Why Nutrition Is Critical For Surviving HIV

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In the last issue of Choices, (July-August 1999, Vol. 3, No. 4) Dr. Alawode Oladele discussed the great importance of nutrition in the treatment of HIV infection. In this brief review, I will elaborate on some of the known and potential mechanisms involved.

Numerous studies have demonstrated that the intake or blood levels of various micronutrients are significantly correlated with disease progression or outcome (i.e., survival vs. mortality) in HIV-1 infection. These nutrients include vitamins B6 and B12, ?-carotene, zinc and selenium (Se); similar correlations exist for nutrition-dependent biomolecules like the antioxidant glutathione, which requires the amino acid cysteine. Deficiencies of these nutrients can have serious to profound effects on resistance to secondary infections, quality of life, and survival time.

Certainly, these correlations seem easily understandable in the light of our ever-expanding knowledge of the role of nutrition (particularly antioxidants and trace minerals) in supporting our natural immunity. For example, in protein malnutrition, even the formation of antibodies (which are proteins) is compromised. And correlations between some of the above-mentioned nutrients and general immunity have been widely documented in the general population in the past.

But is there something more profound going on in HIV infection, that goes beyond this general effect of nutrients on immunity? My answer is a resounding yes, and it relates to the fact that, of all the micronutrients, the most widely documented and statistically significant correlation with HIV disease progression and outcome has been demonstrated for Se status. This is of particular interest, because Se, although classified as a mineral, is a potent dietary antioxidant, and its cellular actions are intimately linked to the oxidative status of the cell, and thereby to the regulation of genes that are important for various immune cell functions. Because an extensive body of evidence shows that “oxidative stress” (increased free radical activity) and antioxidant defects like glutathione deficiency are hallmarks of AIDS, and that oxidative stimuli can activate HIV-1 replication in the test tube, it is not really surprising that Se should prove to be of critical importance in HIV-1 infection. But the core of the matter goes even deeper than that.

In 1994, based on a detailed analysis of the viral genome using "computational biology" techniques, my research group predicted the existence of several novel genes in HIV-1 (Taylor et al., J. Med. Chem. 37: 2637-54). The possibility that

several of these genes might encode Se-containing proteins (“selenoproteins”) also led us to predict that dietary Se levels may play a unique role in HIV pathogenesis and disease progression in AIDS, a prediction that has been strongly supported by several recent papers, e.g. Constans et al., J. AIDS, 10:392, 1995, entitled "Serum selenium predicts outcome in HIV infection" and Baum et al., J. AIDS, 15: 370-376, 1997, "High risk of HIV-related mortality is associated with selenium deficiency". In fact, over 20 papers have been published over the last decade documenting Se depletion in HIV/AIDS (reviewed in Biol. Trace Elem. Res. 56: 63-91, 1997). Furthermore, Se (as sodium selenite) has been shown to inhibit HIV replication by at least two independent labs. We have now shown that one of the potential selenoprotein genes predicted in HIV in 1994 is a virally-encoded homolog of glutathione peroxidase (GPx), the prototypical mammalian selenoprotein (J. AIDS, 15: 393-4, 1997). This gene has now been cloned and shown to have functional GPx enzyme activity when expressed as a selenoprotein in human cells, suggesting a novel molecular mechanism whereby HIV infection can contribute to the depletion of Se from infected cells, and thus exacerbate the effects of Se deficiency. Even more relevant to the pathogenesis of AIDS is the existence of HIV-1 nef gene associated selenoprotein coding potential, the essential features of which are highly conserved, in over 99% of worldwide HIV-1 isolates in the gene databases. The nef gene is considered to be the major source of HIV pathogenic effects; in fact, deletion of nef is the primary feature of experimental “live attenuated” HIV vaccines. A transgenic mouse incorporating the HIV-1 nef gene alone developed AIDS-like symptoms even though the rest of the virus was absent. Thus, I strongly suspect that nef-mediated Se-depletion in infected cells may be one of the primary effects of HIV that leads to immunodeficiency, especially because Se is known to be critical for cellular immunity.

The discovery of selenoprotein genes in HIV also provides a basis for understanding the role of many oxidative stress-inducing cofactors that are known to accelerate the progression of AIDS. HIV infection can be aggravated by cofactors such as malnutrition, coinfection with other microorganisms, and the use of various oxidant drugs, such as nitrites or “poppers”, which has been strongly correlated with the incidence of Kaposi’s sarcoma in HIV-infected individuals. Because the immune system generates free radicals to combat certain bacterial infections, and microorganisms like mycoplasma themselves generate free radicals, it is plausible that the common element in these cofactors is oxidative stress caused by antioxidant deficiency (in malnutrition) or oxidative stimuli (drug abuse and coinfections). Similarly, in hepatitis C virus (HCV) infections, progression to serious liver disease is associated with oxidative stressors (e.g. alcoholism and iron overload), which is significant because we have identified the same selenoprotein gene (GPx) in HCV. And in both HIV and HCV infection, there has always been a significant fraction of infected people who either never develop symptoms, or do so extremely slowly; it seems likely that nutritional status is one of various factors that may be involved in these cases.

The potential significance of the role of Se in AIDS can best be understood by analogy to another disease called Keshan disease, which is a classical Se deficiency disease, named after a region in China where outbreaks occurred because of the very low Se levels in soils of the region. Women and young children seem particularly susceptible to the disease, of which the primary symptom is a non-obstructive cardiomyopathy, leading to death by heart failure in severe cases. Due to the seasonal and clustered nature of outbreaks of the disease, Chinese investigators suspected the involvement of an infectious agent or other cofactor, and eventually isolated from the hearts of disease victims a virus called coxsackievirus, a relative of the common cold virus. The role of coxsackievirus in Keshan disease is strongly supported by demonstrations that a deficiency of Se can trigger a similar cardiomyopathy in coxsackievirus-infected mice, called "viral myocarditis". What is particularly intriguing (and frightening) is the finding by Dr. Melinda Beck and coworkers (Beck et al., Nature Med. 1: 433-436, 1995) that even a "benign" strain of coxsackievirus becomes virulent in Se-deficient mice, where it mutates into a more virulent strain that can produce myocarditis even in normal mice that are not Se-deficient.

Because Keshan disease was thought to be simply a Se deficiency disease, but proved to have a viral cofactor, it would not be unprecedented if AIDS and other chronic viral diseases like hepatitis B and C ultimately prove to be viral diseases with selenium deficiency as a major cofactor. There is also reason to believe that, like many other trace minerals, Se is being depleted from the food chain due to bad agricultural practices, and environmental changes like acid rain, which, in light of the above, could be a factor in “emerging” viral diseases.

A caution must be sounded that toxicity is a concern with Se supplementation; however, 200 micrograms (mcg) per day for adults is generally considered totally safe; that dose was used in a long term cancer prevention trial in the U.S. (Clark et al., JAMA, 276: 1957-1963, 1996). No adverse effects are expected for long-term uptakes of up to 400 mcg daily, or even up to twice that dose, according to some experts. However, because Se levels are tightly controlled by excretion, there is very unlikely to be any benefit in taking over 200 mcg unless GI malabsorption is present. As this is not uncommon, even in asymptomatic HIV positives, the best option in that case is to have your blood levels tested. Above all, remember that Se is likely to be most beneficial along with other antioxidants and vitamins, as part of a comprehensive nutritional program, which can be of benefit even to those on antiviral drug regimens. If antivirals are not an option (as for many people in developing nations), the nutritional approach to HIV treatment may be one of the most promising and low cost interventions available.