~ Lipoic Acid (Thioctic Acid) ~

Alpha-lipoic acid (also known as thioctic acid) is an extremely important antioxidant which quenches many different reactive oxygen species, including hydroxyl radicals, hypochlorous acid, and singlet oxygen.[1] It readily crosses cell membranes and works as an antioxidant in both lipid and aqueous parts of the body. In other words, it can counter many different forms of oxidative stress and prevent the cellular damage they might cause. It both directly reduces oxidative stress in the body and indirectly spares or recycles or regenerates the other major antioxidants, raising their levels in the bloodstream.[2] It can recycle vitamin E from its oxidized form back to its reduced form (in which it again becomes an antioxidant),[3] thus helping to protect cell membranes. Vitamin C can also be regenerated through reaction with alpha-lipoic acid,[4] as can glutathione. In fact, alpha-lipoic acid has been shown to protect against the symptoms of vitamin E or vitamin C deficiency in animals fed diets deficient in those nutrients.[5] One small study (10 HIV+'s in CDC Stage 4) showed a combination of effects from supplementation with alpha-lipoic acid including increases in blood levels of vitamin C and glutathione, increases in CD4 cells, and decreases in the body compounds that result from oxidative stress.[6] The latter shows that it was indeed working well as an antioxidant. Although most of the HIV community has focused in the past on NAC as a way to raise glutathione, research carried out by Dr. Lester Packer at the University of California at Berkeley has shown that alpha-lipoic acid may be the best way to raise glutathione levels in people living with HIV.

Alpha-lipoic acid is very important to the liver cell metabolic pathways and can be rapidly depleted when the liver is under stress. In Europe, it has long been used in the treatment of hepatic disorders because of its liver-sparing effects which can help the liver repair. Although later research has shown that it is not specifically helpful for mushroom poisoning or alcoholic liver degeneration (two things for which it had been used in the past), there are other causes of liver damage for which it may be quite useful. Its effectiveness in raising cellular glutathione levels is probably very important for liver repair with a disease like HIV that induces glutathione deficiency. Especially when used in combination with silymarin, I have seen it work quite well to reduce elevated liver enzymes, even in some people in whom the levels had been elevated for quite some time. Some of my clients, in fact, have successfully used this combination to lower enzymes sufficiently to get into clinical trials of various drugs, where too-high liver enzymes would have otherwise excluded them. [For additional information on silymarin and other useful therapeutics for liver repair, see *Chapter Nine, Treatments for Liver Problems*.] Its combined usefulness in repairing the liver and working as an antioxidant has led to its extensive use in Europe for radiation sickness, drug poisonings, and chemical overdoses. It may provide some protection against the damage induced by radiation therapy during cancer treatment.

In addition, both *in vivo* and *in vitro* research has shown potential for alpha-lipoic acid to serve as an antiretroviral agent. It has been shown to inhibit replication of HIV in both acutely and chronically infected cells by a mode of action different than that of nucleoside analogues. *In vitro*, alpha-lipoic acid has been shown to have synergistic effects when combined with AZT, with the combination of the two showing stronger inhibition of HIV replication than either had when used alone.[7] *In vitro* research done at Kumamoto University in Japan has shown that alpha-lipoic

acid significantly depresses both HIV tat gene activity and HIV infectivity, and is active in both acute and chronically infected cells.[8] Other *in vitro* research done in the Department of Molecular and Cell Biology at the University of California, Berkeley, has shown that alpha-lipoic acid inhibits NF-kappa B activity.[9] German *in vitro* research has also shown that alpha-lipoic acid inhibits the infectivity of virus particles and suppresses viral replication, and follow-up *in vivo* studies by the same researchers showed that it does have antiviral effects in HIV+'s, reducing viral titers just as had been predicted by the *in vitro* research.[10] Since, as discussed in *Chapter Seven*, NF-kappa B is, in essence, an on-off switch for the activation of HIV, and tat inhibition is considered a promising antiviral approach, and anything non-toxic that effectively suppresses viral replication and reduces infectivity is immensely desirable, alpha lipoic acid may be a very important part of a comprehensive antiviral approach. So why haven't other researchers been rushing to pursue its antiviral possibilities? Gee, it couldn't be because it's unpatentable and, thus, unlikely to be profitable, do you think?

Alpha-lipoic acid has long been used in Europe for the treatment of peripheral neuropathy in diabetics. A number of controlled clinical trials have shown its usefulness for reducing both the pain and numbness suffered by those with diabetic neuropathy, and its use for this condition is approved in Germany.[11] Although I have not yet heard of any reports of its successful use for this in those living with HIV, I will watch with interest those who try it. Its antioxidant properties may help protect the nerves from the inflammation and oxidative damage that HIV induces, as has been shown to be true with diabetic neuropathy.[12] Alpha-lipoic acid is also a true oral chelating agent that has been widely used in Europe in the treatment of heavy metal toxicity caused by chemicals such as arsenobenzoles, mercuric chloride, and carbon tetrachloride. Thus, it is possible that it might be removing something that is toxic to nerves. Because of its liver protective and antioxidant benefits, it has been included as a component of the programs of many of my clients for several years now. It may have contributed to the success of the neuropathy elimination programs some of them have used. [For information on other nutrients used for eliminating neuropathy, see *Biotin*, above, and *Chapter Nine, Treatments for Neuropathy*.]

Alpha-lipoic acid may also be useful for cognitive dysfunction in HIV disease. Tissues of the central nervous system are known to be particularly vulnerable to oxidative stress because of their high rate of oxygen consumption and high mitochondrial density. The mitochondria produce lots of free radicals during normal oxidative metabolism and, especially without sufficient antioxidant protection, the mitochondrial tissue may be damaged. It is believed that this sort of oxidative stress damage may be partially responsible for neurodegenerative diseases.[13] In animal studies, alpha-lipoic acid has been shown to improve memory, apparently by reversing the damage that had been induced by oxidative stress.[14] Although no research has been done to look at the possible usefulness of alpha-lipoic acid for neurocognitive degeneration in people living with HIV, it is certainly an interesting possibility.

Because it not only appears to be non-toxic but also may improve T-cell function, while helping keep the liver healthy (especially where there is long-term drug usage that may adversely affect the liver), serving as a powerful antioxidant, and possibly protecting the nerves, it seems like an extremely useful part of a total integrated approach. If it also has an antiviral effect, so much the better.

[Many people take 100-200 mg, three times per day with meals, sometimes increasing the

amounts when liver enzymes are elevated or neuropathy is present. 100 mg capsules are available in Cardiovascular Research's Thioctic; 300 mg tablets are available in the European product Thioctacid 300; usual doses are 300-600 mg per day; no known toxicity; one report shows possibility of thrombocytopenia (decreased platelets) from higher doses; because it is an effective mineral chelating agent, some writers have raised the question of whether lipoic acid might remove important minerals; although no problems have been observed at the doses listed here, to err on the side of safety, its use could be accompanied by the daily intake of a good multiple vitamin/mineral supplement and an iron supplement, and blood cell tests (RBC and platelets) could be monitored while it's being taken; the standard CBC that anyone living with HIV should be doing regularly anyway should suffice; there need be no concern, however, about taking it with meals or supplements because any chelating effect that it has occurs in the liver, not the stomach; thus, it will not adversely affect your uptake of nutrients.]

1. Packer L, Witt EH, and Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. *Free Radical Biology & Medicine* 19(2):227-250, 1995.

2. Fuchs J, et al. Studies on lipoate effects on blood redox state in human immunodeficiency virus infected patients. *Arzneimittel - Forschung/Drug Research* 43-2(12):1359-1362, December, 1993; Scott BC, et al. Lipoic and dihydrolipoic acids as antioxidants: A critical evaluation. *Free Radical Research* 20(2):119-133, 1994; Han D, Tritschler HJ, Packer L. Alpha-lipoic acid increases intracellular glutathione in a human T-lymphocyte Jurkat cell line. *Biochem Biophys Res Commun*. 207(1):258-264, February 6, 1995..

3. Packer L, Witt EH, and Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. *Free Radical Biology & Medicine* 19(2):227-250, 1995; Sies H. Strategies of antioxidant defense. *European Journal of Biochemistry* 215:213-219, 1993.

4. Packer L, Witt EH, and Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. *Free Radical Biology & Medicine* 19(2):227-250, 1995.

5. Rosenberg HR and Culik R. Effect of α-lipoic acid on vitamin C and vitamin E deficiencies. *Archives of Biochemistry and Biophysics*. 80:86-93, 1959.

6. Fuchs J, Schofer H, Milbradt R, et al. Studies on lipoate effects on blood redox state in human immunodeficiency virus infected patients. *Arzneimittel-Forschung/Drug Research* 43-2(12):1359-1362, December, 1993.

7. Bauer A, Harrer T, Peukert M, et al. Alpha-lipoic acid is an effective inhibitor of Human Immuno-deficiency Virus (HIV-1) replication. *Klin Wochenschr* 69:722-724, October 2, 1991.

8. Shoji S, Furuishi K, Misumi S, et al. Anti-HIV effects of redox reagents on HIV-1 infected cell lines. *10th International Conference on AIDS*, Yokohama, Japan, August 7-12, 1994, 10(2):114, Abstract # PA0336; Shoji S, Furuishi K, Misumi S. Thiamine disulfide as a potent inhibitor of human immunodeficiency virus (type-1) production. *Biochem Biophys Res Commun*. 205(1):967-975, November 30, 1994.

9. Suzuki YJ and Packer L. Inhibition of NF-kappa B DNA binding by alpha-lipoic acid. *10th International Conference on AIDS*, Yokohama, Japan, August 7-12, 1994, 10(2):27, Abstract #401A; Packer L and Suzuki YJ. Vitamin E and alpha-lipoate: role in antioxidant recycling and activation of the NF-kappa B transcription factor. *Mol Aspects Med*. 14(3):229-239, 1993; Suzuki YJ, Aggarwal BB, and Packer L. Alpha-lipoic acid is a potent inhibitor of NF-kappa B activation in

human T cells. *Biochem Biophys Res Commun*. 189(3):1709-1715, December 30, 1992.

10. Baur A, Harrer T, Peukert M, et al. Inhibition of HIV-infectivity and replication by alpha-lipoic acid. *7th International Conference on AIDS*, Amsterdam, The Netherlands, Abstract Book 1:110, Abstract #M.A.1075, June 16-21, 1991.

11. Packer L, Witt EH, and Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. *Free Radical Biology & Medicine* 19(2):227-250, 1995.

12. Kèhler W, Kuklinski B, Ruhlmann C, and Plotz C. Diabetes mellitus-α free radical-associated disease: Effects of adjuvant supplementation of antioxidants. In: Gries FA and Wessel K (Eds.) *The role of anti-oxidants in diabetes mellitus: Oxygen radicals and anti-oxidants in diabetes*. Frankfurt am Main: pmi Verl.-Gruppe, 1993:33-53.

13. Packer L, Witt EH, and Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. *Free Radical Biology & Medicine* 19(2):227-250, 1995.

14. Stoll S, Hartmann H, Cohen SA, and Müller WE. The potent free radical scavenger α-lipoic acid improves memory in aged mice: Putative relationship to NMDA receptor deficits. *Pharmacol. Biochem. Behav*. 46:799-805, 1993.