Antioxidant therapy and HIV infection: 1998¹,²

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During the past 2 y the outlook for HIV-infected individuals has improved markedly with the advent of combination antiretroviral therapies containing protease inhibitors. Whereas some have even suggested that HIV can be eradicated from the body, most authors suspect that therapy will be required for life. However, the stunning success of antiretroviral therapy has raised hopes that the infection, previously considered as an inexorable, fatal disease, will come to be a chronic, manageable problem.

The success of antiretroviral therapy has forced a reconsideration of the rationale of using alternative therapies, such as antioxidants, in HIV-infected individuals. Indeed, few people now speak of alternative therapies, referring instead to complementary therapies. The situation is complicated by the widespread familiarity with antioxidant therapy by the general public, by early widespread claims of efficacy and by its promotion and use before publication of definitive supporting data.

Because the absence of proof is not necessarily indicative of failure, and because antiretroviral therapies are limited for economic reasons to only ≈10% of HIV-infected individuals in the world, consideration of the potential for antioxidant therapy remains important. There could be great benefit from relatively low-cost antioxidant therapy, similar to the effect of vitamin A supplementation on childhood mortality in developing countries (1, 2). The major questions are as follows: What is oxidative stress? What are its causes? What are its consequences? What are the effects of antioxidant therapy?

Oxidative stress refers to overproduction of reactive oxygen intermediates (ROIs) with associated pathology. The major cause of oxidative stress is the body’s immune system, although toxic or traumatic injury also may lead to the release of lysosomes and oxidizing enzymes. Both neutrophils and activated macrophages release hydrogen peroxide and other compounds. Because HIV replication and anti-HIV immune reactions now are recognized to occur throughout the disease course, it is not at all surprising that the body is under continuous oxidative stress. The oxygen radical–generating process is self-perpetuating and does not self-extinguish.

The pathology of ROIs is related to oxidation of nucleic acids, chromosome breaks, and peroxidation of unsaturated fatty acids in cell membranes. Limited chromosomal damage can be repaired whereas extensive DNA damage promotes apoptosis of the affected cell. Oxidative stress may promote apoptosis, which is recognized as a major form of cell death of CD4+ lymphocytes in HIV infection (3). Apoptosis is not proinflammatory by itself, and is the result rather than the cause of oxidative stress. On the other hand, extensive membrane damage may lead to cell necrosis, with the release of lysosomal enzymes, which further generate ROIs.

HIV activation via nuclear factor κB (NF-κB) may be a more direct consequence of ROIs (4). This process may not be important if productive HIV infection is suppressed effectively by preventing viral assembly, as is the case with protease inhibitors, or by inhibiting the synthesis of HIV DNA and its integration into the host genome, as is the case with the reverse transcriptase inhibitors. NF-κB is a transcription promoter that may coordinate the body’s rapid response to a wide variety of pathogenic agents by activating many genes involved in inflammatory reactions, as well as many acute phase proteins (5). Normally, NF-κB is inactive and bound in cytoplasm to an inhibitor, factor I κB (I-κB). Compounds that have been found to release NF-κB from I-κB through ROIs include viral transactivators, bacterial lipopolysaccharides, cytokines, mitogens, phorbol esters, calcium ionophores, and protein kinase C (6). The activation is relatively specific for NF-κB, these agents do not activate all transcription factors, and not all cellular stressors affect NF-κB (6). These observations may explain the recent findings of enhanced HIV production during mycobacterial infections (7) and the transient rise in plasma viral burden that has been reported to occur after vaccination (8).

What other adverse outcomes can be attributed to oxidative stress? Reperfusion injury and adult respiratory distress syndrome are acute problems in which ROIs are felt to directly promote the pathologic process. Examples of subacute or chronic effects of ROIs include atherosclerosis and idiopathic or postinflammatory pulmonary fibrosis. No studies have linked oxidative stress with antioxidant depletion in HIV-infected patients. Semb et al (9, 10) showed that decreased serum concentrations of vitamin A in pregnant, HIV-infected women are associated with an increased risk of maternal-fetal transmission and decreased survival, but the studies did not evaluate the antioxidant system. There is little evidence to link oxidative stress with more rapid progression of immune deficiency, the most com-

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monly cited potential outcome in HIV infection.

Given these considerations, what would be necessary to prove that antioxidant therapy benefits HIV-infected individuals? Classically, clinicians consider that satisfaction of Koch’s postulates is proof of a cause-effect relation, although these criteria are more applicable for microbial pathogens. Bradford-Hill’s (11) epidemiologic criteria are more appropriate in determining cause and effect for HIV and include 1) strength of association (relative risk), 2) consistency (persistence of the effect in different studies by different investigators using different methods), 3) specificity of association (a distinct outcome related to exposure to an injurious agent), 4) temporality (the exposure precedes the outcome), 5) biological gradient (dose-response relation), 6) plausibility (biological reasonableness), 7) coherence (compatibility with present concepts of disease effect), 8) reversibility (targeted intervention changes the outcome), and 9) analogy (a similar relation is described in another condition). None of these epidemiologic criteria is absolute.

Allard et al’s (12) study in this issue of The American Journal of Clinical Nutrition shows both lower concentrations of antioxidant compounds and higher contents of the products of oxidative reactions in HIV-infected individuals than in noninfected individuals, and these findings are consistent with those of many but not all of the many studies published previously. Allard et al’s study does not prove that there was an altered cellular redox state in the HIV-infected subjects. Although the infected subjects did have lower steady state concentrations of antioxidants than the noninfected individuals, there still may have been effective consumption of free radicals, with a decrease in antioxidant reserve. On the other hand, a time delay in the quenching of ROS because of diminished concentrations of antioxidant factors could lead to chronic tissue injury.

The present study, along with others, satisfies Bradford-Hill’s criteria of consistency of association, plausibility, coherence, and analogy between HIV infection and the existence of oxidative stress. Several other studies suggest that treatment may improve antioxidant defenses, decrease HIV production in vitro, or even affect clinical outcomes (13–17), although again some studies have not found evidence of benefit (18–20). However, no published clinical study has been evaluated formally for the strength or specificity of association, biological gradient, or reversibility of the adverse outcome. Until such studies are done, it is impossible to determine whether antioxidant therapy should become a standard part of the therapeutic regimen for an HIV-infected individual. Whereas an individual patient or caregiver may decide that the potential benefits of antioxidants exceed the potential risks and choose to pursue therapy, general recommendations as to type or dose of antioxidants cannot be made.

Thus, the potential for therapeutic benefit from antioxidant therapies remains questionable. The relation between HIV viral content and oxidative stress as well as the effect of current antiretroviral therapies on oxidative stress need to be determined. It is possible that maintenance of antioxidant defenses will be more important as survival is prolonged indefinitely because the accumulation of tissue damage due to oxidative stress may take a long time to manifest. It also is possible that antioxidant therapy would be more beneficial in acute rather than chronic conditions because oxidative stress is much greater during acute processes, such as opportunistic infections, than during periods of clinical stability.

REFERENCES

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