Counteracting Inflammation and Tumor Necrosis Factor

Since HIV-caused inflammation, and increased production of unstable free-radicals, play a role in causing or contributing to most of the symptoms described in this guide, the idea of counteracting that inflammation is appealing. A distinct feature of HIV infection is that inflammation becomes exaggerated, generalized and dysfunctional. Certain parts of your immune system become locked into overdrive while other parts diminish. This is known by researchers as *HIV immune hyperactivation*. Various studies have identified different aspects of immune function that go overboard, including defects in B cell function, increases in antibodies including IgG (causing hypergammaglobulinemia) and IgE (an antibody often seen in high levels in allergic reactions), along with high levels of TNF-alpha, IL-4, reduced vitamin E levels, the overproduction of certain cellular messages such as prostaglandin E2, and so forth.

Cytokines are cell-produced proteins that act as messengers, telling the cell to respond in certain ways to local conditions. Several inflammatory cytokines have been seen to be elevated in HIV, contributing to viral activation, high levels of free-radicals, body-wide damage, and wasting. Different types of infections result in different patterns of cytokine expression, and certain cytokines appear to be over-produced in HIV disease. These include *tumor necrosis factor-alpha (TNF*), *interferon-alpha,* and various *interleukins* (IL-1, IL-4, IL-6, IL-10). The interactions between all of these are complex and cyclical.

The more the inflammatory cytokine TNF is present, the more free radicals are produced by the cells, and without sufficient antioxidant protection, the more the cellular switches producing TNF are activated. A cell over-burdened with too much TNF also stimulates further production of other inflammatory cytokines, notably IL-1 and IL-6. The more TNF and free radicals are increased, the more free radical-sensitive switches on the cell tell HIV to become ever more activated. With increased HIV activation, there is increased production of HIV proteins which are, in themselves inflammatory. All this free radical production leads to body-wide inflammation, and the depletion of the primary antioxidants that cells use to protect themselves against free radicals. The depletion of the fundamental antioxidant found inside the cell, glutathione, makes the switches inside cells ever more sensitive to free radicals and in turn induces the cellular switches to begin producing more and more inflammatory messengers (cytokines) and other inflammatory by-products (prostaglandins and leukotrienes), including more inflammatory HIV proteins.

To counteract these inflammatory processes, there are certainly a number of drugs that suppress TNF and inflammation, but there are several problems with long-term use of such drugs. One problem is that over-suppressing the inflammatory response might increase the risk for infections (since the inflammation is part of the immune system's way of countering infections). Indeed with one of the injectable anti-TNF drugs, etanercept (Enbrel), there are a growing number of lawsuits filed by persons (or if they died, by their families) who developed life-threatening infections. In addition, a weaker group of anti-inflammatory oral drugs known as NSAIDs, which do not work directly on TNF, can cause many side effects, particularly gastrointestinal irritation and bleeding.

Perhaps the best anti-inflammatory is a simple buffered aspirin. As long as you don't have most bleeding problems (and even overpriced stuff like Plavix can cause bleeding problems—in fact it may be worse than aspirin). For most, aspirin is the first and best anti-inflammatory and analgesic (pain reliever)!

For these reasons, it would appear much less risky to use foods and nutraceuticals that have natural anti-inflammatory qualities. Because such substance have been used for thousands of years with no apparent adverse effects on immune responses, it seems likely that long-term consumption of them would be considerably safer than long-term use of drugs. Their anti-inflammatory effects would be much more subtle, but might still provide substantial benefit. Included on the list of naturally anti-inflammatory foods and seasonings would be garlic, ginger, curcumin, bioflavonoid-rich fruits, and omega-3 fatty acid-rich foods like fatty fish, flaxseed, and walnuts.

Eating fatty fish (such as salmon, mackerel, sardines, tuna, cod and halibut) is a particularly good source of anti-inflammatory omega-3 fatty acids. Eating several meals weekly that contain such fish would be a good idea. Remember, though, that deeply fried or canned fish have lost much of the value of the omega-3 fatty acids and thus it's better to eat fresh or frozen fish. Ground flaxseed, which can be eaten with cereal or added to casseroles or soups or other foods, is also a rich source of omega-3s. Eating a handful of walnuts several times per week will also contribute to your total intake of these important fatty acids.

The green, yellow, orange, red, blue, and purple fruits and vegetables are particularly important sources of antioxidants, almost certainly including many that science has yet to discover. Dark-skinned berries and other bioflavonoid-containing fruits and vegetables and quercetin-containing foods like onions and garlic may also have anti-inflammatory benefits. Researchers at Tufts University have identified a list of the most potent antioxidant fruits and vegetables. Listing strongest first, they include: blueberries, blackberries, garlic, kale, strawberries, spinach, brussels sprouts, plums, alfalfa sprouts, broccoli florets (the flower part, not the stem), beets, oranges, red grapes, red peppers, cherries, kiwis, pink grapefruits, white grapes, onions, corn, eggplant and cauliflower. Even chocolate: (especially dark) can provide a measure of cardioprotective flavonoids and other minerals (YES! You knew that anything that tasted that

good had to be healthy in some way, right?). NOTE: Some foods, like garlic, may interact with some drugs, such as blood-thinning drugs, and so should be used only after careful discussion with your physician.

The red pigment that colors watermelons, strawberries, and tomatoes is *lycopene*, one of the most powerful antioxidants ever tested. Research carried out at the Aviano Cancer Center in Italy has shown that people who eat raw tomatoes at least seven times each week decrease their risk of stomach, bladder, and colon cancers by half. Research at Harvard University has shown that men who eat ten servings or more of foods made from tomatoes each week (including pizza and pasta sauces) cut in half their risk of developing prostate cancer. Those who eat four to seven servings of tomato-based foods decrease their risk by 20 percent.

Another red pigment is *betacyanin*, an antioxidant found in beets which is not only a powerful cancer preventive but also suppresses the growth of bacteria. The pigment that gives cranberries, pomegranates, radishes, and red cabbage their red color is an *anthocyanin*, one of a class of powerful antioxidants that have been shown to neutralize several common carcinogens.

Other forms of anthocyanins make blueberries blue, eggplants purple, blackberries deep purple, and grapes red or purple. Both orange fruits and vegetables (carrots, yams, cantaloupes, butternut squash), yellow vegetables (yellow peppers), and leafy green vegetables (spinach, kale, mustard greens) contain large amounts of beta-carotene, another powerful antioxidant. These and other vegetables and fruits also contain many of the other more than 600 carotenoids, pigments whose color ranges from pale yellow to orange to deep red. Potatoes and cauliflower contain pale yellow pigments called anthoxanthins that also work as antioxidants. Selenium, a mineral involved in critically important antioxidant activities, is found in high concentrations in Brazil nuts.

Green vegetables (green beans, collard greens, watercress, broccoli, chard, spinach, and so on) contain chlorophyll, another pigment that may provide significant protection against cancer. Lutein, the yellow pigment that colors corn, is a powerful antioxidant that may reduce cancer risk. Along with a green pigment called zeaxanthin, lutein may also help prevent the development of macular degeneration of the retina.

The U. S. Department of Agriculture has a new online database on dietary flavonoids. The new database provides flavonoid values for approximately 220 foods, "By knowing the flavonoid content of foods," she continued, "researchers can assess dietary intakes of flavonoids and perhaps one day identify relationships between those intakes and various chronic-disease risk factors. For more information on this topic, visit HeartCenterOnline's Diet & Nutrition Center http://www.heartcenteronline.com/myheartdr/home/.

NYBC Nutraceuticals for Counteracting Inflammation and Tumor Necrosis Factor:
Berry High is a combination of fruit and berry powders rich in antioxidant flavonoids.

Borage Oil. From the seeds of the borage plant, borage oil is a good source of essential fatty acids (EFAs) , in particular gamma linoleic acid (GLA). Its high GLA content balances the alpha-linolenic (omega-3) and linoleic acid (omega-3) content of flaxseed oil; taken together they provide a complete EFA profile.

Flaxseed Oil Flax oil, derived from the seeds of the *Linum usitatissimum* plant, contains a variety of essential fatty acids, particularly the omega-3 and omega-6 “polyunsaturated” fatty acids. It is also known as “linseed oil.” It may have some benefit in improving fatty acid profiles (e.g., cholesterol) and alleviating rheumatoid arthritis, although one small study showed no benefit. Other small studies, though, have shown some small benefit for the autoimmune disease lupus (as measured by urinary protein) and, interestingly, antimalarial effects.

The effect of these oils is to reduce inflammatory processes. Borage or flaxseed oil may help modestly to reduce TNF levels, however the data on their ability to do so is somewhat mixed. Their better benefit is that they contain healthful omega-3 fatty acids. From the evidence that exists so far, a daily amount of flax and/or fish oil makes good sense. If you eat fresh or frozen fish every day, you probably don’t need to supplement. (You may also use **Max DHA**, Jarrow’s fish oil instead of this.)

Carnitine is available in two forms but it is really the acetylated form which appears to penetrate mitochondria and substantially reduce inflammation inside the cell: L-carnitine (which can be prescribed; the brand name is Carnitor), which should be taken in doses of 1000 to 2000 mg, three times per day; and L-acetyl-carnitine (available over the counter), which should be taken in doses of 500 to 1000 mg, three times daily. Note that L-acetyl-carnitine will release four times the amount of free carnitine into the bloodstream, compared to an equivalent dose of plain L-carnitine. Thus, higher doses of L-carnitine are needed to achieve the same effect.

Carotenoid Complex UltraAntioxidant is a very broad-spectrum, potent combination of the most powerful carotenoids available, including lutein, zeaxanthin, lycopene, alpha carotene, astaxanthin, beta carotene, gamma carotene, astaxanthin

complex and a broccoli extract. These are fat-soluble chemicals that provide the richness of color to many fruits and vegetables: the yellows, reds, purples. Collectively, they help to reduce free radical activity in the fatty parts of cells (like the membrane). Many studies have been undertaken examining the effects of the single agent, beta carotene. They have not had very remarkable results, unfortunately. The best, perhaps, were in women that were HIV+, if they took beta carotene, their kids may have been born with a higher birth weight than had they not used the supplement. Other data suggested that there may have been even a slightly increased risk for the mother passing the virus to her child. However, carotenoids work in tandem with both other physiologically relevant carotenes (as found in fruits and vegetables like tomatoes) as well as working with B vitamins and so forth. And the synthetic form commonly used may not be as beneficial as the natural form because, while it is the same basic make-up, it can come in forms that are shaped differently (*isomers*) and at least one study supports this notion (see *Am. J. Clin Nutr*. 1996;63:729-734), at least when it comes to the beta carotene. Adding these other carotenoids may be of help if you simply will not or cannot eat enough fruits and vegetables. Whether it adds a benefit or not has not been studied either for people in general, people with HIV or for those who do eat a lot of fruits and vegetables.

Flaxseed Oil See Borage Oil, above.

Garlic Bulb (*Allium sativum*): Numerous beneficial cardiovascular effects have been reported for garlic including its ability to lower cholesterol, thin the blood, lower blood pressure, and prevent atherosclerosis. The majority of these effects appear to be associated with a compound known as allicin, which is lacking from odorless and aged garlic products as well as some oils and tinctures. Garlic can be consumed as a regular part of the diet or as a supplement. If using supplements, the product should be characterized on allicin potential or allicin yield as an enteric-coated tablet to prevent degradation of beneficial compounds by stomach acid.

Allicin is pharmaceutical-grade liquid garlic extract. Allicin has the greatest activity of garlic's sulphur-containing compounds. Garlic should not be taken by HIV+ people with low platelets. If taking high dose garlic with an impaired liver, you should always use in conjunction with alpha lipoic acid. 2001 data indicate that garlic supplements may interfere with blood levels of efavirenz (Sustiva or Stocrin), however it is unclear if the findings were clinically relevant. **Garlicin Pro** (MMS Pro) has enterically-coated tablets containing 350 mg of garlic powder from the bulb. Each tablet is guaranteed to contain 2.5 mg of Allicin. (A good product for those who experience a strong aftertaste or repeat with aged garlic formulas.)

Caution: High doses of garlic are prohibited prior to surgery. Those with bleeding disorders or on blood-thinning medications should only use therapeutic doses of garlic under the care of a qualified health care professional. Also HIV+ people using HAART should consult their physician since this herb can effect blood levels of antiretrovirals.

Ginger is another potent natural anti-inflammatory available in capsule form. You can also chop ginger root which can be added to many dishes where it will add its spicy flavor, along with its ability to counter inflammation. It can also be consumed by drinking ginger tea. Chop up two or three tablespoons of fresh ginger root and add to a cup or so of boiling water. Then simmer this for at least five to ten minutes and drink several times daily. You can add lemon or pasteurized honey if you'd like to flavor this tea. The commercially available capsules may be more convenient.

Grape seed Grape Seed Extract 95% proanthocyanidins is, along with bilberry extract, possibly one of the most potent botanical anti-inflammatories. Proanthocyanidins are particular types of bioflavonoids, also found in lesser quantities in pine bark extract, and in blueberries (and more so in their wild counterpart bilberries) as well as cherries and other fruits and vegetables. Tufts University found blueberries to be the most concentrated source of antioxidants that they measured. They did not measure grape seed or bilberries. You can find this in the **Phytoflavonoid Complex**.

Nettle Leaf Extract Pharmaceutical Grade has been used effectively to treat body-wide inflammation in Europe. There are a small number of European studies which show it suppresses Tumor Necrosis Factor and IL1, as well as other inflammatory mechanisms.

Nettle is an herbaceous perennial, infamous for the stinging hairs on its leaf and stem. The genus name is from the Latin "uro" (to burn) in reference to the painful rash caused by its biting hairs. The herb grows in fields, moist thickets and along roadsides and can be found throughout North America and Europe. Nettle has been used since ancient times as a medicinal plant. The Greek physicians Dioscorides and Galen used nettle leaf to treat asthma and pleurisy. During the late 19th and early 20th centuries, Eclectic physicians used this highly nutritious herb to treat eczema and chronic cystitis.

The mechanism(s) of action of nettle leaf remains unclear. Several studies have investigated nettle and its constituents and their affects on the immune system. During the inflammatory response substances such as histamine, leukotrienes, prostaglandins, and inflammatory cytokines such as TNF are released causing a variety of symptoms known

as inflammation and oxidative stress. In vitro and ex vivo studies have found that nettle leaf extract effectively inhibited prostaglandin and leukotriene synthesis and suppressed pro-inflammatory cytokine production.

Phytoflavonoid Complex Ultra-Antioxidant is a potent and broad array of standardized extracts including grape skin and grape seed extract, green tea extract, curcumin, milk thistle, hawthorn and ginger. See the individual entries on each of these. Grape seed extract is the preferred source of the flavonoid molecules known as OPCs. These compounds are among the most potent antioxidants known. One of the advantageous features of OPCs' free radical-scavenging activity is that it's incorporated within cell membranes, with the ability to protect against both water and fat soluble free radicals. Recent studies indicate the antioxidant activity of OPCs may be as much as 50 times stronger than Vitamin E and 20 times stronger than Vitamin C. The substantial amount (750 mg) of Green Tea extract in this Ultra-Antioxidant is the most potent form available. Phytoflavonoid Complex Ultra-Antioxidant is an "all-in-one" formula that may be good for those who wish to use all of the spectrum of antioxidants for their distinctive benefits (e.g., curcumin as an anti-inflammatory, milk thistle for the liver, hawthorn for the heart, ginger for the digestive processes).

Quercetin with Bromelain is a combination of the bioflavonoid Quercetin and bromelain, a group of digestive enzymes that helps to digest protein. Do not use if allergic to pineapple, olive tree pollen or honeybee stings, if using blood thinning agents, or if you have hemophilia.

Turmeric (Curcumin 95%) is the seasoning that gives mustard and many Indian dishes their yellow coloring. It is found in curries, chutneys, and many Indian rice dishes. Adding this seasoning to foods is a good way to obtain its natural anti-inflammatory benefits. **Curcumin**, the main compound in turmeric, can also be taken in capsule form.

NYBC and Other Nutraceuticals to counteract inflammation caused, to a great extent, by increased Tumor Necrosis Factor (TNF):

Acetylcarnitine 500mg x 100	3-6d/ (1-2B, 1-2L, 1-2D)
Berry High x 300g (38 servings)	1-2 servings /d
Carnitine Tartrate 500mg x 120	6/d (2B, 2L, 2D)
Carotenoid Complex UltraAntioxidant x 90	3/d (1B, 1L, 1D)
Curcumin 95% 500mg x 60	6/d (2B, 2L, 2D)
Flaxseed Oil 1000mg x 200 (or MaxDHA)	6/d (2B, 2L, 2D)
Ginger Root 6:1 500mg x 100	6/d (2B, 2L, 2D)
Glutathione 500 mg x 60	Take on an empty stomach, 20 minutes before or 90 minutes after eating.
Grape seed 90% 100mg x 200	3/d (1B, 1L, 1D)
Nettle Leaf Extract Pharmaceutical Grade 145mg x 90	3/d (1B, 1L, 1D)
Phytoflavonoid Complex UltraAntioxidant x 120	4/d (1B, 1L, 2D)
Allicin	6/d (2B, 2L, 2D)
Quercetin with Bromelain 800mg x 120	4/d (1B, 1L, 2D)

NYBC Protocol to Lower Tumor Necrosis Factor:

Acetylcarnitine 500mg x 100	4/d (1B, 1L, 2)
Borage Oil 1000mg x 120	4/d (1B, 1L, 2D)
Flaxseed Oil 1000mg x 200 (or MaxDHA)	4/d (1B, 1L, 2D)
ThiolNAC (NAC, lipoic and MSM)	3/d (1B, 1L, 1D)
Nettle Leaf Extract 145mg x 90	3/d (1B, 1L, 1D)