Nutrients and HIV:
Part One — Beta Carotene and Selenium

by Lyn Patrick, ND

Abstract
Micronutrient deficiencies are common in HIV/AIDS, resulting from both malabsorption and virally-caused depletion. Beta carotene and selenium deficiencies, two of the most common nutrient deficiencies, are important due to their dual function as nutrients necessary for immune modulation and as antioxidants. Beta carotene deficiencies are common in all stages of HIV/AIDS and may signal malabsorption. Supplementation has been shown to affect specific T-lymphocyte populations and decrease markers of lipoperoxides. Selenium levels are highly significant in predicting AIDS-related mortality; and the HIV virus manufactures selenoproteins that are involved in the regulation of viral replication, possibly depleting host levels of selenium. Supplementation trials with individual antioxidants have shown improvement in immunological parameters and decreased evidence of lipid peroxidation.
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Introduction

HIV infection involves a progressive immune dysfunction and loss of CD4 T cells leading to opportunistic infection, wasting syndrome, malignancies, or CD4 depletion significant enough to qualify as CDC-defined AIDS. Several research studies have indicated that the apoptosis of CD4 cells contributing to HIV progression does not result solely from HIV infection, but largely from antioxidant imbalances in the host.[1-3] Activation of latent HIV state can be stimulated in the presence of reactive oxygen species (ROS) through the stimulation of oxygen-responsive transcription factors, specifically NF-kB, which induces HIV replication in the infected T-lymphocyte. The number of reactive oxygen species can be reduced by restoring proper redox balance through adequate availability of antioxidants.

Micronutrient deficiencies are common in HIV, both in early and late stages of the disease. Tomaka[4] found in 129 patients with stratified T-cell counts all cohorts had similar prevalences of nutrient deficiencies. Among the three subgroups (CD4>500, CD4 200-500, CD4<200), each had similar occurrence of deficiencies: 38, 41, and 42 percent, respectively. Beta carotene and selenium figure prominently in these deficiency pictures. Their role as antioxidants provides a logical explanation for the widespread deficiencies of these nutrients seen in HIV and their therapeutic relevance.

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Table 1: Low Carotene Concentrations in HIV Patients and Controls

Population	# with low carotenes/ # studied (%)
Controls	0/33 (0)
All HIV patients	89/116(77)
HIV	19/25(76)
No GI infection	11/15(73)
GI infection	8/10(80)
No diarrhea	9/15(60)
Diarrhea	10/10(100)
AIDS	70/91(77)
No GI infection	43/55(78)
GI infection	27/36(75)
No diarrhea	39/47(83)
Diarrhea	31/44(70)

*(normal ≥ 0.88micromol/1)

No. with low carotenes*/no. studied/(%)

Beta Carotene in HIV/AIDS

Beta Carotene Deficiency

Beta carotene, a fat-soluble antioxidant, is a well-known scavenger of the singlet oxygen radical[5] and can decrease free-radical induced lipoperoxidation damage in HIV.[6]

Deficiencies of serum and plasma beta carotene and other carotenoids (including lutein and lycopene) have been observed in multiple studies in both HIV-positive and AIDS patients.[4,7,8] Depression of serum beta carotene levels is usually indicative of fat malabsorption and diarrhea, common complications of AIDS, secondary to general malabsorption, infection, and altered gut barrier function.[9] While pancreatic function appears to be normal in HIV/AIDS,[10] enterocyte function and villous atrophy occur even without intestinal infection.[11] Ullrich,[7] in a cohort of 116 HIV-infected individuals, found serum carotene concentration did not differ significantly between AIDS-diagnosed individuals who had diarrhea and those who did not: 77 percent of both groups had abnormally low carotene levels. In addition, serum carotene levels did not differ between HIV/AIDS patients with or without the presence of infectious agents in the stool or on intestinal biopsy: 76-percent infected and 77-percent noninfected individuals had abnormal serum carotene levels. The presence or absence of weight loss, fever, or secondary extra-intestinal infection did not correlate with alterations in serum carotene level. See Table 1.

In this study, CD4 percentages (r=0.364; 95% CI, 0.194-0.513; p<0.001), CD4 count (r=0.28; 95% CI, 0.101-0.441; p=0.0013) and the CD4/ CD8 ratio (r=0.38; 95% CI, 0.212-0.526; P<0.001), (but not leukocyte, lymphocyte, or CD8 counts) in peripheral blood correlated with serum carotene levels.

Favier et al[6] examined a cohort of 25 asymptomatic HIV-1 seropositive subjects in CDC stage II (mean CD4 396/mm^3) and 18 HIV-1 seropositive subjects in CDC stage IV (mean CD4 56/mm^3) and followed changes in their antioxidant status for six months. They found severe deficiencies of plasma carotenoids and beta carotene in both groups, and a significantly more rapid fall in the level of beta carotene in the CDC II group than the CDC IV group. The authors related this difference to increased levels of peroxidation in CDC stage II patients. Their malondialdehyde (MDA) and hydroperoxide levels were significantly higher (P<0.05) than in those subjects who had more advanced disease (CDC stage IV). They concluded the reduction in carotene levels was the result of increased antioxidant activity at this stage of HIV infection due to overproduction of oxygen radicals by polymorphonuclear leukocytes in CDC stage II. See Table 2.

Whether carotene depletion is due to malabsorption or increased free radical load or both, it appears to be consistently deficient in HIV-positive subjects. Omene[12] measured beta carotene levels in 15 African-American and Hispanic children. Those with HIV had 6.5 times lower levels of serum beta carotene than age-matched HIV-negative controls; the children with AIDS had a 13-fold lower level than HIV-negative controls. There were no significant differences in the levels of serum vitamin A or E in any of the groups. Periquet et al[13] looked at 21 HIV-1 positive children and found deficiencies of plasma levels of both lycopene (p=0.002) and retinol (p=0.023) but not beta carotene in the AIDS-diagnosed children (n=10).

Serum beta carotene and vitamin A levels were measured in 74 pregnant HIV-1 positive women in the first trimester and compared to pregnant HIV-negative women, also in the first trimester.[14] HIV-infected women with CD4 counts below 200 had 37-percent lower mean serum vitamin A and beta carotene levels when compared to controls (p<0.001). Both serum beta carotene and vitamin A levels correlated with percentage of CD4 lymphocytes, CD4 counts, and CD4/CD8 ratios (p<0.001). Lacey[8] found a significant depletion of plasma carotenoids in 35 HIV-positive individuals compared to controls (p<0.001). Plasma levels of four of the individual carotenoids were correlated with CD4 count, but beta carotene, and vitamins A, C, and E were not.

An evaluation of nutrient supplementation in 64 HIV-1 infected adults[15] revealed that even though 63-73 percent claimed they were taking some form of multi-vitamin,

plasma levels of total carotenoids were still lower than the HIV-negative controls (p=0.009). Lower CD4/CD8 ratios were correlated with lower carotene levels (p=0.02). Although the patients in this study who were taking antioxidant supplements had consistently fewer low concentrations of antioxidants no matter what their disease stage status (p=0.0006), 29 percent still had subnormal levels of one or more antioxidant.

Trials of Beta Carotene in HIV/AIDS

An early trial of 180 mg (300,000 IU) beta carotene in 17 HIV-negative volunteers resulted in a 30-percent elevation of CD4 cells after 14 days.[16] This was the first trial to suggest beta carotene could improve CD4 cell counts and led to further trials with beta carotene supplementation in HIV/AIDS.

Table 2: Beta carotene Levels in CDC stage II and IV Patients over Six Months

	baseline levels of carotene (microM/l)	levels at 6 months (microM/l)
CDC stage II	0.29 ± 0.21	0.17 ± 0.17
CDC stage IV	0.21 ± 0.25	0.22 ± 0.20

A single-blind, non-randomized trial in 11 symptomatic HIV-positive former intravenous drug users dosed 60 mg (100,000 IU) beta carotene twice daily for cycles of 20 days per month.[17] After the first 20-day treatment cycle, the researchers reported a remission of the symptoms of fever, night sweats, diarrhea, weight loss, and fatigue in all 64 patients – an improvement that lasted for the 24-36 month treatment period in all 11 patients. An analysis of another 53 patients, who had a follow-up period of 6-12 months, showed a similar trend. During the treatment period, two of the

original 11 patients progressed to AIDS while the remaining nine had a mean increase in their CD4 count of approximately 11.5 percent.

Fryburg[18] treated seven AIDS patients with 60 mg beta carotene twice daily for four weeks and then monitored them off beta carotene for six weeks. Total lymphocyte counts rose 66 percent at the end of the four-week period ($0.05 < p < 0.10$). In three patients with CD4 cells >10, the mean increase in CD4+ cells was 53+/-10 cells ($p < 0.01$). The CD4+ cells returned to pre-treatment levels at the end of the 10-week period.

Coodley administered 60 mg beta carotene or placebo three times daily in a randomized trial of 72 HIV-positive patients for three months.[19] Both groups were given a multi-vitamin and at the end of the study period there were no significant differences in blood parameters between the groups, either at baseline or at three months. Coodley was not able to replicate the cross-over study he had conducted three years prior. In this earlier study,[20] 21 patients were randomized to receive 60 mg beta carotene or a placebo for four weeks and then crossed over for the same amount of time. During the four weeks of treatment there were significant increases in WBC count ($p=0.01$) and CD4/CD8 ratio ($p=0.02$), and a 17-percent increase in CD4 ($p=0.02$) in both treatment groups. The addition of a multi-vitamin to both groups in the later study may have been a factor in the disparate results between the two studies.

A study of veterans with HIV,[21] receiving 60 mg beta carotene daily for four months, did not result in changes in CD4, CD8, or CD11 cell percentages, but did show significant increases in Leu 11, a marker for natural killer cells. Ia antigen and transferrin receptor, measurements indicating lymphocyte activation, were also elevated. This same phenomenon has been seen in immuno-competent subjects.[22]

Beta Carotene and Oxidative Stress

Other studies with beta carotene have indicated increased antioxidant activity. A study by Delmas-Beauvieux[23] examined 52 HIV-positive patients, randomized to receive either 250 mcg selenomethionine daily, 30 mg beta carotene twice daily, or placebo. At 12 months, data was available on 13 beta carotene recipients and 14 selenium recipients. Although CD4+ cell counts did not improve in either treatment group when compared to controls, glutathione levels were significantly higher in both treatment groups ($p < 0.01$ in the beta carotene group), and malondialdehyde levels (an indication of lipid peroxidation) were significantly lower in both the beta carotene ($p < 0.05$) and the selenium ($p < 0.01$) groups. In this study, the authors remarked that the beta carotene group had more advanced disease at baseline than the other two groups, based on ß-microglobulin elevations. Considering the advanced stage of these patients (CDC stagings were not available in the published data), it is interesting to note that 60 mg beta carotene was sufficient to raise plasma beta carotene levels from a median of 3 mcg/L to 305 mcg/L.

Several studies suggest oxidative stress in HIV may involve vascular and thrombotic dysfunction.[24] The theory that HIV-related antioxidant deficiency causes endothelial cell dysfunction (which puts HIV-positive patients at increased risk for atherosclerosis) was tested in a trial with selenium and beta carotene.[25] Thirty-six HIV+ patients were given either 250 mcg selenomethionine once daily, 30 mg beta carotene twice daily, or placebo. At 12 months the levels of thrombomodulin and von Willebrand factor (two markers of endothelial damage) were significantly elevated in the control group (48 and 28 percent, respectively), yet remained stable in the supplemented groups. Other indicators of endothelial damage (soluble E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular

cell adhesion molecule-1 (VCAM-1)) remained unchanged in all groups. The authors indicated this may be evidence of antioxidant-mediated prevention of further damage to the endothelium.

Selenium and HIV/AIDS

Selenium is required for the activity of the enzyme glutathione peroxidase — a key mediator of oxidant stress, other peroxidase enzymes (PHGHPX and GSHx-PI), and iodothyronine deiodinase (necessary for formation of triiodothyronine from thyroxine). Selenium deficiency is associated with immune dysfunction, impaired resistance to microbial and viral infections, inadequate phagocytosis and antibody production, impaired lymphokine production, natural killer cell cytodestruction, and decreased CD4 cell numbers.[26] Selenium deficiency may be instrumental in cardiomyopathy, skeletal myopathy, anemia, increased cancer risk, and oral Candidiasis.[27]

Viral Selenoproteins and HIV

Research has documented the existence of a selenium-based homolog of glutathione peroxidase produced by the HIV virus.[28] The gene has been cloned and theoretically the virus accelerates the depletion of selenium from HIV-infected lymphocytes, allowing the virus to replicate at the expense of the CD4 cells. There are other viruses that contain genes encoding selenoproteins: mouse mammary tumor virus, hepatitis B virus, coxsackie virus B4,[28] and hepatitis C virus.[29] Mouse mammary tumor virus is the only retrovirus in which selenium has demonstrated a tumor preventive effect in the host.[28] Patients who are co-infected with hepatitis C and HIV-1 have lower levels of selenium than HIV patients with the same stage of disease who are negative for hepatitis C.[30] And, in a cohort of 208 chronic hepatitis B or C carriers followed for an average of 5.3 years, risk for

hepatocellular carcinoma was directly related to plasma selenium levels.[31] Adjusted odds ratios for hepatocellular carcinoma (in increasing quintiles of plasma selenium) were 1.0, 0.52, 0.32, 0.19, and 0.62. The exact mechanism of viral replication or inhibition by these proteins is unknown: selenoproteins in viruses appear to regulate viral growth, both by inhibition and promotion, depending on the redox environment and the concentration of selenium in the host.[32]

Keshan disease, endemic to a region in China that has selenium-deficient soil, may be the result of a specific strain of coxsackie virus that becomes more virulent in a selenium-deficient host. Beck and co-workers[33] demonstrated that benign strains of coxsackie virus, specifically those isolated from a Keshan disease victim, became more virulent in selenium-deficient hosts due to point mutations in the virus. These point mutations can go on to invade even selenium-replete hosts and cause progressive myocardial damage. The same effects of the virus were seen in vitamin E-deficient mice. This is the first evidence of nutritional deficiencies altering viral genotype in a virus, and it is plausible the same mechanisms could occur in a retrovirus like HIV.[34]

There is compelling evidence for the role of selenium in the progression of HIV/AIDS. Selenium supplementation, *in vitro*, has been shown to suppress the replication of HIV in chronically infected T-lymphocytes.[35] In this study, selenium was suppressive in the presence of exogenous tumor necrosis factor-alpha (TNF-α), a cytokine that can be induced by inflammation. TNF-α has been shown to increase levels of oxidized glutathione and, *in vitro*, has been shown to directly increase HIV replication.[36] In latently infected T-lymphocytes, supplemented selenium has been shown to increase glutathione peroxidase levels and effectively reverse HIV-1 viral activation by protecting T-lymphocytes from the effects of H_2O_2 and subsequent NF-kB

Table 3: Blood Selenium Levels in AIDS Patients and Healthy Controls

	Red blood cells selenium (µg/ml)*	Plasma selenium (µg/ml)	Whole blood selenium (µg/ml)
AIDS	0.099 ± 0.03	0.043 ± 0.01	0.064 ± 0.016
Controls	0.13 ± 0.02	0.095 ± 0.016	0.109 ± 0.015
Significance †	p < 0.005	p < 0.001	p < 0.001

* Mean ± SD
† Student's *t*-test

Adapted from Campa A et al. *J Aquir Immune Defic Syndr Hum Retrovirol* 1999;20:508-513.

activation.[37] The latency of HIV disease may be related to a progressive selenium depletion,[38] virally-induced, through malabsorption, or insufficient intake.

Selenium Deficiency in HIV/AIDS

Selenium deficiency, more than any other micronutrient, has been documented to correlate with progression and mortality of HIV.[39] Selenium deficiency has been documented in both HIV and AIDS patients in both plasma and red blood cells.[27,30,38] See Table 3. Low selenium levels correlate with low glutathione peroxidase activity in HIV and AIDS. Low selenium levels have also been found in the myocardium of AIDS patients, possibly leading to dilated cardiomyopathy.[40] Autopsies of AIDS patients who died of cardiac failure have demonstrated cardiac histologies consistent with the cardiomyopathy described in Keshan disease, a disease that occurs with selenium deficiency.[27]

Children with HIV also appear to be at risk for selenium deficiency; a study of 23 pediatric HIV-positive patients in Boston concluded that 61 percent had low selenium levels. Selenium levels correlated with weight, serum albumin levels, and CD4 counts.[41] Frank selenium deficiencies have been found even in early stages of HIV infection. Mantero-

Table 4: Relationship Between Immune Function, Nutritional Status, and Survival

Variables	Number of children in this cell	RR	95% CI	*p* Value
Initial model:				
CD4 count < 200/mm³	6	6.33	1.54 - 26.00	0.01
Albumin < 3.5g/dl	5	2.7	0.59 - 12.36	0.2
Selenium ≤ 85 µg/L	8	4.19	1.17 - 20.3	0.03
Zinc ≤ µg/100 ml	11	1.16	0.23 - 5.74	0.86
Final model				
CD4 count < 200/mm³	6	7.05	1.87 - 26.5	0.004
Selenium ≤ 85 µg/L	8	5.96	1.32 - 26.81	0.02

CI = confidence interval
RR = relative risk

Adapted from Dworkin B et al. *J Parenter Enteral Nutr* 1986;10:405-407.

Atienza et al found frank deficiencies in 14.8 percent, and marginally low levels in 57.4 percent, of 54 asymptomatic HIV-positive males.[42]

A study of 104 HIV-positive individuals found a progressive deficiency of selenium, erythrocyte glutathione peroxidase, and plasma glutathione with progression of the disease.[30] Plasma selenium depletion was correlated with lowering CD4 counts in 89 HIV-positive patients.[43] Cirelli[38] and Constans[40] also documented selenium deficiencies that were more severe in patients with AIDS and AIDS-related complex (ARC) than in asymptomatic HIV patients.

Dworkin[27] examined levels of glutathione peroxidase and plasma selenium in 12 AIDS and eight HIV patients and found low levels of selenium correlated with total lymphocyte counts ($p < 0.001$). This correlation held regardless of malabsorption or diarrhea, indicating that deficiencies cannot be totally ascribed to malabsorption.

A study by Baum and colleagues at the University of Miami[39] studied mortality risk in HIV and found of all factors examined — CD4 count, anti-retroviral treatment, plasma levels of vitamins A, E, B6, B12, selenium, and zinc — only CD4 cells over time (RR= 0.69, $p < 0.04$) and selenium deficiency were significantly related to mortality. The relationship of selenium deficiency to mortality was striking: the relative risk of mortality with selenium deficiency was 10.8 ($p < 0.002$), indicating that selenium deficiency is an independent predictor of survival in HIV infections. Mortality risk also appears to be significant in children. The same group studied 24 HIV-infected children and found only CD4 counts below 200 and plasma selenium levels were significantly and independently related to mortality.[44] See Table 4.

Constans[45] also found selenium levels could predict outcome in 95 HIV-positive patients. Serum selenium correlated with CD4 count ($p < 0.0001$). Death and opportunistic infections (OI) were correlated with CD4 cells ($p = 0.006$ and 0.001, respectively) and serum selenium ($p = 0.01$ and 0.008, respectively). Other predictors of death and OI (p24 antigen levels, β-2-microglobulin levels) were not significant correlates.

Selenium Supplementation Trials in HIV/AIDS

Olmstead et al[46] gave 400 mcg daily of yeast-based selenium to 19 symptomatic HIV and AIDS patients. In 70 days the mean whole blood selenium levels had risen from 0.123+/-0.30 mcg/ml in the AIDS patients and

Figure 1: Reduced Glutathione (GSH) levels in Human Immunodeficiency Virus-Infected Patients.
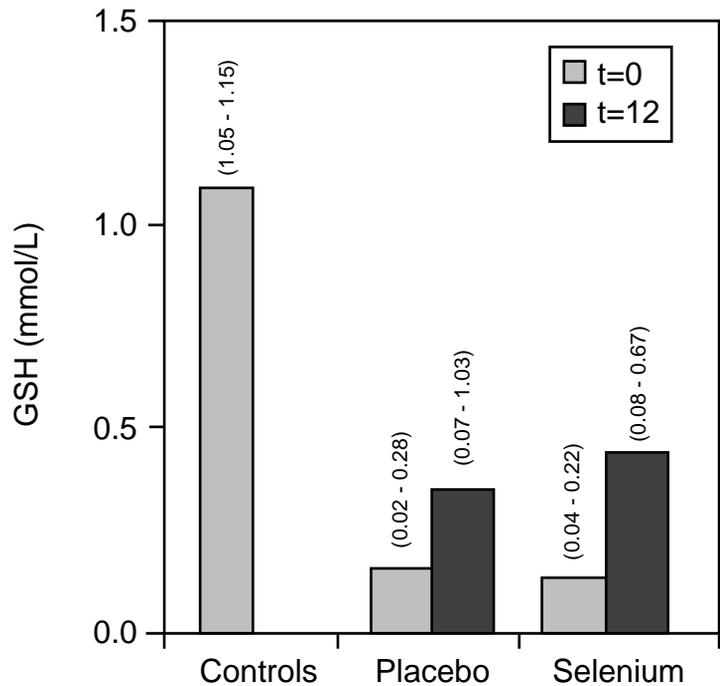
Graph represents values at baseline and after 12 months of supplementation. Median values are represented, minimum and maximum values are stated. Adapted from Delmas-Beauvieux MC et al., 1996[23]

Figure 2: Glutathione Peroxidase (GPX) Activity and Selenium
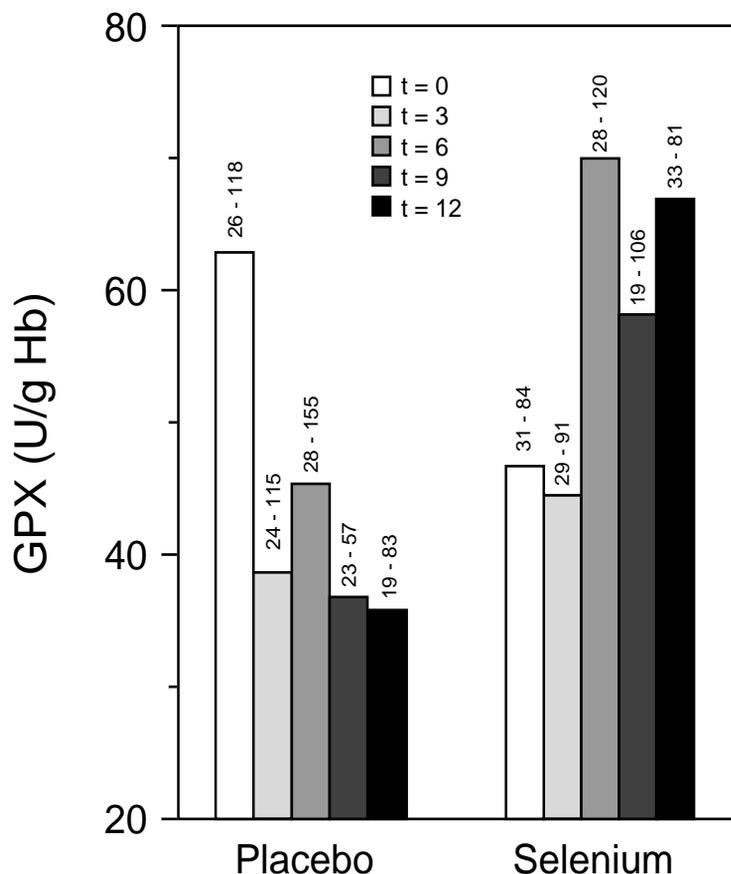
Values measured at baseline and at 3, 6, 9, and 12 months in two groups of HIV-infected patients. Median values are represented; minimum and maximum values are stated. Adapted from Delmas-Beauvieux MC et al., 1996.[23]

followed by 400 mcg (180 mcg selenium) daily for eight days. At the end of the treatment period, left ventricle-shortening fraction returned to normal in six patients, one patient died, and one was diagnosed and treated for thiamin deficiency in the interim.

Cirelli[38] administered 80 mcg selenium as sodium selenite and 25 mg vitamin E to eight patients with AIDS and three with HIV who were symptomatic. Serum selenium levels at the end of two months had risen from 0.77+/-0.23 mM/L to 1.44+/-0.41 mM/L (p<0.001). The control group of HIV-negative subjects had a serum selenium of 1.30+/-0.06 mM/L. There were, however, no parallel improvements in CD4 count, CD4/CD8 ratio, serum albumin, hemoglobin, or erythrocyte sedimentation rate. It should be noted, however, that the levels of both selenium and vitamin E (particularly vitamin E) supplementation were quite low.

Delmas-Beauvieux[23] and her colleagues investigated the effect of 100 mcg selenium (n=14) versus placebo (n=18) on HIV-positive individuals. Results were also compared to 26 HIV-negative healthy adults who took no supplementation. At the beginning of the study, levels of reduced glutathione were drastically lower in the HIV groups compared to the control group. See Figure 1. At the end of one year, the selenium group demonstrated a significantly higher level of both glutathione peroxidase (Figure 2) and reduced glutathione (Figure 1) than either the placebo or control group at baseline.

Many immunological functions in HIV disease are dependent on adequate amounts of reduced glutathione. Cellular apoptosis, the main cause of lymphocyte depletion in HIV, has been linked to glutathione redox status.[48] Supplementation with 100 mcg selenium daily

0.126+/-0.038 mcg/ml in the symptomatic HIV-positive patients (with AIDS-related complex) to a mean of 0.28 +/- 0.08 mcg/ml. Control group whole blood levels were 0.195 +/- 0.20 mcg/ml without supplementation. Fourteen patients reported subjective improvements, including improvement of gastrointestinal function, appetite, and diminished recurrent infections. Four patients reported improvement of oral Candidiasis although one developed oral Candidiasis during the trial.

In a pilot study, ten AIDS patients[47] diagnosed with non-obstructive cardiomyopathy (in whom eight had diagnosed selenium deficiencies) were given 800 mcg sodium selenite (360 mcg selenium) daily for 15 days

for 12 months stabilized levels of von Willebrand factor and soluble thrombomodulin in 10 HIV-positive patients. Levels of the same markers of vascular endothelial damage in 15 controls increased significantly (p<0.01).[25] The researchers concluded that both selenium and beta carotene had significantly, but not completely, prevented free radical-induced endothelial damage. It is possible higher doses of these antioxidants, alone or in combination with other antioxidants, may completely prevent endothelial damage.

Conclusion

Both beta carotene and selenium are deficient in a significant percentage of both HIV and AIDS patients. Their roles as antioxidants in HIV/AIDS appear to be related to both direct immune modulation and inhibition of cytokine and NF-kB activation, inhibiting HIV replication. Beta carotene has been shown to act directly as an immunomodulator by increasing natural killer cell function and improving CD4 count. As an antioxidant, beta carotene appears to support enzymatic defense systems involved in minimizing oxidative damage.

Selenium appears to decline consistently as HIV progresses. This deficiency is correlated with immuno-competence, and deficiencies can predict mortality. Selenium levels in HIV correlate with glutathione peroxidase levels and appear to act as a modulator of lipoperoxide-related activity. Trials of both antioxidants in HIV/AIDS patients have not been consistent, due to a wide variety of treatment protocols, but offer significant promise as adjunctive treatment in HIV/AIDS. The use of other nutrients, including other antioxidants, will be discussed in future articles. Because of the synergistic nature of antioxidants, a combination of several may provide the best therapeutic approach.

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