that cause it to convert to a more virulent form.[13] This discovery, along with the recognition that supplementation of table salt with selenium in the regions of China affected by Keshan's disease greatly reduced the number of cases, brought awareness in the fields of nutrition and virology that selenium status might play a role in diseases caused by other viral infections, especially in HIV disease.[14] In this paper, we have reviewed the literature on selenium and HIV infection. We present here a synopsis of laboratory and animal studies, observational studies, and randomized controlled trials and recommendations for further research.

Laboratory and Animal Studies

Among the approaches that have been considered to control HIV *in vitro*, attempts to discover biological processes that were important in perpetuating the virus's activation and replication were given a high priority. While studying the interaction between the milieu of host cytokines and immunoregulatory proteins, researchers found in the early nineties that antioxidants had a beneficial effect on viral replication *in vitro*.[3,15] In HIV infection, reactive oxygen species upregulate the activation of viral replication, generating additional copies of the virus from an infected cell through the actions of nuclear factor kappa-light-chain enhancer of activated B cells (NFκB) and activator protein 1 (AP-1) as intermediates. [15] In addition, antioxidant proteins such as catalase and glutathione peroxidase, which requires selenium, were subsequently shown to decrease viral activation.[3] Additional studies done in this area, along with those mentioned before, led to the suggestion of oxidative imbalance may contribute to HIV's pathogenesis, working apart from or in addition to the known effects caused by the virus' replication within and destruction of cells in the immune system.[3,4,5,6,7] There were some early efforts made to translate this research into the clinical setting, but other findings showed that increased glutathione peroxidase activity *in vitro* was also associated with increased syncytia formation, and possibly prevention of apoptosis of those infected cells, and therefore, there was concern that selenium supplementation might lead to increased dissemination of the virus in the early stages of infection.[4,5]

Genetic studies of cellular immunity and of HIV's genome revealed an interplay between selenium and genes important for propagation of the virus. Studies of T cells looking at the genes that encode CD4, CD8, and human leukocyte antigen DR 33 (HLA DR 33) were found to have open reading frames with multiples of UGA codons similar to those that encoded selenoproteins. These open reading frames also contained potential stem loop structures that could interact with selenocysteine residues. This was thought to be a highly unlikely coincidence, and suggested that the interaction between selenium and HIV disease might be more complex than was previously understood. It was further proposed that selenoproteins might lie within the viral genome for some purpose.[16] Two years later, this

hypothesis was verified by finding frameshift sites and RNA pseudoknots that would lead to selenoprotein synthesis when the encoding module for the selenoprotein overlapped another functioning gene. At that time, similar structures were found in a wide range of other viruses, suggesting selenium has a role to play in the virulence of multiple pathogens.[17] A separate study found structures that encode glutathione peroxidase in a molluscum contagiosum virus, and suggested that such structures might be found commonly in other viruses.[18] Within a short time, the hypothesis that HIV might encode selenoproteins was investigated, and using a computer model it was discovered that the coding sequence in question was homologous to human glutathione peroxidase. When this gene was cloned and transfected into canine kidney cells, it increased the output of glutathione peroxidase by 21 to 43%, and in transfected MCFV7 cells by 100%.[19] Within the field, many once again postulated that selenium might be important to the needs of HIV itself or the virus' interaction with the cell's oxidative machinery when integrating into the host genome.

Later advances in virology and immunology brought a T-cell model that could be used to study increases and decreases in oxidative signaling through an immortalized T-cell line that had been given a selenium dependent glutathione peroxidase construct via a retroviral vector.[20] The same year as this result, another experiment showed that selenium was important in the regulation of NFκB, which is important in mitigating the effect of HIV pathogenesis through its effects in upregulating glutathione peroxidase.[21] Following this, it was discovered that selenium supplementation will decrease the replication of HIV *in vitro* when the virus is exposed to TNF-α, confirming selenium's role in up regulating other antioxidant enzymes.[22] Researchers then found that the levels of normal selenoproteins that are expressed in T-cells, including thiodoxin reductase, glutathione peroxidase, and phospholipids hydroperoxide glutathione peroxidase, are increased in the presence of selenium, but diminished when the T cell is infected with HIV.[22,23] Instead, low molecular mass compounds containing selenium are produced.[23] Therefore, in many papers, it had been shown that HIV benefited from the disruption of normal selenoprotein synthesis and from disrupting the functions of normal cellular oxidative activity. The question of whether HIV's replicative machinery incapacitated the oxidative machinery of the T cell intentionally or unintentionally remained an open one, but many researchers began to think it was intentional.

Selenium appears to play a role as an immunomodulator as well. *In vitro* exposure of chronically infected T-lymphocyte and monocytic cell lines to selenium prior to exposure to TNFα resulted in decreased induction of HIV-1 replication. Interestingly, there was a similar effect for acutely infected monocytic cell lines, but not for T-cell lines.[22] Selenium has also been shown to have a beneficial *in vitro* effect on production of both interleukin 2 (IL-2) and its receptor expression, leading to generation of cytotoxic T lymphocytes and natural killer cells.[24,25] It is also inversely correlated levels of interleukin 8 (IL-8) *in vivo*, which is a marker of severe inflammation during opportunistic infections that portends worsened outcomes.[26,27]

Another beneficial breakthrough came in 2002 when it was found that *Rhesus* monkeys infected with the simian immunodeficiency virus also suffer from progressive selenium deficiency similar to humans, opening up animal models for testing.[28]

Cross-Sectional Studies (Table 1)

The earliest studies examined whether selenium deficiency was common in HIV-infected persons. A cross-sectional study performed in New York in 1989 found significantly lower serum selenium level when comparing patients with AIDS and "AIDS related complex" to healthy controls, as well as significantly decreased erythrocyte glutathione peroxidase activity.[29] Another study done in 1990 looking at multiple different micronutrients found

that lower serum levels of phosphorus and selenium were associated with HIV infection.[32] Persons in earlier stages of HIV disease do not appear to differ significantly from controls in their serum selenium concentrations, but those in advanced disease stage showed low serum selenium concentrations.

Additional studies looked at various predictors and endpoints related to selenium and HIV disease progression. Female gender was found to be a predictor of poorer nutritional status in HIV-infected injecting drug users, and also predicted decreased serum selenium levels, which was confirmed by several researchers.[46,47] Higher serum selenium status was associated with slower rates of mental decline in AIDS related dementia, improved mood, and improved self assessed quality of life.[48] Another study reported changes in fatty acid levels associated with decreases in selenium across the spectrum of HIV disease, and a nonrandomized supplementation trial found that serum glutathione peroxidase could be increased at 3-6 months and 12 months of follow up.[49,50] A study in Ethiopia showed an association between persons who had TB and decreased serum selenium. Persons who had both HIV and TB were seen to have serum selenium levels that were even lower than those either TB or HIV alone.[41]

Cohort and Case-Control Studies (Table 2)

Studies have consistently found that low serum selenium levels are associated with an increased risk of mortality among HIV-infected adults and children. Among 95 HIV-infected patients in France, lower serum selenium levels were significantly associated with the risk of mortality after adjusting for CD4 cell counts.[49] Another study of 125 HIV-infected adults with IV drug use in the U.S. showed that selenium deficiency is associated with a 10.8-fold increased risk of mortality after adjusting for CD4 cell counts and other nutritional deficiencies.[51] In Tanzania, lower plasma selenium levels were significantly associated an increased risk of mortality among 949 HIV-infected women during 5.7 median years of follow up period.[55]

Similar findings are reported among children. A study of 24 children in the U.S.with perinatally acquired HIV found that low plasma selenium levels were associated with a 6-fold increased risk of mortality after adjusting for CD4 cell counts.[52] A prospective cohort study of 670 children born to HIV-infected women in Tanzania also showed that low plasma selenium levels were associated with an increased risk of mortality after adjusting for CD4 cell counts and other nutritional status.[57]

Researchers also examined whether the serum selenium levels are associated with other important clinical outcomes. For example, HIV is known to be associated with cases of dilated cardiomyopathy. A prospective cohort study involving 416 HIV-infected persons in Rwanda found that low serum selenium status was associated with an increased risk for developing dilated cardiomyopathy.[58] Some have therefore speculated that many cases of HIV related cardiomyopathy could in fact be cases of Keshan's disease.[59] A case- control study of HIV-infected patients with IV drug use demonstrated higher relative risk for patients with lower selenium levels to have mycobacterial disease after adjusting for BMI, CD4 cell counts, and antiretroviral treatment.[54]

Shedding of the virus in various bodily secretions has been a well studied area of interest in HIV research, due to the consideration that decreasing viral load in bodily secretions will decrease transmission, especially from mothers to children. In a longitudinal study performed in Dar Es Salaam, Tanzania, persons with increased plasma selenium levels had associated increases in cervicovaginal shedding of HIV-1 RNA.[59] On the other hand, low serum selenium was associated with the outcomes of increased risks of fetal death, child death, and HIV transmission through the intrapartum route, and higher risk of mortality and

various morbidities for the HIV-infected pregnant mothers themselves.[55,56,57] Paradoxically, a decreased risk of small for gestational age babies was seen in those mothers who had reduced selenium.[56]

When the course of HIV disease was fundamentally altered by the advent of antiretroviral therapy (ART), especially with highly ART (HAART), researchers were able to pose the question of whether immune status in persons with HIV was dependent on selenium status, or whether it was the other way around. Once immune status could be improved by HAART, would the selenium status be corrected or not? One study followed 44 persons living with HIV over three years from 1995 when none of them were receiving HAART to 1998 when almost all were. They classed them into two groups, based on total CD4+ T-cell count being greater or less than 250/mm^3 at baseline. In follow-up, they found that a difference in serum selenium status evident at baseline had disappeared over time, drawing the conclusion that selenium and zinc status were dependent on immune status in some way, and that HAART could reduce such deficiencies.[53]

Intervention Studies: (See Table 3)

Early trials of selenium supplementation were small and designed to test whether giving oral selenium would increase serum levels of selenium in persons living with HIV. A nonrandomized trial conducted among 10 patients in France showed improved plasma selenium measurements from a mean of 0.75 +/− 0.27 μmol/L to 1.63 +/− 0.27 μmol/L after 21 days of supplementation.[30] Another trial in the U.S. found that average serum selenium level in patients with AIDS was 1.55 +/− 0.38 μmol/L (n = 24), and 1.59 +/− 0.48 μmol/L (n = 26) in persons with AIDS-related complex (ARC), compared to 2.47 +/− 0.25 μmol/L (n = 28) in controls. 19 of those symptomatic patients with positive HIV antibodies agreed to take selenium supplements, and after 70 days, average serum selenium concentration increased to 3.54 +/− 1.01 μmol/L.[31] The French trial also reported additional benefits for six of their eight patients suffering from nonobstructive cardiomyopathy, though the sample size was too small to make any generalizations.[30] An Australian trial examined the effect of two different dosages of antioxidant supplements that included selenium, vitamins A, C, and E and found that both high and low dosage of supplements produced similar improvements in antioxidant measures.[61]

A trial with 186 persons living with HIV found that daily selenium supplements were associated with reduced rates of hospital admission (RR = 0.38; p = .002) and reduced health related costs (58% reduction vs. 30% reduction, p=0.001) during a two year course of follow up.[62] In a trial of 262 HIV-positive individuals, participants in a selenium supplemented group who were found to have responded to selenium showed a significant increase in CD4 cell counts and a decrease in viral load compared to participants in the control group during 9 months of treatment, with a positive response being defined by a serum increase of selenium greater than 26.1 μg/L during the period of supplementation.[64] However, several limitations were evident in this trial. Division of the supplemented group into responders and nonresponders based on cutoffs in measured plasma selenium during post-hoc analysis was not part of the original plan of the study. Another major limitation was a loss of a third of participants during follow-up. These two studies were also relatively small, and therefore did not provide the certainty of interpretation that larger trials would afford.

Additional trials have been conducted in the settings hardest hit by both HIV and malnutrition. A 1999 randomized controlled trial in Zambia examined the effect of short term supplementation with a multivitamin containing vitamin A, C, E, zinc, and low dose selenium (150 μg) plus albendazole versus albendazole and placebo on 106 persons with HIV diarrhea wasting syndrome. Supplementation did not affect morbidity (p=0.96),

mortality (RR 1.06, *P* = 0.87), or provide symptomatic relief.[60] A 2004 randomized controlled trial in Kenya with 400 participants looked at primary outcomes of cervicovaginal shedding of virus, CD4+ T cell counts and viral load. Participants received a supplement containing B-complex vitamins, vitamins C and E, and 200μg of selenium over 6 weeks. They found shedding of HIV infected cells was increased 2.5 fold (p=0.001) in supplemented participants, and viral RNA in vaginal secretions increased 0.37 $\log_{10}$ units (p=0.004), all of which are adverse outcomes. Supplementation also resulted in higher CD4 (+23 cells/mL, P = 0.03) and CD8 (+74 cells/mL, p = 0.005) counts compared with placebo (potentially beneficial outcomes), but no change in plasma viral load.[63] A small trial in 2008 in Nigeria found nonsignificant increases in T-cell count for a selenium and aspirin regimen versus selenium alone, but there were problems with the randomization scheme.[66] Another 2008 randomized controlled trial in Tanzania of selenium supplementation in HIV infected pregnant women found an association with a reduced risk of low birth weight [relative risk (RR = 0.71; 95% CI: 0.49, 1.05; p=0.09), but an increased risk of fetal death (RR=1.58; 95% CI=0.95, 2.63; p=0.08). There was no effect seen on maternal mortality, neonatal or overall child mortality, but mortality at 6 weeks was reduced (RR = 0.43; 95% CI = 0.19, 0.99; p =0.048).[65] Secondary outcomes for this trial showed a reduction in diarrheal morbidity (RR= 0.60; 95% CI, 0.42-0.84), with no effect on maternal hemoglobin or other morbidity measures.[67]

Based on the trials, selenium may offer some modest beneficial effects for birth outcomes and diarrheal morbidity. The safety and efficacy of supplementation as an adjunct therapy needs to be further examined, however, due to possible increases in viral shedding, and additional research among individuals on HAART is warranted.

Potential Mechanisms of Observable Selenium Deficiency

Various mechanisms have been proposed for the observed deficiency in selenium in persons living with HIV. Among the first to be explored was whether gastrointestinal absorption of selenium was so altered that oral supplementation would not be effective. A study performed in 1989 found that oral supplementation with 400 micrograms of selenium significantly increased serum selenium levels after 70 days of supplementation.[31] Another study mentioned previously noted decreased selenium levels in AIDS patients compared to controls along with malabsorption defined by the D-xylose test in 60% of the cases, but also noted that inadequate intake was seen in 71% of the cases.[35] A later study done in 1996 whose main goal was to see if supplementation with selenium would increase enzymatic activity also found it was possible to increase serum selenium levels with supplementation in persons infected with HIV.[50] The literature therefore supports the conclusion that selenium can be replaced via oral supplementation in persons with HIV, and that possible mechanisms for selenium deficiency included malabsorption and inadequate intake. Later, a study looking at a population of HIV-infected injection drug users in 1996 found that dietary intake of selenium was actually higher than in noninfected injection drug using controls.[68] The result was speculated to be due to an unconscious attempt to achieve selenium homeostasis through diet.

The literature does not currently support the hypothesis that selenium is excreted at a greater rate in persons living with HIV. One result found that urinary selenium excretion was relatively unchanged in persons with HIV compared to controls. Urinary selenium is a good marker for dietary intake of selenium, and so poor intake also became a less likely hypothesis. Via this method, it was also seen that study participants were excreted approximately as much selenium as they were taking in, which made the malabsorption hypothesis less likely as well.[69] Another group subsequently excluded malabsorption as being the underlying cause of selenium deficiency and suggested that serum selenium status

was therefore a good marker for monitoring HIV disease progression, though it is not without inaccuracies in its measurement.[55]

Serum selenium has been found to be a reasonable measure that roughly approximates long term intake, and is a preferred way to measure selenium status, though it is more challenging to draw conclusions from individual specimens.[70,71] Its measurement can be confounded by matrix and spectral interference problems that must be corrected by skilled technicians, such that it is challenging to perform in a routine clinical laboratory.[72,73,74] The challenges present in measurement do not appear to challenge the overall conclusions of the available research, however. Based on the available studies, it appears that selenium is somehow being overutilized and depleted in a form that cannot be recycled during the course of HIV disease or of its concomitant opportunistic infections, leading to lower serum selenium levels in persons with HIV disease.

Conclusion

Selenium supplementation remains a possible adjunct therapy in HIV, but one whose clinical role will be defined by future research that answers some of the major reservations that remain. In the area of bench work, the field is getting closer to outlining the multiple mechanisms by which selenium impacts HIV, and may soon answer lingering questions as to whether selenium supplementation is more beneficial to the virus than the patient at certain stages of disease. Observational studies have mostly shown an association between decreasing serum selenium and progression through HIV disease stages to poorer outcomes, but experience in the post-HAART era is limited. They have also raised the question of whether the observed selenium deficiency is more strongly associated with certain subsets of the HIV population, such as those with HIV associated cardiomyopathy or opportunistic infections. Clinical trials have reported some risks of increased viral shedding with supplementation, but also benefits of decreased hospitalizations, and better outcomes such as suppression of viral load, increased CD4+ T-cell counts, and decreased risk of diarrhea. The future of selenium and HIV research will therefore need to address outstanding clinical concerns, to answer new questions that have arisen, and to verify previously reported outcomes, but there remains a good possibility that there will be a role for selenium supplementation to play in HIV care.

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Table 1

Cross Sectional Studies of Serum Selenium Status and HIV Disease Progression

Author and Year	Population (Location)	Results	Variables Adjusted For
Dworkin et. al. 1988[29]	13 patients with AIDS, compared to 8 patients with AIDS-related complex (ARC), 14 healthy controls (US)	Serum selenium levels reduced in patients with AIDS compared to patients with ARC ($p < 0.0001$) and controls ($p < 0.02$). Erythrocyte selenium levels reduced in both patients with AIDS and ARC compared to controls ($p < 0.02$).	disease duration, weight loss, albumin
Zazzo et. al 1988[30]	10 persons with HIV related cardiomyopathy, 10 controls (France)	Serum selenium levels in persons with AIDS and cardiomyopathy (0.75 ± 0.27 μmol/L) are lower than the control (1.10 ± 0.15 μmol/L; $p<0.01$).	
Olmstead et al.1989[31]	24 patients with AIDS, 26 Patients with ARC, 28 healthy controls (US)	Serum selenium level of patients with AIDS (0.123 ± 0.030 μg/mL) and ARC (0.126 ± 0.038 μg/mL) were significantly lower than the healthy control (0.195 ± 0.020 μg/mL).	
Beck et al. 1990[32]	Walter Reed Staged HIV-infected men compared to healthy controls (Germany)	Selenium significantly lower in HIV-infected persons vs. controls, lower selenium levels correlated with Zn, but not with Walter Reed Stage or absolute CD4 cell count	Ca, Cu, Fe, K, Mg, P, Se, and Zn
Cirelli et al. 1991[33]	HIV-infected men with 23 asymptomatic and 44 symptomatic, and 15 control (Italy)	Compared to the control (1.30 ± 0.06 μmol/L), HIV-infected symptomatic patients had significantly lowered serum selenium (AIDS = 0.82 ± 0.22 μmol/L; ARC = 0.86 ± 0.16 μmol/L; persistent generalized lymphadenopathy = 0.87 ± 0.11 μmol/L). No difference between HIV-infected asymptomatic (1.18 ± 0.27 μmol/L) and control.	hemoglobin, erythrocyte sedimentation rate, zinc
Revillard et al 1992[34]	26 asymptomatic HIV-infected cases, 37 symptomatic HIV-infected cases, 32 uninfected controls (France)	Plasma selenium in asymptomatic AIDS was 1.19 ± 0.23 μmol/L, and in symptomatic AIDS was 0.93 ± 0.30 μmol/L. Plasma selenium in controls was 1.05 ± 0.13 μmol/L. 10 asymptomatic cases and 30 symptomatic cases were on antiretroviral therapy.	retinol, tocopherols, lipids, zinc, glutathione peroxidase, cholesterol, triglycerides
Dworkin, 1994[35]	12 patients with AIDS compared to healthy, autopsy hearts of deceased HIV infected persons (US)	Plasma selenium in AIDS (0.043 ± 0.01 μg/ml) was significantly lower in controls (0.095 ± 0.016 μg/ml). Cardiac selenium in AIDS was 0.327 ± 0.082 μg/ml dry weight versus 0.534 ± 0.184 μg/ml in controls ($P < 0.01$).	Malabsorption, diarrhea, dietary intake, drug abuse
Sappey et. al, 1994[36,37]	25 asymptomatic and 18 symptomatic HIV-infected cases, 16 uninfected (France)	Plasma selenium in asymptomatic HIV-infected was 0.93 ± 0.19 μmol/L. Symptomatic AIDS patients (0.59 ± 0.25 μmol/L) had significantly lower plasma selenium than controls (0.96 ± 0.17 μmol/L).	
Longombe et. al, 1994[38]	18 asymptomatic and 82 symptomatic HIV-infected cases, 99 uninfected (Zaire)	There were no significant differences among the groups. Plasma selenium in asymptomatic was 0.801 ± 0.262 μmol/L, symptomatic AIDS 0.678 ± 0.280 μmol/L and controls 0.781 ± 0.262 μmol/L.	CDC stage of participant
Look et al, 1997[26]	104 HIV-infected patients and healthy control (Germany)	The mean serum selenium levels among AIDS (0.0514 ± 0.0147 μg/mL) and non-AIDS symptomatic patients (0.0667 ± 0.0209 μg/mL) were significantly lower as compared to asymptomatic HIV-infected (0.0823 ± 0.0205 μg/mL) and HIV-negative individuals (0.0892 ± 0.0209 μg/mL).	

Author and Year	Population (Location)	Results	Variables Adjusted For
Abuye et al 2005[39]	38 HIV-positive and 121 HIV-negative individuals (Ethiopia)	Serum selenium concentrations did not differ among the groups: 1.89 µmol/L in HIV negative, whereas 2.27 µmol/L in HIV positive with CD4 cell counts >500, 2.00 µmol/L with CD4 between 500 and 200, and 1.95 µmol/L with CD4 < 200	BMI, study site, gender, cigarette consumption, khat,
Jones, et al 2006[40]	171 HIV positive men and 117 HIV positive women receiving HAART (US)	Prevalence of selenium deficiency (< 85 µg/L) in the sample was 8% in men and 3% in women. Absence of trends towards progression of HIV disease (lower CD4 counts or higher viral load) when comparing quartiles of serum selenium.	Age, gender, race, housing insecurity, poverty, years of HIV infection, BMI
Kassu, et al 2006[41]	74 patients infected with HIV and TB, 81 with TB alone, 34 HIV negative (Ethiopia)	Serum selenium level significantly lower in persons with TB and HIV (7.55 ± 2.63 µg/dL) compared to patients with TB alone (8.86 ± 3.93 µg/dL) and controls (10.70 ± 4.81 µg/dL).	copper, zinc, iron, stage of anti-Tb therapy, age, sex, BMI
Ogunro et al, 2006[42]	62 HIV-1 positive persons and 30 HIV negative (Nigeria)	The plasma selenium concentrations significantly lower in HIV-infected persons with CD4 counts > 200 (0.53 ± 0.06 µmol/L), and CD4 counts 200-499 (0.71 ± 0.10 µmol/L), when compared to controls (1.01 ± 0.10 µmol/L).	HIV disease stage, viral subtype
Drain et al 2006[43]	400 HIV-1 positive women (US)	Univariate analysis showed serum selenium significantly associated with CD4 cell count, viral load, serum albumin and acute phase response. Multivariate model showed that only serum albumin was associated selenium.	CD4+ T-cell counts, Serum albumin, plasma viral load, C-reactive protein, alpha-1 acid glycoprotein, HIV symptoms, HIV signs, BMI,
Stephensen et al 2007[44]	365 adolescent and young adults (244 HIV-positive and 121 HIV-negative) (US)	Plasma selenium in HIV-positive individuals (0.120 ± 0.0013 µg/mL) was not significantly different (P = 0.07) from that in HIV-negative (0.125 ± 0.002.0 g/mL). Multivariate analysis showed a negative association between HIV-associated immune activation and serum selenium (P =0.002).	age, sex, BMI, pregnancy status, race, ethnicity, smoking, HIV status, CD4+ T-cell count, plasma viral load, use of ART, CD8+ T-cell count, neopterin, neutrophils, glutathione, glutathione peroxidase, plasma protein carbonyls and malonaldehyde
Khalili et al 2008[45]	100 HIV-infected persons, 100 healthy controls (Iran)	Selenium deficiency present in 38% of HIV-infected persons and 2% of controls (p<0.001). Average serum selenium concentration was (0.0664 ± 0.0112 µg/mL in HIV-infected persons was significantly lower in controls (0.0917 ± 0.0119 µg/mL). Decreases in serum selenium occurred with worsening overall nutrition status (p = 0.04).	age, weight, height, BMI, socioeconomic status, serum albumin, CD4+ T-cell count, IV drug use, zinc

Table 2

Cohort and Case-Control Studies of Serum Selenium Status and HIV Disease Progression

Author and year	Population (Location)	Endpoint	Results	Variables Adjusted for
Constans et al, 1995[49]	95 HIV-positive patients. Followed for 1 year. (France)	Mortality	Serum selenium was associated with death (p = 0.01) and occurrence of opportunistic infections (p = 0.008).	CD4 cell counts
Baum et al, 1997[51]	125 patients with HIV-infected IV drug users. Followed over 3.5 years. (US)	Mortality	Selenium deficiency (<85 μg/L) was associated with an increased risk of mortality (Adjusted RR = 10.8; 95% CI, 2.37-49.2, p <0.002).	Prealbumin, vitamins A, B6, B12, and E, zinc, antiretroviral treatment, CD4 cell counts at baseline and over time
Campa et al, 1999[52]	24 children with perinatally acquired HIV followed over 5 years. (US)	Mortality	Plasma selenium levels <85 μg/L were associated with an increased risk of mortality (Adjusted RR = 5.96; 95% CI, 1.32-26.81; p = 0.02).	CD4 cell counts at baseline.
Rousseau et al, 2000[53]	44 HIV infected patients followed over 3 years. (France)	Plasma selenium levels	At baseline, patients with CD4 cell counts < 250/mm^3 had significantly lower (p<0.05) levels of plasma selenium. After most patients started antiretroviral therapy with protease inhibitors, selenium levels between patients with CD4 cell counts <250/mm^3 and those with >250/mm^3 no longer differ.	
Shor-Posner et al, 2002[54]	12 cases and 32 control in HIV-infected IV drug users. A case-control study followed 2 years (US)	Mycobacterial disease	Lower levels of selenium was significantly associated with the risk of mycobacterial disease (Adjusted RR=3, p = 0.02).	Antiretroviral treatment, BMI, CD4 cell counts
Kupka et al 2004[55]	949 HIV infected women, followed over the median, 5.7 years. (Tanzania)	Mortality, CD4 cell counts	Lower plasma selenium levels were significantly associated with an increased risk of mortality (p, test for trend < 0.01). Lower plasma selenium levels were marginally associated with decreased CD4 cell counts in the first year.	Sociodemographic factors, mid-upper arm circumference, plasma vitamin A and E, hemoglobin, CD4 cell counts, HIV disease stage, erythrocyte sedimentation rare, malaria
Kupka et al 2005[56]	610 children born to HIV-infected mothers followed over 24 months (Tanzania)	Mortality, morbidity	Lower plasma selenium levels in children were associated with an increased risk of all-cause mortality (p, test for trend < 0.05). Plasma selenium levels were not associated with risk of diarrhea or respiratory outcomes.	Age, baseline CD4 cell counts, weight-for-age, plasma albumin, ferritin, vitamins A and E
Kupka et al 2005[57]	670 HIV positive pregnant women in followed from 12-27 weeks gestation to 24 months postpartum (Tanzania)	Pregnancy outcomes, HIV infection, child mortality	Infants born to women with low plasma selenium levels were at increased risks for fetal death (p, test for trend =0.02), child mortality (p = 0.03), and HIV transmission through the intrapartum route (p = 0.01).	Mid-upper arm circumference, HIV disease stage, plasma vitamin A and E, CD4+ cell counts, hemoglobin, and history of adverse pregnancy outcome
Twagirumukiza et al 2007[58]	416 HIV positive patients followed for 12 months (Rwanda)	Dilated cardiomyopathy	18% of patients developed dilated cardiomyopathy. Low plasma selenium levels were associated with development of HIV-associated cardiomyopathy (p=0.003).	Socio-economic status, estimated duration of HIV infection, total lymphocyte count, CD4 cell count, HIV-1 viral load, HIV disease stage

Table 3

Trials of Selenium Supplementation among HIV-positive individuals

Author and year	Study Type	Method (Location)	Intervention	Results
Zazzo et. al 1988[30]	Trial without control group	10 persons with AIDS related cardiomyopathy, (France)	800 μg of sodium selenite for 15 days, followed by 400 μg for 8 days.	After selenium supplementation, 6 of 8 patients returned to normal left ventricular shortening fraction, one died, and one had thiamine deficiency. Serum selenium levels increased from a mean of 0.75 ± 0.27 μmol/L to 1.63 ± 0.27 μmol/L after supplementation.
Olmstead, et. al 1989[31]	Trial without control group	19 AIDS or ARC patients (US)	400 μg, of selenium	Average serum selenium concentration increased from 0.14 +/− 0.03 μg/mL to 0.28+/− 0.08 μg/mL after 70 days of supplementation.
Kelly, et. al 1999[60]	Randomized Controlled Trial	106 persons with HIV diarrhea wasting syndrome (Zambia)	Albendazole plus daily vitamin A, C, E, zinc and selenium (150 μg) vs. albendazole alone	Micronutrient supplements had no effect on recovery from diarrhea, mortality, or change in CD4 cell counts.
Batterham et al 2001[61]	Trial without control group (dose comparison study)	66 persons enrolled, 48 completed study. (Australia)	Low doses of antioxidants (vitamins A, C, and E and 100 mg selenium) vs. high doses of antioxidants including 200 mg selenium	Serum selenium increased from 2.24 ± 0.73 to 2.50 ± 0.49 after 12 weeks ($p < 0.001$). Measures of oxidative defense also increased over time, but HIV viral load did not change. There was no significant difference between low dose vs. high dose.
Burbano et. al 2002[62]	Randomized Controlled Trial	186 HIV positive men and women followed for two years (US)	Selenium 200 μg daily vs. placebo	Selenium supplementation reduced the rates of hospitalization (RR=0.4, $p = 0.01$) and health related cost.
McClelland et. al 2004[63]	Randomized Controlled Trial	400 HIV positive women (Kenya)	Supplement containing B-complex vitamins, vitamins C and E plus 200 mg selenium vs. placebo	Supplementation resulted in higher CD4 (+23 cells/mL, P = 0.03) cell counts, but no change in serum viral load. Increased vaginal shedding (2.5 fold, p=0.001) of HIV-infected cells with supplementation.
Hurwitz et al. 2007 [64]	Randomized Controlled Trial	262 HIV positive men and women followed over 9-month (US)	High selenium yeast supplement containing 200μg/d	Selenium “responders” whose serum selenium level increased by 3 SD above placebo during treatment, had greater increases in serum selenium concentration ($p<.001$), less viral load increase ($p<.02$), and greater CD4 count increase ($p<.02$) than did the placebo and nonresponder groups, who did not differ.
Kupka et al 2008[65]	Randomized Controlled Trial	913 HIV positive pregnant women (Tanzania)	200 μg of daily selenium supplementation in the form of selenomethionine	Selenium was marginally associated with a reduced risk of low birth weight (RR = 0.71; p=0.09) and increased risk of fetal death (RR=1.58; p=0.08). Selenium had no effect on maternal mortality, CD4 cell counts or viral load. Selenium supplements may reduce the risk of infant death after 6 week (RR = 0.43; p =0.048).
Durosinmi et al 2008[66]	Randomized Controlled Trial	23 HIV-infected patients (Nigeria)	300 mg aspirin 4-6 times daily plus 200 μg of selenium and multivitamin vs. 200 μg selenium and multivitamin . Multivitamin contained vitamin A, B-complex vitamins, vitamins C and D.	The combined selenium and aspirin regimen showed a nonsignificant increase in T-cell count, as did selenium alone. Weight increased significantly for both groups.

Author and year	Study Type	Method (Location)	Intervention	Results
Kupka et al 2009[67]	Randomized Controlled Trial	913 HIV positive pregnant women (Tanzania)	200 μg of daily selenium supplementation in the form of selenomethionine	Selenium had no effect on hemoglobin concentrations. Selenium supplements reduced diarrheal morbidity risk by 40% (RR= 0.60; 95% CI, 0.42-0.84), had no effect on other morbidity endpoints.