

NEUROPATHY

What's the Problem, and How Do You Diagnose It?

There are two main types of neuropathy that may develop in HIV+ people. One is the more commonly experienced peripheral neuropathy which affects the nerves in the arms, legs, feet, and hands. Researchers have reported that peripheral neuropathy may occur in almost half of those living with HIV. Peripheral neuropathy results from nerve damage that can cause numbness, burning, tingling, over-sensitivity, and sometimes severe pain in the hands, feet, arms and legs.

The symptoms may range from extremely mild (perhaps just a small amount of numbness in the toes) to quite severe (agonizing feelings of burning and pain from nothing more than a sheet touching the leg). It is common for numbness or tingling that begins in the toes to eventually spread upwards into the legs, sometimes accompanied by similar symptoms in the fingers that may spread upwards into the arms. What may begin with mild weakness in the foot muscles may become severe over time. With more extreme neuropathy, many will experience severe burning pain in the extremities. Some people will experience sharp shooting pains that travel up the legs, a condition that may occur more frequently when the person is at rest. Foot pain can sometimes be so severe as to make walking difficult. Some people also experience severe muscle cramping, hair loss on the legs, and reddened skin.

In HIV+ people, there may be many different nerves affected in a given area (as with peripheral neuropathy in the feet and hands), or there may be a mononeuropathy, an injury to one specific nerve, sometimes caused by HIV-induced inflammation. This might cause carpal tunnel syndrome (pain in the wrist), or "scapular winging," a condition in which one shoulder will appear to be dropped, or will be sticking out from the back, causing shoulder and mid-back pain.

The other most common form of neuropathy experienced by some HIV+ people is autonomic neuropathy, a condition in which the autonomic nerves (those that work in many automatic body processes) are affected. Autonomic neuropathy seems to be far more prevalent in people living with HIV than is generally recognized. One study found that 13 out of 17 HIV+ people tested (76.5 percent) had developed autonomic neuropathy, 11 of whom were symptomatic. The two most common symptoms caused by autonomic neuropathy are sexual dysfunction (impotence in some men), and digestive problems. A third is a potentially life-threatening effect called orthostatic hypotension where the blood pressure becomes so low that blood flow to the brain is affected. This sometimes causes fainting or weakness upon standing up. Autonomic neuropathy may also affect bladder function, causing urinary incontinence (inability to "hold it"), a symptom that can have a very debilitating impact on quality of life.

Digestive problems can occur when the nerves needed to activate the muscles to propel food out of the stomach and through the intestines are adversely affected. The result can be gastrointestinal motility problems in which the stomach fails to empty properly or food is not properly moved through the intestines. This can cause intestinal cramps, stomach discomfort, and nausea. With severe autonomic neuropathy, morning nausea that results in vomiting up the food eaten the night before may occur. A feeling of bloating and heaviness after meals is also common, as is the feeling that food sits in the stomach for long periods of time. In other words, there may be a feeling that the food eaten for lunch is still sitting in the stomach when it's time for dinner, and so on. Autonomic neuropathy will sometimes result in diarrhea.

Although research studies will use nerve biopsies to ascertain the extent of nerve damage, this has seldom been done for individuals. However, recent studies have measured nerve damage via a small skin biopsy. It is possible that this assessment may become more common. Physicians most often use a combination of your own self reporting of symptoms, accompanied perhaps by simple tests in which you are poked or prodded in certain ways to ascertain whether you respond appropriately to the stimuli. Simple tests include comparing ankle and knee reflexes, or testing the sensations that are perceived from the toes up the leg when a pin is poked on the skin. A tuning fork may also be used because it can show a reduced vibration in a foot with neuropathic damage. Sensitivity tests that assess your reaction to different pressures are also sometimes used.

What are the Causes?

Although all the specifics of how nerves are damaged in HIV disease are not well understood, it is clear that neuropathy has two main causes in HIV+ people: the virus itself (and the body's reactions to it which lead to oxidative stress and inflammation) and drugs. In many people, both of these will contribute to the development of neuropathy. In some cases, neuropathy may already exist (due to the effects of HIV disease) but the symptoms which make it apparent will only become noticeable when the condition is worsened by the addition of neuropathy-inducing drugs. Careful assessment to determine what causes are present and are most likely to be contributing to the development or worsening of neuropathy is important.

HIV and the body's responses to it can cause neuropathy. Long before antiretroviral therapy existed, there were reports of neuropathy in HIV+ people. A study that followed viral loads and CD4 cell counts in a large cohort of HIV-infected men who had not progressed to AIDS found that viral load over 3000 and CD4s below 500 were predictive

of neuropathy. The study authors suggested that effective suppression of HIV might reduce the risk of developing neuropathy. In another study, the impact of HAART (mostly indinavir-based) on neuropathy-associated pain was assessed in 49 HIV+ people. After eight months, patients whose viral loads decreased in response to treatment also had significant improvements in pain.

Although the ways in which HIV disease results in nerve damage are not well defined, it may result from some combination of directly caused damage to the nerves, as well as damage created by the body-wide inflammation and oxidative stress that are common in HIV disease. Oxidative stress—a condition that occurs when the body's supply of antioxidants is insufficient to counter the various body processes (including the body's immune responses to HIV) that generate unstable molecules called free radicals and reactive oxygen species—is extremely common in HIV disease. It can contribute to damaging many different cells and tissues in the body, and may contribute significantly to nerve damage. The elevated levels of certain pro-inflammatory cytokines that are produced in response to HIV result in body-wide inflammation which may also contribute to nerve damage.

Neuropathy is often caused by drugs. The most common antiretroviral drug sources of nerve damage are the “d” drugs: d4T (Zerit®), ddC (Hivid®) or ddI (Videx®). Hydroxyurea (Hydrea) can also cause neuropathy. Less commonly, 3TC (Epivir®) may contribute to neuropathy. Some chemotherapies used in the treatment of cancer can cause neuropathy. Other drugs that are common sources of nerve damage are metronidazole (Flagyl), thalidomide, isoniazid, vincristine, and dapsone. In addition, alcohol, cocaine, and amphetamines can all cause nerve damage.

Diabetes. Over time, elevated blood sugar can cause neuropathy. With the increasing incidence of blood sugar problems and diabetes in HIV+ people, this may become a possible source of neuropathy for more and more people.

What are the possible treatments?

The first must for effective treatment of neuropathy is identification of the probable causes followed by elimination of as many of these as possible. This would include identifying problematic drugs, assessing whether an elevated viral load may be contributing, and considering the possibility of nutrient deficiencies that may cause or contribute to neuropathy.

Key Therapies for Peripheral Neuropathy

Antiretroviral medications. Physicians who specialize in the treatment of neuropathic pain know that controlling HIV helps prevent problems. By suppressing the virus and improving immune function, you both stop HIV from causing nerve damage and, by improving immune function, decrease the chances of secondary infections that could attack the nerves. So beginning HAART medications in those who have not yet done so may be important to prevent or stop the worsening of neuropathy. However, there may be a Catch 22 in this. If it appears likely that HIV is a major contributor to neuropathy because the symptoms were already present before beginning drug therapy, it is obviously important to suppress the virus. Yet, as you no doubt know, a number of the most commonly used HAART meds can cause neuropathy. If these are the drugs you are taking at the time that neuropathy develops and they are working well to suppress the virus, you will have to discuss the pros and cons of any possible changes very carefully with your physician.

For those with pre-existing problems (prior to beginning HAART), it may be particularly important to try to choose antiretrovirals that are less likely to cause this problem, and avoid other drugs that may also contribute to nerve damage. On the list of drugs that it may be best to avoid if possible are the antiretrovirals d4T (Zerit®), ddC (Hivid®), and ddI (Videx®).

Drug switches. When possible, it is extremely important that drugs (antiretrovirals or others) that are causing peripheral neuropathy be stopped immediately after the beginning of symptoms. Any delay in cessation may result in permanent problems. It has usually been the case that when causative meds are stopped shortly after symptoms begin, the pain and numbness will be likely to subside over time, and will eventually be completely eliminated. This process may take a number of months, but in the end, the neuropathy and the symptoms it causes will fade away.

However, failure to immediately cease the use of problematic drugs may greatly reduce the chances for complete reversal of symptoms. It appears that the longer the nerve damage continues, the less likely it is that the symptoms caused by it will disappear. Too many people have ended up with permanent pain, numbness, and burning because drug discontinuation was delayed. It is very important to report any symptoms that might indicate neuropathy to your physician immediately. It is equally important for physicians to seriously consider drug switches, where possible, in order to stop the nerve damage quickly. HIV-knowledgeable physicians are usually very aware of this, and won't hesitate to consider changing meds. For those stuck with less knowledgeable docs, this may not be the case so educating the physician on these facts may be crucial.

When considering drug switches, there is one important caveat. Although it would seem appropriate to look for possible substitutions for any drug that appears likely to be contributing to neuropathy, there may not always be available substitutes. This may be a particular problem for people who are very treatment experienced with HAART meds. They may have become resistant to many previously used drugs, and might well be on the only combo currently available to them. In addition, since nucleoside analogues are the most common cause of neuropathy, an obvious substitution is to put together a nuke-sparing combo. However, some people may be intolerant of protease inhibitors or NNRTIs because of the symptoms that they cause. [In such cases, it would be worth trying all the therapies discussed in this guide to counter whatever symptoms are problematic when those drugs are used. You might find that you will be able to use those drugs by accompanying them with appropriate symptom-countering therapies, and thus avoid the use of nucleoside analogue drugs that are contributing to neuropathy.]

In some cases, if the current HAART combo is otherwise working well and providing the anti-HIV benefits needed, and your drug history or med intolerance makes finding substitutes difficult or impossible, it may be necessary to stay with those meds, while attempting to address the neuropathy with the nutrient therapies discussed here that provide mitochondrial support (since damage to the mitochondria is believed to be a cause of neuropathy) and protection against oxidative stress (another cause of nerve damage) and the building blocks to repair nerves. Natural anti-inflammatories might also be useful.

When nukes must be continued to maintain viral control, it would be advisable to try to use the drugs that may be the least likely to cause mitochondrial dysfunction and the neuropathy that could result from that. In general, it is thought that d4T (Zerit®), ddC (Hivid®), ddI (Videx®), and AZT (alone in Retrovir® and also in the combination drugs Combivir® and Trizivir®) have the greatest potential for mitochondrial toxicity, while 3TC (Epivir®), abacavir (Ziagen®), and tenofovir (Viread®) are less likely to cause the problem. It is important to note that most of the evidence in support of this ranking has been derived from in vitro (test tube) research so whether this will actually be the case in HIV+ people is not perfectly known. However, you will notice from this list that the drugs well known to most often cause neuropathy (the “d” drugs) are at the top of the list of those known to cause mitochondrial dysfunction.

Nutrient therapies. For all the reasons discussed above, doing everything possible to help counter oxidative stress, prevent mitochondrial damage, and provide the building blocks that the body can use to repair nerves may greatly help to prevent (or prevent worsening of) or even reverse neuropathy. The best results will usually come with a combination of the nutrients discussed here. For example, Phoenix naturopathic physician Kären Van der Veer has found that an integrated treatment approach that includes acupuncture combined with an aggressive nutrient supplementation program is often extremely effective. She recommends giving B-12 injections every day for two weeks, accompanied by folic acid, and then every other day for the next two weeks, and then twice weekly from then on. She also recommends use of B-6, and has found that B-6 will work much faster if injected intramuscularly once every week or two, although oral supplementation will work. She notes that the B-6 injections are painful, but seem to work wonders for neuropathic pain. Along with the B-6, B-12, and folic acid, she recommends oral supplementation with B complex, alpha-lipoic acid, acetyl-carnitine, lecithin, and a broad spectrum of antioxidants. In her patients, this integrated approach is highly successful in reversing neuropathy, and eliminating pain.

Based on the research done to date, the most important nutrients for countering mitochondrial toxicity would be a broad spectrum of antioxidants (which will also counter oxidative stress), the B complex, and the amino acid, acetyl-L-carnitine. Acetylcarnitine was shown to be effective in a study by Youle et al., at 3,000 mg per day.

The most important antioxidants would include vitamin E (800 to 1,200 IU daily), vitamin C (1,000 to 2,000 mg, three times daily with meals), bioflavonoid complex (1 capsule with each meal), carotenoid complex (1 capsule with each meal), selenium (400 to 600 mcg daily, total from all sources, including your multiple), N-acetyl-cysteine (500 mg, three times daily), coenzyme Q-10 (100 to 500 mg daily), and alpha-lipoic acid (200 to 400 mg, three times daily). The latter nutrient may be particularly important. Please see *NYBC's Core Nutraceutical Protocols* in this *Guides' Introduction*.

Acetyl-L-Carnitine is also crucially important for reversing neuropathy. In non-HIV research, it has been shown that treatment with acetyl-carnitine can help raise nerve myoinositol content, a nutrient needed for peripheral nerve function, while also protecting nerve membranes from oxidative stress-caused damage. In HIV+ people with peripheral neuropathy due to d4T, ddI or ddC, researchers have reported that blood serum (without cells) levels of acetyl-carnitine are abnormally low. After an initial small trial had shown improvement in symptoms in HIV+ people with neuropathy given carnitine, a second small trial was carried out at London's Royal Free Center for HIV Medicine in order to assess changes in nerve tissue as well as in symptoms. HIV+ people suffering from neuropathy related to “d” drugs (d4T, ddI, ddC) were given acetyl-carnitine in doses of 1,500 mg twice daily for six months. Michael Youle, MD, reports that the result was improvement in symptoms, including pain reduction, and improved nerve biopsy results, even though the “d” drugs were

continued. Symptom improvement usually required several months of acetyl-carnitine therapy. Dr. Youle described one person who required narcotic pain medication before supplementation with acetyl-carnitine and no longer required it several months after beginning the nutrient. The only side effect noted in some people was mild diarrhea. In a recent presentation of this information, Dr. Youle concluded by saying "L-acetyl carnitine is an effective pathogenesis-based therapy for HIV-associated peripheral neuropathy." Studies on the use of acetyl-carnitine for the treatment of neuropathy are currently ongoing in the U.S., Great Britain, Italy, and France.

Carnitine is available in two forms: L-carnitine and L-acetyl-carnitine. There are both over-the-counter and prescription forms of L-carnitine. The brand name of the prescription form is Carnitor. L-carnitine should be taken in doses of 1,000 to 2000 mg, three times per day. ***L-acetyl-carnitine (available over the counter) should be taken in doses of 1,000 mg, three times daily (about 3,000 mg per day at least.*** 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, the need for higher doses of L-carnitine to achieve the same effect. If insurance or Medicaid coverage for Carnitor is available, this could provide substantial savings. If it is not, then the over-the-counter L-acetyl-carnitine may be best since it requires lower doses for the same effect. [For more information on these, see *NYBC's Basic Nutrient Protocols and Counteracting Inflammation* in this guide's *Introduction*. Note that high doses of carnitine can sometimes cause watery diarrhea so watch for this.]

Alpha-lipoic acid is a fatty acid that 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. In addition to its protective effects against mitochondrial toxicity, alpha-lipoic acid's 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.

The B complex vitamins are also important for mitochondrial support. For any program aimed at reversing any condition associated with mitochondrial dysfunction, it will be important to supplement with a B complex formula (1 capsule with each meal, preferably with a formula that contains at least 50 mg of the B vitamins) or a potent multivitamin/mineral formula that includes the whole B complex (as directed, with meals). Although there are two B vitamins that have been mentioned as being important for countering mitochondrial damage—thiamine (vitamin B-1) and riboflavin (vitamin B-2)—it should never be forgotten that the B vitamins work together, that deficiencies of several B vitamins and many other nutrients are common in HIV disease, that nutrients work as a package in the body, and that one missing link could sabotage the effectiveness of other nutrients. For this reason, a B complex formula or a multiple containing the whole B complex should always be given in conjunction with any separate supplementation with individual B vitamins.

In addition to their role in mitochondrial support, certain B vitamins and associated factors may contribute to neuropathy resolution by providing the building blocks for nerves or improving nerve conduction. Among these are biotin, choline, inositol, and thiamine, all of which have been found useful in treating the peripheral and autonomic neuropathies found in diabetes and may also help with HIV-related neuropathies.

Biotin was studied at the University of Athens, where it was shown that regular, long-term use of the nutrient in diabetics was very effective both for improvement in nerve conduction and relief of pain. Improvement in nerve conduction occurred after only 4 to 8 weeks of therapy. In this study, biotin was given via daily intramuscular injection (10 mg/day) for 6 weeks; then 3 times per week (10 mg), intramuscularly, for 6 weeks; then 5 mg per day taken orally for up to two years. The researchers hypothesize that deficiency, inactivity, or unavailability of biotin may result in disordered activity of the biotin-dependent enzyme pyruvate carboxylase, leading to an accumulation of pyruvate and/or a depletion of aspartate, either of which could adversely affect nervous system metabolism. There are a number of reasons why HIV+ people may be deficient in biotin and, thus, potentially at risk for this. It has been suggested that those with neuropathy symptoms might try 10 to 20 mg per day orally (10,000 to 20,000 mcg; most biotin supplements will show the dosage in micrograms or mcg), taken in conjunction with the other B vitamins found useful for improving nerve function.

B-12 deficiency, extremely common in HIV+ people, is a known cause of neuropathy so this vitamin, along with its coworker folic acid, should certainly be included in any program aimed at eliminating this symptom. Typical symptoms of peripheral neuropathy related to B-12 deficiency include the type of leg and foot pains experienced by many. It is important to remember that standard blood tests do not always accurately reflect B-12 deficiencies. Researchers point out that B-12 deficiency is present in a significant percentage of HIV+ people, but does not always cause the red blood cell changes that physicians look for as a sign of deficiency. In addition, because the standard blood test reflects only what's in the bloodstream and not what is in the body's cells, a reading that appears normal may not truly reflect the

body's status. Neurologists who have studied this often recommend simply supplementing with B-12 when any of the symptoms that could indicate a deficiency are present. This would include neuropathy.

B-12 and folic acid should always be given together since taking folic acid alone could prevent the blood cell changes that might otherwise indicate B-12 deficiency. Doses of B-12 (1,000 mcg given daily via pills, or one to several times weekly with prescription nasal gel or injections) and folic acid (800 mcg daily via pills) may be useful in treating neuropathy (as well as restoring energy and overall feelings of well being), even when tests don't indicate obvious deficiencies. The injections or nasal gel forms of B-12 bypass absorption problems that may be present in many HIV+ people due to problems with the parietal cells that produce the intrinsic factor that is needed for absorption of B-12 consumed orally.

Vitamin B-6 deficiencies, also common in HIV+ people, are known to cause both carpal tunnel syndrome (with symptoms of numbness, tingling, and pain in the hands and wrists) and degeneration of peripheral nerves, and may be responsible for some peripheral neuropathy problems. B-6 is vital for the formation of the sphingolipids which are involved in the development of the myelin sheath surrounding nerve cells. Supplementation with B-6 (50 mg, three times daily; this amount will be found in many B complex formulas and potent multivitamins) may help ensure adequate levels to support this process, and help prevent neuropathy. [Note that a long ago study showed that extremely high overdosing with B-6 (doses of 2,000 to 6,000 mg daily, continued for months) could actually cause neuropathy; although this neuropathy mostly vanished after discontinuation of these absurd doses, this has led to a myth that any B-6 supplementation could be harmful; that is simply not true; just avoid ridiculous overdoses.]

Choline and inositol also seem to be very important parts of the combination of vitamins needed for neuropathy resolution. As discussed above, diabetic neuropathy is known to be associated with a reduction in myoinositol levels in nerves and tissues. The decreased level of myoinositol is believed to cause a decrease in the activity of the sodium-potassium pump and, thus, to change the sodium permeability of nerves. Both diets high in inositol and inositol supplementation have been shown to improve diabetic neuropathy. Researchers at the University of Alabama found a statistically significant improvement in nerve function in diabetics placed on a diet high in inositol. Included in the diet were high-inositol foods such as cantaloupe, peanuts, grapefruit (or grapefruit juice), and whole grains. Other researchers have reported that supplementation with inositol in doses of 2,000 mg to 6,000 mg daily has resulted in improvements in neuropathy. A combination of choline (400 to 800 mg of choline citrate or 1,000 to 3000 mg of phosphatidylcholine, 3 times per day) and inositol (500 to 2000 mg of myoinositol, three times per day) may be useful for treating neuropathy.

Thiamine has also been seen to be useful in treating diabetic neuropathy. Stanley Mirski, M.D., has reported that a large percentage of his diabetic patients who suffer from neuropathy have achieved improvements with daily thiamine supplementation in doses of 50 to 100 mg. Using a fat-soluble form of thiamine such as thiamine tetrahydro-furfuryl disulfide may be preferable because of the poor absorption of water-soluble forms of this vitamin. This type is contained in Cardiovascular Research's Allithiamine. Doses of two capsules daily might be useful.

Lecithin and fatty acids. Lecithin (phosphatidylcholine) is a phospholipid, a type of fat important in the structure of all membranes. They are beneficial to myelin sheath production and, thus, nerve protection. Cell membranes are largely composed of phosphatidylcholine, as are the protective sheaths surrounding the brain. Food-grade lecithin is a substance commonly used as a food additive and nutritional supplement that contains phosphatidylcholine, as well as other phospholipids, including phosphatidylinositol and phosphatidylethanolamine. [To avoid confusion, note that to a chemist lecithin *is* phosphatidylcholine; we are using the term here to refer to the food-grade lecithin granules available in health food stores as a supplement. It consists mostly of the B-vitamins choline and inositol along with linoleic acid and other fatty acids, glycerin, and phosphorus.

Although lecithin is a lipid, it is partly water-soluble and thus acts as an emulsifying agent. Most lecithin is derived from soybeans, but egg lecithin (from egg yolks) is also available; some studies show that this form is more beneficial for HIV+ people. Other sources of lecithin include brewer's yeast, grains, legumes, fish, and wheat germ.

For anyone concerned about preventing or treating neuropathy, some naturopathic physicians recommend 1 tablespoon of lecithin granules twice daily. It can be blended into protein or fruit shakes (which it will make them creamier), or sprinkled on cereal or oatmeal or on salads. For those with serious neuropathy, try using 1 tablespoon, four times daily, along with a plentiful intake of omega-3 and omega-6 fatty acids.

Gamma linolenic acid is an omega-6 essential fatty acid that may help the body repair nerves. Gamma linolenic acid, found in borage oil, grape seed oil, black currant oil, and evening primrose oil, has been shown to be successful in reversing nerve damage in diabetics suffering from peripheral neuropathy. In a double-blind, placebo-controlled study using 480 mg of GLA daily, all the diabetics given the fatty acid experienced gradual reversal of nerve damage and

improvement in the symptoms related to the peripheral neuropathy, while those on placebo gradually worsened. It is thought that GLA may help to rebuild the myelin sheath around the nerves. The least expensive source of GLA is usually borage oil. GLA doses of 240 mg, twice daily, with meals, might be appropriate.

For information on good sources of omega-3 fatty acids, see the Natural Anti-inflammatories discussion in the *Counteracting Inflammation* section of the *Introduction*.

Magnesium and chromium are two minerals that may also be important for treating neuropathy. Magnesium, shown by Canadian researchers to be deficient in a significant percentage of HIV+ people, is also known to be necessary for nerve conduction. Deficiency of this mineral can cause peripheral neuropathy symptoms. Thus, including optimal amounts of magnesium might contribute to elimination of neuropathy. Doses of 500 to 600 mg daily, taken with a meal, might be useful. [Note that excessive magnesium can cause watery diarrhea so watch for this.] There have also been reports of chromium deficiency causing peripheral neuropathy. Since chronic infection is known to deplete body stores of chromium, supplementing with chromium (200 mcg, three times daily) in the context of a complete nutrient protocol might be reasonable.

Cod liver oil, a source of vitamins A and D, has been reported to result in neuropathy improvement in some, especially when symptoms are mild. One to two tablespoons daily have been suggested. There are flavored cod liver oils available today that many prefer to older versions of this oil.

NYBC and Other Nutraceuticals for Neuropathy:

Acetylcarnitine 500mg x 100	6/d (2B, 2L, 2D)
B-50 Complex x 250	3/d (1B, 1L, 1D)
Biotin 5000mcg x 60	2-4/d (0-1B, 1L, 2B)
Borage Oil 240mg GLA x 120	2/d (1L, 1D)
Choline & Inositol 250/250mg	6-10+/d (2-3B, 2-4L, 2-3D)
Chromium GTF 200mcg x 250	3/d (1B, 1L, 1D)
Flaxseed Oil 1,000mg x 200	6+/d (2B, 2L, 2D)
Folic Acid 800mcg x 250	3/d (1B, 1D, 1D)
Lecithin 35% 1200mg x 200	3/d (1B, 1L, 1D)
Lipoic Acid 100mg x 180	9-12/d (3-4B, 3-4L, 3-4D)
Magnesium glycinate 220mg x 120	2-3/d (0-1B, 1L, 1D)
Methylcobalamin (B-12) 5000mcg x 100	3/d (1B, 1L, 1D)
P-5-P (B-6) 50mg x 60	3/d (1B, 1B, 1D)

Natural anti-inflammatories. 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. Rather than using anti-inflammatory drugs, which are potentially toxic and may interfere with the natural benefits of the inflammatory response (since the inflammation is part of the immune system's way of countering infections), it is probably preferable to use foods that have natural anti-inflammatory qualities.

Because such foods 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 are more subtle but might still provide substantial benefit. Naturally anti-inflammatory substances are found in the following foods and seasonings:

- garlic, ginger, turmeric
- bioflavonoid- and antioxidant-rich fruits and vegetables
- omega-3 fatty acid-rich foods such as fatty fish (e.g. salmon, mackerel, sardines, tuna, cod and halibut), flaxseed, and walnuts.
- chlorophyll-containing foods such as wheat grass juice and blue-green algae.

There are also specific nutritional supplements and herbs that counteract excess inflammation and may help to lower levels of tumor necrosis factor. These include N-acetyl-cysteine (NAC), carnitine, nettle leaf extract, grape seed extract and bilberry extract, as well as a broad spectrum of all the other important antioxidants (vitamin E, vitamin C,

bioflavonoid complex, carotenoid complex, selenium, coenzyme Q-10, and alpha-lipoic acid). For more detailed information on the above foods and supplements, please see *NYBC's Core Nutrient Protocols* and *Counteracting Inflammation and Tumor Necrosis Factor* in the *Introduction*, as well as the description of *Health-Enhancing Nutrients* in *NYBC's Self-Care Guide*.

Pain medications. Please see *Muscle Aches and Pains* in this *Guide*. For those whose neuropathy is causing pain, adequate treatment of that pain will be very important. Unfortunately, although opiates are generally considered to be the most powerful pain medications, neuropathic pain is the kind of pain for which they are the least effective. In the past few years, however, an alternative has come along. The anti-seizure drug gabapentine (Neurontin) has been found to act as a nerve stabilizer that can quiet the misfiring nerves responsible for neuropathic pain. It is now generally recommended that Neurontin be the first pain medication that is tried for neuropathic pain. Doses usually start at 100 mg daily but can be increased to as much as 3000 mg to 3,600 mg daily, taken in from 1 to 3 doses. Neurontin has sedating effects that some find difficult.

For pain that mostly occurs at night, the standard recommendation is for oral amitriptyline (Elavil, a tricyclic antidepressant), beginning with low doses in order to minimize certain side effects (dry mouth, sedation, urinary retention, and low blood pressure upon suddenly sitting up or getting out of bed, termed orthostatic hypotension. A starting dose of 25 mg at bedtime is gradually increased to 75 mg (or as high as 100–150 mg if needed). Elavil may be particularly useful when sleep problems accompany the neuropathy because it has sedative effects.

For predominantly daytime pain, oral nortriptyline (Pamelor) is often advised since it is less sedating, also beginning with a low dose of 10 mg per day, and gradually increasing to 30 mg, 3 times daily. With these drugs, effective reduction of pain may not occur for up to two or three weeks, so patience is required. When one of these is not effective, another may still be.

For occasional pain, standard anti-inflammatories such as ibuprofen (Motrin, Advil) may help with mild neuropathic symptoms. The use of topical analgesic or anesthetic creams can also sometimes be effective. In addition, topical aspirin has been reported to work to relieve pain in some people. An aspirin tablet is crushed and dissolved in a small amount of water or gel or cream, and then applied topically to a painful area.

Two other therapies have recently shown promising results for treatment of neuropathic pain. A pilot study showed that lamotrigine (Lamictal), an anticonvulsant, worked significantly better than placebo to decrease neuropathic pain in HIV+ people. However, severe rash, a known side-effect of lamotrigine treatment, occurred more frequently than in studies of lamotrigine treatment for epilepsy so the possibility of this should be carefully monitored. This drug is approved for the treatment of seizures and, thus, is available for off-label use. Another recent study looked at the effects of NGF, a neurotrophic growth factor that stimulates regeneration of damaged nerve fibers, on HIV-associated peripheral neuropathy. Results showed that twice-weekly injections of NGF reduced neuropathic pain. The drug was well tolerated, although some patients complained of injection-site pain. (This drug is not yet approved, and its development has been halted, at least for now.)

If the above meds are insufficient for treating the pain, it is generally recommended that the World Health Organization (WHO) four-step approach to drug treatment of pain be used. In general, it is thought best for medications on each step of the WHO ladder to be given in the maximum tolerated doses before moving up to the next step. Where there is chronic pain, it is thought best to treat around the clock in order to prevent pain. If necessary, the usual meds can be augmented by short-acting drugs in order to treat breakthrough pain. With all these drugs, individual responses may vary and will be the best guide for proper med use.

The choice of specific pain meds should take into consideration a number of factors. First, discuss with your physician any possible interactions with other drugs you are taking before beginning any pain med. Second, consider any other medical conditions you have and the effect that certain pain meds, most of which have side effects that could be serious, may have on them.

Topical medication: A transdermal gel of acetyl-carnitine, pyroxidol-5-phosphate, and geranium oil is showing positive signs of effectiveness. The gel is rubbed into the hands and/or feet and is absorbed locally as well as systemically. **The gel is available from Life Science Pharmacy at 845-781-7613.**

□ **Step One:** try acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) such as aspirin, naproxen, sulindac, or ibuprofen. These are most effective for mild pain. Possibilities include: ibuprofen (200-600 mg, 3-4 times per day); aspirin (500-1,000 mg, every 4-6 hours); or naproxen (500 mg initial dose, followed by 250-375 mg, every 6-8 hours). When one NSAID doesn't work, another might. Long-term use can cause gastrointestinal bleeding and should be avoided, if possible. Those with low platelets, kidney dysfunction, or low serum albumin levels (common in those with wasting) should not take NSAIDs. Those with gastric Kaposi's sarcoma should either take them with an antacid or avoid them.

Note that for those with liver problems, acetaminophen (Tylenol) would be inadvisable. For those with ulcers, gastrointestinal bleeding problems, intestinal Kaposi's sarcoma, low platelets, kidney dysfunction or low serum albumin levels (common in those with wasting), aspirin and other NSAIDs would be inadvisable.

In general, unless any such issues make it problematic, aspirin or buffered aspirin is probably the best choice for this first step in pain treatment. Tylenol (acetaminophen) significantly lowers the body's level of the antioxidant glutathione. Since glutathione levels are already too low in HIV+ people, worsening this is not a good idea. In addition, the lowered levels of glutathione already present in those living with HIV may significantly increase the chance for acetaminophen toxicity. Even in doses considered to be in the routine therapeutic range, it is known that acetaminophen can cause liver injury in people with a tendency for glutathione deficiency. Aspirin also lowers glutathione, but to a much lesser extent than acetaminophen.

If you are taking either aspirin or acetaminophen long-term, the use of the nutrients that help normalize glutathione levels is very important. Included are alpha-lipoic acid, N-acetyl-cysteine (NAC), glutamine, and vitamins E and C. Appropriate doses would be NAC (500 mg, three times daily; always take with food to prevent gastrointestinal irritation); glutamine (5,000 to 10,000 mg daily, spread across four doses; a powdered form is best; mix in water or juice and take on an empty stomach); vitamin E (800 to 1,200 IU daily); vitamin C (because individual needs vary widely, recommended dosages range from 1,000 to 6,000 mg or more daily, with doses spread across the day and taken with meals; note that amounts in excess of individual tolerance can result in gas and diarrhea; if you develop sudden watery diarrhea when you begin or increase a vitamin C dose, know that this may be the cause.); selenium (200 to 400 mcg daily); SAME (S-adenosyl-L-methionine; 800 to 1,600 mg daily); and alpha-lipoic acid (200 to 400 mg, taken three times daily, preferably on an empty stomach; note that a time-released form is very important because alpha-lipoic acid has a very short half-life in the bloodstream; by using products that release the alpha-lipoic acid gradually over time, you increase the total time that the nutrient will be available and working in the body.) For much more information on these nutrients and their usefulness in restoring glutathione in HIV+ people, see *Mitochondrial Support and Protection Against Oxidative Stress*.

Always remember that long-term use of aspirin or other NSAIDs can cause damage to the intestines and gastrointestinal bleeding. In general, it is always best to only use such meds when you absolutely need them to reduce pain, and avoid long-term use, if possible.

□ **Step Two:** if NSAIDs are not enough, try using a weak opiate derivative either alone or along with a Step One agent. Possibilities include codeine alone (30-60 mg); codeine (30 mg) with acetaminophen (325 mg); hydrocodone (5 mg) with acetaminophen (325 mg); or oxycodone (5 mg) with acetaminophen (325 mg). Any of these combos would be repeated every 4 to 6 hours.

□ **Step Three:** if the above are inadequate, switch to a stronger opiate such as hydromorphone, transdermal fentanyl patches, levorphanol, morphine sulfate (intravenous), sustained-release morphine sulfate (oral), or meperidine. The minimum daily dose that affords pain relief should be used.

□ **Step Four:** at any point during the preceding steps, add adjuvant therapies to boost the effectiveness of the other drugs. At the top of this list, due to good effectiveness with few side effects, is gabapentine (Neurontin), starting at 100 mg daily and going as high as 3000 mg daily, taken in 1 to 3 doses. As is discussed above, Neurontin may also sometimes be effective when used as a sole agent. Other boosters include antihistamines like hydroxyzine (Vistaril); butyrophenones like haloperidol (Haldol) and pimozide (Orap); psychostimulants like methylphenidate (Ritalin), dextroamphetamine (Dexedrine), and pemoline (Cylert); amine precursors like tryptophan; selective serotonin re-uptake inhibitors such as fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft); and heterocyclic and non-cyclic antidepressants like trazodone (Desyrel) and maprotiline (Ludiomil).

[For additional information on the treatment of pain in HIV disease, see *Pain*.]

Reducing symptoms by countering overexertion, reducing pressure, and soothing affected areas. Several physical practices may help relieve pressure on hypersensitive feet or hands and, thus, reduce pain. This includes limiting walking distances, avoiding standing for lengthy periods, wearing loose-fitting shoes and socks, avoiding repetitive pressure on the hands, and soaking the feet or hands in ice water on a regular basis.

Regular exercise also seems to help in some cases, possibly by increasing circulation to the nerves. Support stockings also seem to help some people, although in others they may actually cause pressure that worsens pain.

Some people experience increased pain in certain areas when sleeping. For example, neuropathy in the heels that only causes a slight feeling of numbness during the day may cause serious pain when the mattress presses into the heels during sleep. A simple measure that can help is to raise such an affected area (the heels or the hands, etc.) off the mattress by using a small pillow. Place a small tubular pillow (sold by many chiropractors; a piece of foam rubber with a pillowcase wrapped around it would also work) under the legs (or the arms) just above the heels (or the wrists) so that the affected areas are slightly elevated. This can remove the pressure that's causing the pain and allow for uninterrupted sleep. Keeping heavy covers off of painful areas can also help. If the heels or toes are the problem areas, arrange the covers so

that only a sheet or light covering is over the feet. Pull any heavier covers farther up so that they stop just above the feet. An egg crate-type foam mattress will relieve pressure spots from head to heel and may make sleeping much more restful.

Acupuncture or acupressure. Acupuncture has been reported to be very effective for the relief of neuropathic pain, with improvement often occurring with the first treatment. Repeated treatments may, however, be necessary for long-term relief. Note that one study of acupuncture found no benefits from its use; however, acupuncturists believe that the study was invalid because according to the standards of Traditional Chinese Medicine, acupuncture should always be individualized for each person; in the study, the identical points were used for everyone. There are many anecdotal reports from the community that support the belief that acupuncture is often helpful with neuropathy. Where acupuncture is not available, acupressure—in which energy points are pressed or massaged—may be another possibility for treating neuropathy.

Sympathetic electrical current therapy. Recent research has shown that the application of an electrical current designed to affect the nervous system systemically may significantly reduce pain and improve sleep in people diagnosed with chronic peripheral neuropathy. In a study recently published in the *American Journal of Pain Management*, Texas neurologist Ernesto H. Guido, M.D., reported effective treatment of neuropathy sufferers (not limited to HIV+ people but anyone with chronic neuropathy) with the Dynatron STS, a device approved by the FDA. This device delivers low frequency, high intensity electrical current in a way that is designed to gain access to the autonomic nervous system via peripheral nerves. The treatment was administered daily for 28 days to 20 people with a primary diagnosis of peripheral neuropathy. Pain duration for these people ranged from one to 25 years. Most people reported decreases in pain after only a few days. Of being treated. By the end of the study period, significant pain relief was reported by 19 of the 20 people, and half of the sufferers reported complete relief. The one individual who did not report pain relief, did experience improved sleep and a 30 percent reduction in the use of pain medication. The researchers note that the pain reduction outcomes of this study may indicate that this therapy could be an effective means of providing symptomatic relief of chronic intractable pain, even in those who have suffered symptomatically for many years, or have been unresponsive to other therapies. More information is available at the manufacturer's website (Dynatronics Corporation, Salt Lake City, Utah; www.chronicpainrx.com)

Key Therapies for Autonomic Neuropathy

Antiretroviral medications, nutrient therapies, and natural anti-inflammatories. For preventing or countering damage to autonomic nerves, it will be important to consider many of the same remedies discussed above for peripheral neuropathy. Consideration should be given to the use of antiretroviral medications to counter HIV-caused nerve damage, nutrients that may help protect or rebuild nerves, and natural anti-inflammatories to counter the inflammation that may contribute to autonomic nerve problems. For information on these, see the sections above entitled *Antiretroviral medications*, *Nutrient therapies*, and *Natural anti-inflammatories*.

Although we know much less about the use of any of these for the protection of autonomic nerves, there are anecdotal reports that these therapies may work to improve autonomic neuropathy. Suppressing HIV with antiretrovirals may be very important for protecting the autonomic nerves.

The most important nutrient therapy for autonomic neuropathy may be acetyl-carnitine (1,000 mg, three times daily on an empty stomach) combined with alpha-lipoic acid (400 mg, three times daily; absolutely do use an extended release form such as MRI's Extended Release Alpha-Lipoic Acid). There have been anecdotal reports that using these in combination has resulted in improved stomach functioning, and a reduction in the symptoms that damage to stomach nerves can cause (bloating, sometimes to the extent of distention, after meals, discomfort, and gas). Adding to these nutrients the others discussed above would always be best.

Countering stomach dysfunction. With nausea caused by autonomic neuropathy, there may be a long-term need for use of metoclopramide (Reglan). Reglan speeds the emptying of the stomach and small intestine, thus relieving the digestive symptoms of bloating and uncomfortable fullness in the stomach. By ensuring that food moves on through the digestive tract as it is supposed to do, the use of Reglan will often not only improve digestion significantly but also eliminate the nausea and abdominal cramping that the food sitting undigested for long periods of time can cause. Reglan is available in oral form as a tablet or syrup, and in injectable form for intramuscular or intravenous use. The dosage range is from 5 to 20 mg, with the most common dosage for digestive problems being 10 mg, given approximately 30 minutes before meals and sometimes also at bedtime. Reglan has a sedating effect in some people so watch for this (and avoid driving if it occurs).

One note on this is important. With constant daily use of Reglan, its effectiveness may diminish. Thus, it will always be best to only use the drug when truly necessary. Many people will find that if they eat smaller meals, and always avoid over-filling the stomach, they may not need to take Reglan all of the time. Then on occasions when a bigger meal will be eaten (it's Thanksgiving or you're at your favorite restaurant and want to indulge), the Reglan can be used effectively. By using it only when definitely needed, people report that its usefulness is maintained. However, chronic

daily use with every meal has resulted in losing the drug's effectiveness, a serious problem for those times when the stomach really locks up and the food just keeps sitting there.

Countering orthostatic hypotension. For those with orthostatic hypotension (low blood pressure) that is caused by autonomic neuropathy, the use of elastic antiphlebotic (compression) stockings can help. These are thigh-high stockings that apply pressure to the legs in a way that helps to prevent pooling of the blood in the lower legs, thus helping to ensure normal blood flow to the head.

Countering urinary incontinence. If urinary incontinence is present, it is very important to see a urologist who can determine the cause(s) since autonomic neuropathy is only one of several potentially serious causes of this problem. There are drugs such as Hytrin or Ditropan which can help with some types of urinary incontinence.