Chapter 30
Role of Selenium in HIV/AIDS

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Abstract HIV/AIDS continues to be a major health priority worldwide as the number of people living with HIV grows due to the life-prolonging effects of antiretroviral therapy. Nutrient deficits, however, may interfere with the effectiveness of antiretroviral therapy by delaying the recuperation of the immune system and aggravating side-effects, such as oxidative damage, which have been associated with treatment. Selenium status influences HIV disease progression through its role in cytokine modulation and antioxidant systems. Selenium supplementation in HIV-positive patients has shown benefits on biomarkers of disease progression, morbidity and mortality. Further research is needed to elucidate its effect on other aspects of the disease such as HIV shedding, mitochondrial damage, and HIV transmission.

30.1 Introduction: HIV Epidemic

HIV/AIDS continues to be a major health priority worldwide. The absolute number of people living with HIV has grown due to the life-prolonging effects of antiretroviral therapy (ART) [1]. Despite limitations in the reporting system, the Centers for Disease Control and Prevention (CDC) reported an incidence of approximately 35,000 new cases of HIV infection in the United States in 2008, and currently there are approximately half a million people living with HIV/AIDS in this country [2].

The latest national estimates suggest that the number of AIDS cases remained stable and that the number of deaths is decreasing. In developed countries, antiretrovirals and behavioral prevention interventions have contributed to abating

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the incidence of adult cases. In addition, maternal HIV testing, coupled with the introduction of successful interventions during prenatal, perinatal, and postnatal care have dramatically reduced the incidence of pediatric AIDS [3].

Worldwide, the situation is different. The number of people living with HIV were 33.3 million at the end of 2009 with 2.6 million newly infected in this year [1]. Despite the success of ART in the majority of countries around the world, including Africa, the gap between developed and developing countries in the control of the pandemic and treatment of infected persons continues to grow, and one of the factors that increases case fatality in limited-resource countries is malnutrition. Poor nutritional status can affect immune function independent of HIV infection [4, 5]. Death rates appear to be higher among HIV-infected persons with malnutrition, including those who already were started on ART [6, 7]. Numerous studies have demonstrated that nutritional deficiencies accelerate HIV disease progression and decrease survival [8–17]. Moreover, nutrient deficits interfere with the effectiveness of ART by delaying the recuperation of the immune system and aggravating side-effects, such as oxidative damage that appears to be one of the side-effects of HIV treatment [18–22].

30.2 Selenium and Immunity

The relationship between selenium and immunity might be derived from its role as an essential nutrient. Selenium deficiency produces changes in several metabolic functions, including the immune system. Among several potential mechanisms, selenium status influences the immune response through its role in cytokine modulation [23]. In an in vitro model, the addition of selenium regulated and enhanced the production of interleukin-2 through the increased expansion of high-affinity cytokine receptors in a dose-dependent manner [24]. In animal models, phagocytic neutrophils and macrophages exposed to selenium deficiency had reduced ability to destroy antigens. The immunostimulatory properties of selenium have been documented in animal supplementation studies [25], and in elderly subjects [26], as well as in patients with chronic uremia, psoriatic lesions, and gastrointestinal failure syndrome [27–29].

In HIV-1 infected patients, plasma selenium levels have been associated with markers of immune parameters. Plasma selenium levels were positively related with CD4 cell counts and CD4/CD8 ratio, and inversely correlated with β_2-microglobulin, a marker of CD4 depletion and HIV disease progression, and with thymidine-kinase activity, which seems to have a role in nucleoside analog activation and toxicity [30]. Selenium status was also shown to affect production of TNF-α, a cytokine related to anorexia, wasting and Kaposi's sarcoma [31]. Look et al. [30] demonstrated that plasma selenium levels were inversely associated with TNF type II receptors in HIV-positive patients. Hori et al. [32] showed that selenium supplementation reduced viral replication and suggested that this effect was through the synthesis

of selenoprotein in the glutathione and thioredoxin systems. In addition, several in vitro and in vivo reports provided evidence that adequate selenium status decreases neuropathogenesis, and that selenium appears to act through suppression of interleukin-induced HIV-1 replication, neuronal apoptosis, reduction of blood brain barrier damage, and of the potential interactions between selenium and cytokines [30, 32–34].

30.3 HIV, Antiretroviral Treatment, Oxidative Stress, and Selenium

HIV infection has been characterized by increased oxidative stress [35–40], and a decrease in the levels of major antioxidant nutrients, most notably vitamins E and C, carotenoids, and zinc and selenium [41–45]. The mechanism appears to be through increased chronic immune activation by HIV, which increases the production of reactive oxygen species (ROS). In healthy persons, ROS are continually produced in tissues as a consequence of substrate oxidation, aerobic respiration, and immune activation. These ROS are useful to many of the processes of the cell including cell growth, apoptosis, immunity, and microbial defense [46–48]. Because excessive oxidative products, such as the one observed in HIV infection, can be damaging to tissues, multiple enzymatic and nonenzymatic antioxidant defense systems exist to prevent damage by oxygen radicals.

Among the major antioxidant micronutrients, selenium is critical due to its role in the synthesis of glutathione peroxidase and other selenoproteins [49]. Selenium supplementation to increase the effectiveness of the enzymatic antioxidant defense systems has been investigated for the prevention and treatment of cancer [50]. In HIV-infected patients, supplementation with 100 μg of selenium daily for an year has been demonstrated to increase glutathione peroxidase activity in latently HIV-infected T-lymphocytes [34, 51]. The antioxidant demand in HIV infection is also reflected in declining total glutathione levels with HIV disease progression [52]. In addition, the major antioxidant defense enzymes are also altered, including superoxide dismutase, catalase, and glutathione peroxidase [38, 39, 43]. Gil et al. [40] reported that, compared to HIV-negative patients, HIV-positive patients have shown a reduction in glutathione and glutathione peroxidase, an increase in malonaldehyde (MDA – a marker of lipid peroxidation) and lymphocyte DNA fragmentation, as well as increasing superoxide dismutase activity. The total antioxidant status of the HIV-infected group was also significantly lower than that of the HIV-negative group in this study [40].

Antiretroviral therapy, rather than decreasing the importance of antioxidant supplementation, has created new research challenges for the role of selenium in HIV-1 disease. Antiretrovirals have been associated with increased oxidative stress and oxidative damage [53–56]. However, some studies have found increased antioxidant capacity

and DNA damage repair with the use of ART [57– 59]. Although the effect of different types of antiretrovirals on oxidative stress may vary, protease inhibitors (PIs) have generally been found to increase the production of ROS including peroxides, which are associated with endothelial dysfunction and dyslipidemias leading to increased cardiovascular risk [54, 60]. Nucleotide reverse transcriptase inhibitors have a well-established effect on mitochondria which results in increased measures of oxidative damage including lipid peroxidation products, protein carbonyls, and mitochondrial damage [55, 56]. Studies that combine several types of antiretrovirals have also been shown to produce increased oxidative stress. A study of oxidative stress in 85 HIV-infected patients who were either ART-naïve or on three different ART regimens showed increased lipid peroxidation measured by MDA in the HIV-infected patients vs. healthy controls, and in the ART treated groups compared to the ART-naïve group [61]. Exposure to ART has also been found to increase the generation of ROS in human aortic endothelial cells [62]. Increasing oxidative stress due to mitochondrial toxicity may affect the pathophysiology of HIV disease and the cellular damage seen in AIDS [63].

Low plasma selenium levels have been associated with hyperglycemia, and thrompocytopenia in HIV chronic drug users on ART [64]. No association was found, however, between these two conditions and ART [65]. Lipodystrophy, hyperlipidemias, and insulin resistance in patients receiving PIs [66] may increase the long-term risk of oxidative damage associated with development of atherosclerosis and coronary heart disease [67]. Supplementation of antioxidants, including selenium, may prove to be an important part of the therapy used to fight the sequelae of HIV disease and its treatment.

30.4 Observational Studies of Selenium Deficiency and HIV

Selenium deficiency has been associated with HIV disease progression and mortality [15, 16, 68–70]. In Africa, lower levels of selenium in pregnant women has been found to be predictive of higher risk of intrapartum transmission, and fetal and child death [71]. Several observational studies have reported prevalence of selenium deficiency between 7 and 33% among various HIV-1 infected cohorts, with increasing prevalence as the disease advances to AIDS [45, 68]. Similar findings have been observed in simian immunodeficiency virus models [72].

Before the advent of antiretrovirals, in a study of HIV-1 infected chronic drug users, selenium deficiency was an independent predictor of survival (relative risk 10.8; 95%CI [2.37–49.2], $p<0.002$) after controlling for the joint effects of nutritional deficiencies associated with mortality. This significant effect of selenium deficiency was evident when controlling for CD4 cell count <200 cells/mm^3 at baseline and CD4 cell count over time [15]. When similar analyses were conducted in a cohort of HIV-infected men who had sex with men (MSM) the odds ratio (OR) was

7.2 for mortality in those with low plasma selenium compared to those with normal selenium levels, after controlling for age, race, and CD4 cell count <200 cells/mm^3 at baseline. In this cohort, selenium deficiency was also associated with decreased survival; patients with selenium deficiency lived 31.4 months, compared with 57.4 months for those with normal plasma selenium levels after controlling for CD4 cell levels, viral load, and antiretroviral medications [45]. In HIV-infected persons, adequate dietary selenium intake was strongly associated with reduced measures of oxidative stress [73].

In HIV-infected children, selenium deficiency has been associated with advanced immune-deficiency [74] and mortality [68]. In agreement with the previous findings, a two-year study of 610 children born to HIV-infected women in Tanzania showed that the children's plasma selenium levels were inversely associated with risk of mortality for all causes [16]. In addition, depressed maternal plasma selenium levels significantly predicted risks of fetal death, child death, and intrapartum HIV transmission, but were not associated with risk of delivering a small for gestational age child [71].

Genital HIV shedding, a marker of risk of HIV transmission, has been associated with selenium deficiency. Baeten el al. [75] showed that selenium deficiency was associated with increased vaginal HIV-RNA shedding in Kenyan women. However, higher levels of plasma selenium levels (≥114 μg/L) reported by Kupka et al. [76] were also significantly associated with increased risk of genital shedding of HIV-RNA in Tanzanian HIV + pregnant women. After excluding women with genital infections, this association was strengthened (RR tertile 2 = 1.46, 95% CI = 1.10, 1.92; RR tertile 3 = 1.39, 95% CI = 1.05, 1.84). Consistent with Kupka's findings, a short-term (6 weeks) randomized clinical trial in Kenya that supplemented a multivitamin formula that included 200 μg of selenium, compared to placebo, reported an increase in genital HIV shedding (OR = 2.5, 95% CI (1.4–4.4), $p = 0.001$), after adjusting for baseline $\log_{10}$ vaginal HIV-1 RNA, and body mass index [77]. On the positive side, the report from this trial showed that the parameters for disease progression, CD4 (+23 cells/mm^3, $p = 0.03$) and CD8 cell counts (+74 cells/mm^3, $p = 0.005$) significantly increased with selenium supplementation when compared to placebo, with no effect on serum HIV viral load [77] (Table 30.2).

Selenium deficiency has shown significant association with herpes and candida infections in HIV-infected drug users in Miami [78]. Furthermore, participants with low plasma selenium levels were at a significantly higher risk for mycobacterial disease, both TB and mycobacterium avium ($RR = 3$, $p = 0.015$), after controlling for ART and CD4 cell count [79].

The significant association of selenium status with HIV-related morbidity and mortality may be related not only to selenium's role in maintaining immune competence, but also to its activity in modulating viral expression and protection against oxidative damage caused by the chronic infection and its treatment [80–84].

30.5 Selenium Supplementation in HIV

Selenium supplementation for the treatment of other conditions besides HIV has shown mixed results. A long-term clinical trial of selenium supplementation as a chemopreventive agent in cancer [85] demonstrated safety and efficacy at nutritional doses (200 μg of selenium) [85]. In contrast, a recent report on the preliminary findings of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) demonstrated no effect of selenium or vitamin E alone, or in combination, on the risk of prostate cancer [86, 87]. Other studies, however, have shown that nutritional supplementation of selenium significantly reduced the incidence of primary liver cancer in China [88], and provided significantly greater resistance to aflatoxin B1-induced carcinogenic damage in lymphocytes from healthy human subjects administered daily selenium [88].

In an early case study of a child with HIV/AIDS, Kavanaugh-McHugh et al. [89] described complications with features of Keshan disease, a disease associated with selenium deficiency [90]. Upon supplementation of the child with selenium (4 μg/kg), the deficiency symptoms improved [89]. An improvement in general health has been described after daily selenium supplementation [44, 91, 92], without apparent adverse effects in HIV-positive patients [44, 91]. The association of high risk of HIV-related mortality with selenium deficiency highlights the importance of maintaining adequate selenium status in HIV infection [15].

In two early reports from a small one-year study, French researchers [51, 93] reported benefits from supplementing HIV-positive patients with 100 μg of selenium daily, compared to 30 mg of beta-carotene twice daily, and also compared to a control group without supplementation. The control group increased markers of endothelial damage at the end of the first year while those in the supplementation groups were unchanged [93]. Glutathione peroxidase activity increased significantly ($p=0.04$) in the selenium group between 3 and 6 months of supplementation compared to those receiving beta-carotene or no supplements [51].

In Miami, 186 HIV-positive adults, some of whom were already on ART or started on ART during the study, were randomized into receiving 200 μg of selenomethionine or placebo in a randomized, double-blind, placebo-control trial. Those supplemented with selenium had a reduced cost of health care and were 60% significantly less likely ($p=0.01$) to be hospitalized during the two-year follow-up [94]. In a 9-month, randomized clinical trial of selenium supplementation in HIV-positive adults, also in Miami, Hurwitz et al. [95] demonstrated that those supplemented with 200 μg of selenium, whose serum selenium increased as evidence of treatment adherence, maintained their HIV-1 viral load (□ $=-0.04\pm0.7$ $\log_1 0$units), and increased CD4 cell count (□ $=+27.9\pm150.2$ cells/p□L) over time. A greater increase in plasma selenium concentration predicted a decrease in viral load ($\beta=-0.14$) ($z=-2.2$; $\beta=0.09$; $p<0.03$), and their models showed that the effect of selenium supplementation on CD4 cell count was secondary to the effect on viral load ($\beta=-0.29$), ($z=2.3$; $\beta=0.06$; $p=0.03$).

In a large randomized trial of supplementation with selenium (200 μg in the form of selenomethionine) in 915 HIV-infected pregnant women in Tanzania, who were supplemented from the 12–27th week of gestation until 6 months after delivery, Kupka et al. [96, 97] reported a reduction of 40% of diarrhea without significantly increasing the risk for anemia in the women, and a reduction in risk of child mortality after 6 weeks postdelivery.

30.6 Clinical Trials of Supplementation in HIV-Positive Patients that Included Selenium in the Experimental Formula

Selenium doses have been tested in several clinical trials in HIV-positive patients. Trials of selenium alone [51, 93–97] (Table 30.1), or in combination with other antioxidants, vitamins and minerals in the experimental formula (Table 30.2) [77, 98–102] have provided evidence of beneficial outcomes. In those trials in which selenium was part of a formula with other antioxidants and micronutrients, it is not possible to separate the benefits of selenium from those of the rest of the components of the intervention. Moreover, separating this effect may not be desirable, because the benefits of supplementation might be magnified by the interactive and synergistic character of nutrients and antioxidants.

Formulas with selenium have been tested as experimental or standard-of-care formulas with other medications in Africa [98, 103]. Kelly et al. [98], in a short-term 2 week randomized clinical trial of supplementation with a micronutrient formula that contained selenium, compared to placebo, explored the effect of supplementation on enhancing the effect of 800 mg of Albendazole, an anthelmintic, in Zambia. The trial randomized 106 HIV-positive adults with diarrhea-related wasting, who were not on ART, into a micronutrient formula with vitamins A, C, and E, zinc and selenium plus Albendazole or into the anthelmintic and placebo. After 2 weeks of supplementation, the addition of the nutrient formula to albendazole did not improve outcomes. In a recent pilot study in Nigeria involving the advantages of adding daily aspirin to a nutrient formula, 32 HIV-positive, ART-naïve patients were supplemented with 200 μg of selenium, vitamin A, B-complex, C, and D. Twenty-three patients were randomized into the multivitamin/mineral formula with 300 mg of aspirin 4–6 times daily, and a second group that included nine patients, into the multivitamin/mineral formula alone without aspirin. After 6 months of supplementation, the post-therapy mean weight was significantly higher (61.6 ± 15.2 kg vs. 60.0 ± 14.3 kg, $p = 0.015$) in the experimental arm with aspirin compared to the micronutrient formula alone, and CD4 cell count increased by an average of 36.2 cells/mm^3, showing a strong trend towards improvement ($p = 0.059$), albeit not significant [103].

Kaiser et al. [99] supplemented 40 HIV-positive adults on ART with controlled viral load and a combined formula of antioxidants, minerals and vitamins that contained 200 μg of selenium for 12 weeks that resulted in an improvement in their

Table 30.1 Summary of clinical trials that supplemented selenium in HIV-positive patients and findings

Authors	Population	Methods	Formula composition and selenium doses	Findings
Kupka et al. 2009 [96]	915 HIV+pregnant Tanzanian women Participants were not on ART at baseline	Randomized, double-blind, placebo-controlled trial of supplementation to women who were recruited between 12 and 27 weeks of gestation and followed until 6 months after delivery	*Supplement:* selenomethionine, 200 μg daily, compared to placebo *All women received*: antenatal ferrous iron (60 mg/day), and 20 mg riboflavin, 110 mg niacin, 25 mg B_6, 50 μg B_{12}, 500 mg C, 30 mg E, and 0.8 mg folic acid	Supplementation with selenium during pregnancy and postpartum reduced diarrheal morbidity risk by 40% with no significant risk for anemia. No effect on morbidity endpoints
Kupka et al. 2008 [97]	913 HIV-infected pregnant women in Tanzania and their children Participants were not receiving ART at baseline	Randomized, double-blind, placebo-controlled trial of supplementation to women who were recruited between 12 and 27 weeks of gestation and followed until 6 months after delivery	*Supplement*: selenomethionine, 200 μg daily, compared to placebo *All women received*: antenatal ferrous iron (60 mg/day), and 20 mg riboflavin, 110 mg niacin, 25 mg B_6, 50 μg B_{12}, 500 mg C, 30 mg E, and 0.8 mg folic acid	Maternal supplementation with selenium during pregnancy and postpartum reduced risk of child mortality after 6 weeks of delivery
Hurwitz et al. 2007 [95]	262 HIV-infected adults in Miami, Florida, USA 73.5% on ART at baseline	Randomized, double-blind, placebo-controlled trial of supplementation for 9 months	*Supplement*: selenium yeast providing 200 μg elemental selenium daily, compared to placebo	Daily selenium supplementation suppressed the progression of HIV-1 viral burden and provided indirect improvement of CD4 cell count

Burbano et al. 2002 [94]	186 HIV-positive adults with some of them on ART at baseline	Randomized, double-blind, placebo-controlled trial of supplementation for two years in Miami, USA	*Supplement:* selenium yeast providing, 200 μg daily, compared to placebo	Daily selenium supplementation reduced the rates of hospitalization significantly ($p=0.01$) and health-related costs
Constans et al. 1998 [93]	36 HIV-seropositive subjects supplemented for one year. Study before the ART era	10 subjects supplemented with selenium, 11 supplemented with beta-carotene and 15 controls who were not supplemented for one year	*Supplement:* 100 μg of selenium daily *or* 30 mg beta-carotene twice daily compared to no supplements for the control group	The comparison group experienced increased von Willebrand factor and soluble thrombomodulin implying increased damage to the endothelium over an year of the study. Both supplemented groups had no change in these parameters
Delmas-Beauvieux et al. 1996 [51]	36 HIV-seropositive subjects supplemented for one year. Study before the ART era	14 subjects supplemented with selenium, 13 subjects with beta-carotene and 18 controls not supplemented	*Supplement:* 100 μg of selenium daily *or* 30 mg beta-carotene twice daily compared to no supplements for the control group	GPX activity increased significantly after selenium treatment ($p=0.04$ between 3 and 6 months)

Table 30.2 Summary of randomized clinical trials that included selenium in the experimental formula in HIV-positive patients

Authors	Population	Methods	Formula composition and selenium doses	Findings
Villamor et al. 2008 [101]	471 HIV-positive and 416 HIV-negative adults with pulmonary TB in Tanzania Participants were not receiving ART	Randomized clinical trial of multivitamins and selenium compared to placebo and followed from initiation of TB therapy for a median of 43 months	*Multivitamin supplement*: 20 mg thiamin, 20 mg riboflavin, 100 mg niacin, 25 mg B_6, 50 μg. B_{12}, 0.8 mg folic acid, 500 mg C, 30 mg E, and 200 μg of selenium, compared to placebo	Multivitamin supplementation with the multivitamin increased CD3+ and CD4+ cell counts and decreased the incidence of extrapulmonary TB and genital ulcers in HIV-negative patients. Reduced the incidence of peripheral neuropathy by 57%, irrespective of HIV status
Range et al. 2006 [102]	213 patients with TB + HIV, 286 patients with TB and HIV-negative Participants were not receiving ART at the onset of the study	Randomized, factorial design 2×2 to Zn (45 mg), or Multivitamins with minerals (including selenium), or multivitamins and minerals + zinc or placebo. Participants were supplemented for 8 months	*Multivitamin and mineral supplement:* 5,000 IU Vitamin A, 20 mg thiamin, 20 mg riboflavin, 25 mg B_6, 40 mg niacin, 50 μg. B_{12}, 0.8 mg folic acid, 200 mg vitamin C, 60 mg vitamin E, 200 IU vitamin D3, 200 μg selenium, 5 mg copper, and 45 mg zinc, compared to placebo	Supplementation with multivitamins and minerals, including Zn, Cu, and Se during treatment of pulmonary TB reduced mortality in those coinfected with HIV and tuberculosis

Kaiser et al. 2006 [99]	40 HIV-infected participants on stable ART	Randomized, double-blind, placebo-controlled trial comparing a supplementation formula to placebo for 12 weeks	*Supplement*: 1,200 mg *N*-Acetyl cysteine, 100 mg Acetyl L-carnitine, and 400 mg α-lipoic acid. *Vitamins*: A 8000 IU, β-carotene 20,000 IU, C 1800 mg, 60 mg thiamin, 60 mg riboflavin, 60 mg pantothenic acid, 60 mg niacinamide, 60 mg Inositol, 50 µg. Biotin, 260 mg B_6, 2.5 µg. B_{12}, 400 IU vitamin D, 800 IU vitamin E, 300 mg Bioflavonoid complex, 800 µg folic acid, and 60 mg Choline. *Minerals*: 800 mg Ca, 18 mg Fe, 30 mg Zn, 400 mg Mg, 200 µg Se, 150 µg iodine, 100 µg Cr, 10 mg Mn, 2.0 mg Cu, 300 µg Molybdenum, 2.0 mg Boron, 99 mg Potassium, and 150 mg Betaine HCL, compared to placebo	Micronutrient supplement administered to HIV-infected patients taking stable ART significantly enhanced CD4 lymphocyte reconstitution
McClelland et al. 2004 [77]	400 HIV-infected women in Kenya Participants were not receiving ART	A double-blind, randomized, placebo-controlled trial of 6 weeks of multi vitamins plus selenium supplementation or placebo	*Supplement*: 20 mg thiamin, 20 mg riboflavin, 25 mg B_6, 100 mg niacin, 50 µg B_{12}, 500 mg vitamin C, 30 mg vitamin E, 0.8 mg folic acid, and 200 µg selenium, compared to placebo	Supplementation resulted in higher CD4 (+23 cells/µL, $p=0.03$) and CD8 cell counts (+74 cells/µL, $p=0.005$) than placebo, but increased genital shedding

(continued)

Table 30.2 (continued)

Authors	Population	Methods	Formula composition and selenium doses	Findings
Jiamton et al. 2003 [100]	481 HIV-infected men and women in Thailand with CD4 cell counts in the range of 50–550 cells/mm^3 Participants were not receiving ART	Randomized, double-blinded controlled clinical trial of micronutrient supplementation compared to placebo and followed for 48 weeks	*Supplement: Vitamins:* 3,000 μg vitamin A, 6 mg β-carotene, 20 μg or 800 IU vitamin D_3, 80 mg vitamin E, 180 μg vitamin K, 400 mg vitamin C, 24 mg thiamin, 15 mg riboflavin, 40 mg vitamin B_6, 30 μg vitamin B_{12}, 100 μg folacin, and 40 mg panthothenic acid; and *Minerals*: 10 mg Fe, 200 mg Mg, 8 mg Mn, 30 mg Zn, 300 μg Iodine, 3 mg Cu, 400 μg selenium, 150 μg Cr, and 66 mg cystine (Immunace®, Vitabiotics Ltd, London, UK), compared to placebo	Multiple micronutrient supplementation improved the survival of HIV-infected individuals with CD4 cell counts <200
Kelly et al. 1999 [98]	106 HIV-positive adults in Zambia with diarrhea-related wasting syndrome who were not on ART	Randomized, placebo-controlled clinical trial of micronutrient supplementation and 800 mg Albendazole compared to Albendazole alone	*Supplement:* 10,500 IU of vitamin A, 300 mg vitamin C, 300 mg vitamin E, 200 mg zinc, and 150 μg selenium given as three tablets of Selenium-ACE (Boots Co plc, Nottingham, UK) plus 800 mg of Albendazole, compared to Albendazole alone	Adding micronutrients to Albendazole did not significantly affect outcomes

CD4 cell counts. Jiamton et al. [100] supplemented a complex formula containing selenium that resulted in improved survival in those with advanced HIV disease (CD4 cell count<200 cells/mm^3) [100].

HIV/TB coinfection is one of the main causes of mortality in resource-limited countries [104, 105]. In a randomized controlled clinical trial in Tanzania, Villamor et al. [101] randomized 887 TB patients, of whom 471 were also HIV-positive, into a micronutrient formula containing selenium or into placebo. Supplementation increased CD3 and CD4 cell counts, decreased the incidence of extrapulmonary TB and genital ulcers in those who were HIV-negative, and reduced peripheral neuropathy by 57% irrespective of HIV status [101]. In addition, participants in a cohort study, that included patients infected with TB alone and patients coinfected with HIV and TB, were provided with a multivitamin/mineral supplement that contained 200 μg of selenium in their daily dose. This trial reported significant reduction in mortality in those supplemented who were coinfected with HIV and TB [102].

In summary, randomized clinical trials of selenium (using doses ≤tolerable upper intake of 400 μg/day for adults) [106] either with selenium alone (Table 30.1) or with multivitamin/mineral formulas that included selenium in the experimental intervention (Table 30.2) in HIV-positive patients have shown benefits on biomarkers of disease progression, morbidity and mortality. Further research is needed on the effect of selenium on other aspects of the disease such as HIV shedding, mitochondrial damage, and HIV transmission.

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