Role of selenium in HIV infection

Cosby A Stone, Kosuke Kawai, Roland Kupka, and Wafaie W Fawzi

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 and 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.

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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 in 1981, over 25 million people are estimated to have died from the disease.¹ It is currently a leading cause of death in many parts of the world, and a disease that disproportionately affects the marginalized and socially disadvantaged. Many of those affected also suffer from chronic food insecurity and malnutrition, so therapies that could potentially target both HIV disease and 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 been examined frequently.³⁻⁷

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 signaling 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.⁸⁻¹⁰ 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 tRNAse.¹¹ Selenium deficiency has also been found to be involved in Keshan’s disease, a cardiomyopathy first described in China and 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 to 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

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The present article, reviews the literature on selenium and HIV infection, presents a synopsis of laboratory and animal studies, observational studies, and randomized controlled trials, and outlines recommendations for further research.

LABORATORY AND ANIMAL STUDIES

Among the in vitro approaches that have been considered to control HIV, attempts to discover the biological processes with important roles in perpetuating the virus’s activation and replication have been given a high priority. While studying the interaction between the milieu of host cytokines and immunoregulatory proteins, researchers found in the early 1990s that antioxidants had a beneficial effect on viral replication in vitro.\(^4,5\) 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 B (NFkB), which is a light-chain enhancer of activated B cells, and activator protein 1 (AP-1) as intermediates.\(^6\) In addition, antioxidant proteins such as catalase and glutathione peroxidase, which require selenium, were subsequently shown to decrease viral activation.\(^3\) Studies in this area, in addition to those mentioned before, led to the suggestion that oxidative imbalance may contribute to HIV’s pathogenesis, working apart from or in addition to the known effects of the virus’s replication within and destruction of cells in the immune system.\(^3,5,7\) Some early efforts were 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; consequently, 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 interplay between selenium and the genes important for propagation of the virus. Studies of T cells that looked 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 it 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.\(^6\) Two years later, this hypothesis was verified by the finding of frameshift sites and RNA pseudoknots that would lead to selenoprotein synthesis when the encoding module for the selenoprotein overlapped with that of another functioning gene. At that time, similar structures were found in a wide range of other viruses, suggesting selenium plays a role in the virulence of multiple pathogens.\(^8\) 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, the output of glutathione peroxidase was increased by 21–43%, and in transfected MCFV7 cells, it was increased by 100%.\(^19\) Within the field, many scientists once again postulated that selenium might be important for the needs of HIV itself or the virus’s interaction with the cell’s oxidative machinery when integrating into the host genome.

Later advances in virology and immunology led to 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 emerged, another experiment showed that selenium was important in the regulation of NFkB, 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 tumor necrosis factor-alpha (TNF-\(\alpha\)), thus confirming selenium’s role in the upregulation of 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 phospholipid hydroperoxide glutathione peroxidases, 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, many reports showed that HIV benefited from disruptions to normal selenoprotein synthesis and to 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 unanswered, 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 monocyctic cell lines to selenium prior to exposure to TNF-\(\alpha\) resulted in decreased induction of HIV-1 replication. Interestingly, a similar effect was
observed for acutely infected monocytic cell lines, but not for T-cell lines. Selenium has also been shown to have a beneficial in vitro effect on the production of interleukin-2 (IL-2) and expression of its receptor, leading to the generation of cytotoxic T lymphocytes and natural killer cells. It is also inversely correlated with in vivo levels of interleukin-8 (IL-8), a marker of severe inflammation during opportunistic infections that portends worsened outcomes. 

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

CROSS-SECTIONAL STUDIES

A summary of the cross-sectional studies on serum selenium status and HIV progression is provided in 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 levels of selenium in the serum samples of patients with AIDS and AIDS-related complex compared to those of healthy controls, and erythrocyte glutathione peroxidase activity was also significantly lower. A study conducted in 1990, which looked at multiple different micronutrients, found that lower serum levels of phosphorus and selenium were associated with HIV infection. Overall, serum selenium concentrations of persons in early stages of HIV disease do not appear to differ significantly from those of controls, but those in advanced stages of the disease show 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 it predicted decreased serum selenium levels, as confirmed by several researchers. 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. 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 at 12 months of follow up. A study in Ethiopia showed an association between decreased serum selenium and persons who had tuberculosis (TB). Persons who had both HIV and TB had serum selenium levels that were even lower than those with either TB or HIV alone. 

COHORT AND CASE-CONTROL STUDIES

A summary of cohort and case-control studies of serum selenium status and HIV progression is provided in 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. Another study of 125 HIV-infected adult intravenous drug users in the United States showed that selenium deficiency was associated with a 10.8-fold increased risk of mortality after adjusting for CD4 cell counts and other nutritional deficiencies. In Tanzania, lower plasma selenium levels were significantly associated with an increased risk of mortality among 949 HIV-infected women during 5.7 median years of follow up.

Similar findings were reported for children. A study of 24 children in the United States with perinatally acquired HIV found that low plasma selenium levels were associated with a sixfold increased risk of mortality after adjusting for CD4 cell counts. 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 measures of nutritional status.

Researchers have also examined whether 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 of developing dilated cardiomyopathy. Some have subsequently speculated that many cases of HIV-related cardiomyopathy could, in fact, be cases of Keshan’s disease. A case-control study of HIV-infected intravenous drug users demonstrated a higher relative risk for mycobacterial disease among patients with lower selenium levels after adjusting for body mass index, CD4 cell counts, and antiretroviral treatment.

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 the 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. On the other hand, low serum selenium was associated with increased risk of fetal death, child death, and intrapartum HIV transmission, as well as a higher risk of mortality and...
Table 1  Cross-sectional studies of serum selenium status and HIV disease progression.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population (Location)</th>
<th>Results</th>
<th>Adjusted variables</th>
</tr>
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<tbody>
<tr>
<td>Dworkin et al. (1986)</td>
<td>13 patients with AIDS, compared to 8 patients with AIDS-related complex, 14 healthy controls (USA)</td>
<td>Serum selenium levels reduced in patients with AIDS compared to patients with AIDS-related complex (P &lt; 0.0001) and controls (P &lt; 0.02). Erythrocyte selenium levels reduced in patients with AIDS and AIDS-related complex compared to controls (P &lt; 0.02).</td>
<td>Disease duration, weight loss, albumin</td>
</tr>
<tr>
<td>Zasso et al. (1986)</td>
<td>10 persons with HIV-related cardiomyopathy, 10 controls (France)</td>
<td>Serum selenium levels in persons with AIDS and cardiomyopathy (0.75 ± 0.27 µmol/L) lower than in controls (1.10 ± 0.15 µmol/L; P &lt; 0.01).</td>
<td>Ca, Cu, Fe, K, Mg, P, Se, and Zn</td>
</tr>
<tr>
<td>Olimstead et al. (1989)</td>
<td>24 patients with AIDS, 26 patients with AIDS-related complex, 28 healthy controls (USA)</td>
<td>Serum selenium level of patients with AIDS (0.126 ± 0.038 µmol/L) significantly lower than those of healthy controls (0.195 ± 0.020 µmol/L).</td>
<td>Hemoglobin, erythrocyte sedimentation rate, zinc</td>
</tr>
<tr>
<td>Beck et al. (1990)</td>
<td>Walter Reed Staged HIV-infected men compared to healthy controls (Germany)</td>
<td>Selenium significantly lower in HIV-infected persons vs. controls; lower selenium levels correlated with Zn, but not with Walter Reed Stage or absolute CD4 count cell.</td>
<td>Retinol, tocopherols, lipids, zinc, glutathione peroxidase, cholesterol, triglycerides</td>
</tr>
<tr>
<td>Grelli et al. (1991)</td>
<td>HIV-infected men (23 asymptomatic and 44 symptomatic) and 15 controls (Italy)</td>
<td>Compared to controls (1.30 ± 0.06 µmol/L), HIV-infected symptomatic patients had significantly lower serum selenium (AIDS = 0.82 ± 0.22 µmol/L; ARC = 0.86 ± 0.16 µmol/L; persistently generalized lymphadenopathy = 0.87 ± 0.11 µmol/L). No difference between HIV-infected asymptomatic subjects (1.18 ± 0.27 µmol/L) and controls.</td>
<td>Malabsorption, diarrhea, dietary intake, drug abuse</td>
</tr>
<tr>
<td>Reviell et al. (1992)</td>
<td>26 asymptomatic HIV-infected cases, 37 symptomatic HIV-infected cases, 32 uninfected controls (France)</td>
<td>Plasma selenium 1.19 ± 0.23 µmol/L in subjects asymptomatic for AIDS, 0.93 ± 0.30 µmol/L in symptomatic AIDS patients and 1.05 ± 0.13 µmol/L in controls. 10 asymptomatic subjects and 30 symptomatic subjects were on antiretroviral therapy.</td>
<td></td>
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<tr>
<td>Dworkin (1994)</td>
<td>12 patients with AIDS compared to healthy, autopsy hearts of deceased HIV-infected persons (USA)</td>
<td>Plasma selenium in asymptomatic HIV-infected subjects 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).</td>
<td>CDC stage of participant</td>
</tr>
<tr>
<td>Sappey et al. (1994)</td>
<td>25 asymptomatic and 18 symptomatic HIV-infected cases, 16 uninfected (France)</td>
<td>No significant differences among the groups. Plasma selenium in asymptomatic subjects 0.801 ± 0.262 µmol/L, symptomatic AIDS subjects 0.678 ± 0.280 µmol/L, and controls 0.781 ± 0.262 µmol/L.</td>
<td>BMI, study site, gender, cigarette consumption, khat</td>
</tr>
<tr>
<td>Longombe et al. (1994)</td>
<td>18 asymptomatic and 82 symptomatic HIV-infected cases, 99 uninfected (Zaire)</td>
<td>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 ± 0.0039 µg/mL).</td>
<td>BMI, site, gender, race, housing insecurity, poverty, years of HIV infection, BMI</td>
</tr>
<tr>
<td>Look et al. (1997)</td>
<td>104 HIV-infected patients and healthy controls (Germany)</td>
<td>No differences in serum selenium concentrations among the groups: 1.89 µmol/L in HIV-negative subjects; 2.27 µmol/L in HIV-positive subjects with CD4 cell counts &lt;200; 2.00 µmol/L in HIV-positive subjects with CD4 between 200 and 400; and 1.95 µmol/L in HIV-positive subjects with CD4 &gt;200.</td>
<td>CDC stage of participant</td>
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<tr>
<td>Abuoye et al. (2005)</td>
<td>38 HIV-positive and 121 HIV-negative individuals (Ethiopia)</td>
<td>Plasma selenium concentrations in asymptomatic HIV-infected subjects 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).</td>
<td>CDC stage of participant</td>
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<tr>
<td>Jones et al. (2006)</td>
<td>171 HIV-positive men and 117 HIV-positive women receiving HAART (USA)</td>
<td>Prevalence of selenium deficiency (&lt;45 µg/L) in the sample 8% in men and 3% in women. Absence of trends towards progression of HIV disease (lower CD4 cell counts or higher viral load) when comparing quartiles of serum selenium.</td>
<td>Age, gender, race, housing insecurity, poverty, years of HIV infection, BMI</td>
</tr>
<tr>
<td>Kasu et al. (2006)</td>
<td>74 patients infected with HIV and TB, 81 with TB alone, 34 HIV-negative (Ethiopia)</td>
<td>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).</td>
<td>Copper, zinc, iron, stage of anti-TB therapy, age, sex, BMI</td>
</tr>
<tr>
<td>Ogunro et al. (2006)</td>
<td>62 HIV-1-positive and 30 HIV-negative persons (Nigeria)</td>
<td>Plasma selenium concentrations significantly lower in HIV-infected persons with CD4 cell counts &lt;200 (0.53 ± 0.06 µmol/L) and CD4 cell counts 200–499 (0.71 ± 0.10 µmol/L) compared to controls (1.01 ± 0.10 µmol/L).</td>
<td>HIV disease stage, viral subtype</td>
</tr>
<tr>
<td>Drain et al. (2006)</td>
<td>400 HIV-1-positive women (USA)</td>
<td>Univariate analysis showed serum selenium significantly associated with CD4 cell count, viral load, serum albumin, and a cut-off response. Multivariate model showed that only serum albumin was associated selenium.</td>
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<tr>
<td>Stephens et al. (2007)</td>
<td>365 adolescent and young adults (244 HIV-positive and 121 HIV-negative) (USA)</td>
<td>Plasma selenium concentration in HIV-positive individuals (0.120 ± 0.0013 µg/mL) not significantly different (P = 0.07) from that in HIV-negative subjects (0.125 ± 0.0020 µg/mL). Negative association between HIV-associated immune activation and serum selenium (P = 0.002) in multivariate analysis.</td>
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<tr>
<td>Khaili et al. (2008)</td>
<td>100 HIV-infected persons, 100 healthy controls (Iran)</td>
<td>Selenium deficiency present in 38% of HIV-infected persons and 2% of controls (P &lt; 0.001). Average serum selenium concentration in HIV-infected persons (0.0664 ± 0.0112 µg/mL) significantly lower than in controls (0.0917 ± 0.0119 µg/mL). Decreases in serum selenium occurred with worsening overall nutrition status (P = 0.04).</td>
<td>Age, weight height, BMI, socioeconomic status, serum albumin, CD4+ T-cell count, IV drug use, zinc</td>
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</table>
## Table 2  Cohort and case-control studies of serum selenium status and HIV disease progression.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population (location)</th>
<th>Endpoint</th>
<th>Results</th>
<th>Adjusted variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constans et al.</td>
<td>95 HIV-positive patients followed for 1 year (France)</td>
<td>Mortality</td>
<td>Serum selenium associated with death ($P = 0.01$) and occurrence of opportunistic infections ($P = 0.008$).</td>
<td>CD4 cell counts</td>
</tr>
<tr>
<td>Baum et al.</td>
<td>125 patients with HIV-infected IV drug users followed over 3.5 years (USA)</td>
<td>Mortality</td>
<td>Selenium deficiency (&lt;85 µg/L) associated with an increased risk of mortality (adjusted RR, 10.8; 95% CI, 2.37–49.2; $P &lt; 0.002$).</td>
<td>Prealbumin, vitamins A, B6, B12, and E, zinc, antiretroviral treatment, CD4 cell counts at baseline and over time</td>
</tr>
<tr>
<td>Campa et al.</td>
<td>24 children with perinatally acquired HIV followed over 5 years (USA)</td>
<td>Mortality</td>
<td>Plasma selenium levels &lt;85 µg/L associated with increased risk of mortality (adjusted RR, 5.96; 95% CI, 1.32–26.81; $P = 0.02$).</td>
<td>CD4 cell counts at baseline</td>
</tr>
<tr>
<td>Rousseau et al.</td>
<td>44 HIV-infected patients followed over 3 years (France)</td>
<td>Plasma selenium levels</td>
<td>Patients with CD4 cell counts &lt;250/mm$^3$ at baseline had significantly lower ($P &lt; 0.05$) levels of plasma selenium. After most patients started antiretroviral therapy with protease inhibitors, selenium levels between patients with CD4 cell counts &lt;250/mm$^3$ and those with &gt;250/mm$^3$ no longer differed.</td>
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<tr>
<td>Shor-Posner et al.</td>
<td>12 cases and 32 control in HIV-infected IV drug users; case-control study followed for 2 years (USA)</td>
<td>Mycobacterial disease</td>
<td>Lower levels of selenium significantly associated with risk of mycobacterial disease (adjusted RR, 3; $P = 0.02$).</td>
<td>Antiretroviral treatment, BMI, CD4 cell counts</td>
</tr>
<tr>
<td>Kupka et al.</td>
<td>949 HIV-infected women, followed over a median of 5.7 years (Tanzania)</td>
<td>Mortality, CD4 cell counts</td>
<td>Lower plasma selenium levels significantly associated with increased risk of mortality ($P$, test for trend &lt; 0.01). Lower plasma selenium levels marginally associated with decreased CD4 cell counts in the first year.</td>
<td>Sociodemographic factors, mid-upper-arm circumference, plasma vitamin A and E, hemoglobin, CD4 cell counts, HIV disease stage, erythrocyte sedimentation rate, malaria Age, baseline CD4 cell counts, weight-for-age, plasma albumin, ferritin, vitamins A and E</td>
</tr>
<tr>
<td>Kupka et al.</td>
<td>610 children born to HIV-infected mothers followed over 24 months (Tanzania)</td>
<td>Mortality, morbidity</td>
<td>Lower plasma selenium levels in children associated with increased risk of all-cause mortality ($P$, test for trend &lt; 0.05). Plasma selenium levels not associated with risk of diarrhea or respiratory outcomes.</td>
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</tr>
<tr>
<td>Kupka et al.</td>
<td>670 HIV-positive pregnant women followed from 12–27 weeks gestation to 24 months postpartum (Tanzania)</td>
<td>Pregnancy outcomes, HIV infection, child mortality</td>
<td>Infants born to women with low plasma selenium levels at increased risk for fetal death ($P$, test for trend = 0.02), child mortality ($P = 0.03$), and intrapartum HIV transmission ($P = 0.01$).</td>
<td>Mid-upper-arm circumference, HIV disease stage, plasma vitamin A and E, CD4$^+$ cell counts, hemoglobin, and history of adverse pregnancy outcome</td>
</tr>
<tr>
<td>Twagirumukiza et al.</td>
<td>416 HIV-positive patients followed for 12 months (Rwanda)</td>
<td>Dilated cardiomyopathy</td>
<td>18% of patients developed dilated cardiomyopathy; low plasma selenium levels associated with development of HIV-associated cardiomyopathy ($P = 0.003$).</td>
<td>Socioeconomic status, estimated duration of HIV infection, total lymphocyte count, CD4 cell count, HIV-1 viral load, HIV disease stage</td>
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</table>
various morbidities for the HIV-infected pregnant mothers themselves.\textsuperscript{38,40,44} Paradoxically, a decreased risk of bearing small-for-gestational-age babies was seen in mothers who had reduced selenium.\textsuperscript{44}

When the course of HIV disease was fundamentally altered by the advent of antiretroviral therapy, especially highly active antiretroviral therapy (HAART), researchers were able to investigate 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 with HIV over 3 years, from 1995, when none of them were receiving HAART, to 1998, when almost all were. The subjects were classed into two groups, based on their total CD4\(^+\) T-cell count being greater or less than 250/mm\(^3\) at baseline. During follow-up, it was found that the differences in serum selenium status that were evident at baseline disappeared over time, leading the researchers to conclude that selenium and zinc status were dependent on immune status in some way, and that HAART could reduce such deficiencies.\textsuperscript{45}

**INTERVENTION STUDIES**

A summary of trials of selenium supplementation in HIV-positive individuals is provided in 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 with 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.\textsuperscript{46} Another trial in the United States found that the 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, compared to 2.47 ± 0.25 μmol/L (n = 28) in controls. Nineteen of the symptomatic patients who tested positive for HIV antibodies agreed to take selenium supplements, and after 70 days, the average serum selenium concentration increased to 3.54 ± 1.01 μmol/L.\textsuperscript{47} The French trial also found additional benefits for six of eight patients suffering from nonobstructive cardiomyopathy, but the sample size was too small to allow any generalizations to be made.\textsuperscript{46} An Australian trial examined the effect of two different doses of antioxidant supplements containing selenium and vitamins A, C, and E; the results showed that both the high- and low-dose supplements produced similar improvements in antioxidant measures.\textsuperscript{48}

A trial performed with 186 HIV-positive persons found that daily selenium supplements were associated with reduced rates of hospital admission (relative risk [RR], 0.38; \(P = 0.002\)) and reduced health-related costs (58% reduction versus 30% reduction; \(P = 0.001\)) during a 2-year follow-up period.\textsuperscript{49} 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 their CD4\(^+\) cell count and a decrease in viral load compared to participants in the control group during 9 months of treatment. In this study, a positive response was defined as an increase of serum selenium greater than 26.1 μg/L during the period of supplementation.\textsuperscript{50} However, several limitations were evident in this trial. Division of the supplemented group into responders (n = 50) and nonresponders (n = 40) based on cutoffs in the measured levels of plasma selenium during post-hoc analysis was not part of the original study design. Another major limitation was that a third of the participants were lost during follow-up. These two studies of selenium supplementation were also relatively small, and 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 randomized controlled trial performed in Zambia in 1999 examined the effect of short-term supplementation with a multivitamin containing vitamins A, C, and E, zinc, and low-dose (150 μg) selenium plus albendazole versus albendazole and placebo on 106 persons with HIV diarrhea wasting syndrome. Supplementation did not affect morbidity (\(P = 0.96\)) or mortality (RR 1.06, \(P = 0.87\)), nor did it provide symptomatic relief.\textsuperscript{51} A 2004 randomized controlled trial performed with 400 participants in Kenya in 2004 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 200 μg of selenium over 6 weeks. The researchers found that shedding of HIV-infected cells was 2.5-fold greater (\(P = 0.001\)) in supplemented participants, and viral RNA in vaginal secretions was increased by 0.37 log\(_{10}\) units (\(P = 0.004\)); both of these are adverse outcomes. Supplementation also resulted in higher CD4\(^+\) (+23 cells/mL, \(P = 0.03\)) and CD8\(^+\) (+74 cells/mL, \(P = 0.005\)) cell counts compared with placebo (potentially beneficial outcomes), but there was no change in plasma viral load.\textsuperscript{52} A small trial conducted in 2008 in Nigeria found nonsignificant increases in T-cell counts for subjects on a selenium and aspirin regimen versus those receiving selenium alone, but there were problems with the randomization scheme.\textsuperscript{53} Also in 2008, a randomized controlled trial in Tanzania investigated selenium supplementation in HIV-infected pregnant women. This study found that supplementation was associated with a reduced risk of low birth weight (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; \(P = 0.08\)). No effect
Table 3: Trials of selenium supplementation among HIV-positive individuals.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Method (location)</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zazzo et al. (1988)⁴⁸</td>
<td>Trial without control group</td>
<td>10 persons with AIDS related cardiomyopathy, (France)</td>
<td>800 µg of sodium selenite for 15 days, followed by 400 µg for 8 days</td>
<td>After selenium supplementation, 6 of 8 patients had improvement in echocardiographic measurement of left ventricular systolic function, one died, and one was found to have 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.</td>
</tr>
<tr>
<td>Olmstead et al. (1989)⁴⁷</td>
<td>Trial without control group</td>
<td>19 AIDS or ARC patients (USA)</td>
<td>400 µg of selenium</td>
<td>Average serum selenium concentration increased from 0.14 ± 0.03 µg/mL to 0.28 ± 0.08 µg/mL after 70 days of supplementation.</td>
</tr>
<tr>
<td>Kelly et al. (1999)¹¹</td>
<td>Randomized controlled trial</td>
<td>106 persons with HIV diarrhea wasting syndrome (Zambia)</td>
<td>Albendazole plus daily vitamins A, C, and E, zinc, and selenium (150 µg) vs. albendazole alone</td>
<td>Micronutrient supplements had no effect on recovery from diarrhea, mortality, or change in CD4 cell counts.</td>
</tr>
<tr>
<td>Batterham et al. (2001)⁴⁶</td>
<td>Trial without control group (dose comparison study)</td>
<td>66 persons enrolled, 48 completed study (Australia)</td>
<td>Low doses of antioxidants (vitamins A, C, and E and 100 mg selenium) vs. high doses of antioxidants including 200 mg selenium</td>
<td>Serum selenium increased from 2.24 ± 0.73 to 2.50 ± 0.49 after 12 weeks (P &lt; 0.001). Measures of oxidative defense also increased over time, but HIV viral load did not change. There was no significant difference between the low-dose and high-dose groups.</td>
</tr>
<tr>
<td>Burbano et al. (2002)⁴⁹</td>
<td>Randomized controlled trial</td>
<td>186 HIV-positive men and women followed for 2 years (USA)</td>
<td>Selenium 200 µg daily vs. placebo</td>
<td>Selenium supplementation reduced the rates of hospitalization (RR, 0.4; P = 0.01) and health-related costs.</td>
</tr>
<tr>
<td>McClelland et al. (2004)⁵²</td>
<td>Randomized controlled trial</td>
<td>400 HIV-positive women (Kenya)</td>
<td>Supplement containing B-complex vitamins and vitamins C and E, plus 200 mg selenium vs. placebo</td>
<td>Supplementation resulted in higher CD4 (+23 cells/µL; 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.</td>
</tr>
<tr>
<td>Hurwitz et al. (2007)⁴⁰</td>
<td>Randomized controlled trial</td>
<td>262 HIV-positive men and women followed over 9 months (USA)</td>
<td>High-selenium yeast supplement containing 200 µg/d</td>
<td>Selenium &quot;responders&quot; whose serum selenium level increased by 3 SD above placebo during treatment, had greater increases in serum selenium concentration (P &lt; 0.001), less viral load increase (P &lt; 0.02), and greater CD4 cell count increase (P &lt; 0.02) than did the placebo and nonresponder groups, which did not differ.</td>
</tr>
<tr>
<td>Kupka et al. (2008)⁴⁴</td>
<td>Randomized controlled trial</td>
<td>913 HIV-positive pregnant women (Tanzania)</td>
<td>200 µg of daily selenium supplementation in the form of selenomethionine</td>
<td>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 weeks (RR, 0.43; P = 0.048).</td>
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<tr>
<td>Durosinsimi et al. (2008)⁵³</td>
<td>Randomized controlled trial</td>
<td>23 HIV-infected patients (Nigeria)</td>
<td>300 mg aspirin 4–6 times daily plus 200 µg of selenium and multivitamin vs. 200 µg selenium and multivitamin; multivitamin contained vitamins A, B-complex, C and D</td>
<td>The combined selenium and aspirin regimen showed a nonsignificant increase in T-cell count, as did selenium alone. Weight increased significantly for both groups.</td>
</tr>
<tr>
<td>Kupka et al. (2009)⁵⁵</td>
<td>Randomized controlled trial</td>
<td>913 HIV-positive pregnant women (Tanzania)</td>
<td>200 µg of daily selenium supplementation in the form of selenomethionine</td>
<td>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.</td>
</tr>
</tbody>
</table>
was seen on maternal mortality, neonatal mortality, or overall child mortality, but mortality at 6 weeks was reduced (RR, 0.43; 95% CI, 0.19–0.99; P = 0.048). Secondary outcomes for this trial showed a reduction in diarrheal morbidity (RR, 0.60; 95% CI, 0.42–0.84), but there was no effect on maternal hemoglobin or other morbidity measures.55

Based on these trials, selenium appears to offer some modest benefits in terms of birth outcomes and diarrheal morbidity. However, the safety and efficacy of supplementation as an adjunct therapy needs to be examined further, 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 selenium deficiency observed in HIV-infected individuals. Among the first to be explored was whether gastrointestinal absorption of selenium was so altered that oral supplementation with selenium would not be effective. A study performed in 1989 found that oral supplementation with 400 µg of selenium significantly increased serum selenium levels after 70 days of supplementation.47 Another previously mentioned study found decreased selenium levels in AIDS patients compared to controls, along with malabsorption, as defined by the D-xylose test, in 60% of cases; however, it also found that inadequate intake was seen in 71% of cases.56 A later study performed in 1996, which primarily aimed to determine whether supplementation with selenium would increase enzymatic activity, found it was possible to increase serum selenium levels via supplementation in persons infected with HIV.55 The literature therefore supports the conclusion that selenium levels can be raised in HIV-infected individuals via oral supplementation, and that possible mechanisms for selenium deficiency include malabsorption and inadequate intake. A later study looking at a population of HIV-infected intravenous drug users in 1996 found that dietary intake of selenium was actually higher in that group than in the control group of non-HIV-infected intravenous drug users.57 The result was speculated to be due to an unconscious attempt on the part of the HIV-infected study participants to achieve selenium homeostasis through diet.

The literature does not currently support the hypothesis that selenium is excreted at a greater rate by persons with HIV. One study found that urinary selenium excretion was relatively unchanged in persons with HIV compared to controls. Since urinary selenium is a good marker for dietary selenium intake, poor intake was considered a less likely reason for selenium deficiency. The measurement of urinary selenium also showed that study participants excreted approximately as much selenium as they were taking in, which made the hypothesis that the deficiency could be caused by malabsorption less likely as well.58 Another group subsequently excluded malabsorption from consideration as 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.59

Serum selenium has been found to be a reasonable measure that roughly approximates long-term intake, and it is a preferred way to measure selenium status, though it is more challenging to draw conclusions from individual specimens.59,60 Its measurement can be confounded by matrix and spectral interference problems that must be corrected by skilled technicians, making it challenging to perform in a routine clinical laboratory.61–63 However, the challenges present in measurement do not appear to invalidate the overall conclusions of the available research. Based on the available studies, it appears that selenium is somehow being overutilized and depleted in a manner that prevents its restoration during the course of HIV disease or its concomitant opportunistic infections, thus 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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Declaration of interest. The authors have no relevant interests to declare.

REFERENCES


