

BONE PROBLEMS (OSTEOPENIA, OSTEOPOROSIS, OSTEONECROSIS, AVASCULAR NECROSIS)

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

Several different kinds of bone problems have now been reported in HIV+ people. Included are:

- **osteopenia**—a reduction in bone mineral density; in essence, an early stage of what may lead to osteoporosis
- **osteoporosis**—a more advanced bone problem in which bone mass is decreased and there is an increased risk of fractures
- **osteonecrosis (also called avascular necrosis)**—a problem in which there is actually death of bone tissue, generally secondary to impairment of the blood supply to the bone.

A DEXA scan is the best way to diagnose bone mineral loss, whether it is still at the stage of osteopenia or has developed into the more severe osteoporosis. The best approach for diagnosis is to have a baseline scan (preferably before starting HAART) that could be compared to later readings. Without a baseline scan, physicians can compare the current results with standard values based on the person's age, weight, and build, thus estimating the probable bone loss.

Diagnosis of osteonecrosis requires first a comprehensive physical exam, followed if appropriate by an MRI scan of the bone.

What are the Causes?

Definitive causes for these problems have not been established. Based on research done to date, it appears that there are likely links between these bone problems and the use of some HAART drugs, particularly protease inhibitors, but that HIV disease itself may also contribute. There are also additional risk factors, unrelated to HIV disease or its treatment, that some people may have.

Osteopenia and Osteoporosis

In osteopenia and the more severe osteoporosis, there is a gradual loss of bone tissue that occurs when the body's normal constant loss of bone cells (bone resorption) is not equaled by constant replacement (bone formation), resulting in gradually thinning and weaker bones that may become brittle and break easily.

It is possible that HIV infection itself contributes to this. HIV+ people are known to have abnormally high levels of pro-inflammatory cytokines (cell-produced chemicals that cause inflammation) as well as vitamin D deficiency, both of which could contribute to disturbed bone metabolism.

In one significant study, researchers compared levels of osteocalcin, a blood serum marker for bone formation, to levels of C-telopeptide, a serum marker for bone resorption, and found that HIV+ people with advanced disease and high viral loads had increased levels of C-telopeptide (indicating more than usual bone loss), markedly depressed osteocalcin levels (indicating less than usual bone formation), and higher levels of pro-inflammatory cytokines. Interestingly, there was no correlation between osteocalcin and C-telopeptide levels. In the HIV-negative, these are normally in balance with each other, an indication that bone loss and growth are matched. After 24 months of HAART treatment, there was a decrease in the inflammatory cytokines and a marked rise in serum osteocalcin levels, with the result that osteocalcin and C-telopeptide levels were once again appropriately correlated. So it appears that in these people HAART had the beneficial effect of normalizing bone growth and loss processes. That's the good news.

The bad news is that at least some HAART meds, particularly protease inhibitors, have been tied to an increased incidence of osteoporosis. A Washington University study found that compared to those on non-PI regimens, HIV+ people on PIs were twice as likely to develop low bone mineral density (as gauged by the full-body X-ray scan called DEXA). Senior researcher Pablo Tebas, MD, and his colleagues found that 50 percent of PI takers had low bone mineral density, and more than a fifth had severe osteoporosis. Only 23 percent of those on non-PI regimens had lowered bone mineral density, and only 11 percent had severe osteoporosis, both of which were fairly close to the readings in HIV negative controls (29 percent of whom had some level of bone loss, and 6 percent severe osteoporosis). And in a vicious circle, the osteoporosis in some HIV+ people might actually be contributing to the development of avascular necrosis, a known complication of severe osteoporosis.

In addition to the possible contributions of HIV and protease inhibitors, many people may have additional risk factors for the development of osteoporosis:

- **Lowered sex hormone levels, common in both men and women with HIV disease, may increase risk,** making hormone testing and appropriate replacement a must.
- **Nutritional deficiencies resulting from malabsorption and other problems may contribute to the bone problems,** leaving the body with insufficient nutrient building blocks for bone—particularly calcium, magnesium, and vitamin D, all of which have been shown to be deficient in a significant percentage of HIV+ people.
- **Long-term consumption of an acid-forming diet could contribute.** Foods such as proteins and starchy carbohydrates tend to acidify the blood, as opposed to the alkalizing effects of fruits (even citrus fruits that seem acidic) and vegetables. If your daily diet consists mostly of meats and white foods (those made with white flour and sugar), with few balancing fruits and vegetables, then your blood pH (the measure of acidity vs alkalinity) will tend to be acidic. With an acidic blood pH, the body has to borrow alkalizing minerals from the bone tissue in order to neutralize the acidity. Over time, this can result in bone loss. Aiming for a diet high in fresh fruits and vegetables will help prevent this. [For more info, see *NYBC's Self-Care Guide*.]
- **Certain drug treatments that many people with more advanced HIV disease may have been given—especially corticosteroid drugs such as those used in the treatment of PCP—are also tied to an increased risk of osteoporosis,** although the level of risk associated with short-term use (as in the treatment of an infection) as compared to long-term use (as when such drugs are used for years in the treatment of chronic conditions like rheumatoid arthritis) is not clear.
- **Many people may also have one or more of the additional risk factors that affect the general population—**smoking, extended immobilization of the body (due to injury or other illness) or anything else that results in lack of weight-bearing exercise, alcoholism, failure to achieve an optimal bone mass by age 30, thyroid problems, adrenal gland abnormalities, and others.
- **Last but not least, research has shown that people who are coinfectd with HIV and either hepatitis B virus (HBV) or hepatitis C virus (HCV) may be at even greater risk for bone disorders.** It appears that the more advanced the liver disease is, the higher the likelihood of bone loss, another fact to consider when deciding on treatment for hepatitis B or C. The reported prevalence of osteoporosis among patients with chronic liver disease ranges from 20 percent to a shocking 100 percent, depending on various studies' patient selection and diagnostic criteria. It's not surprising that increases in bone fractures and pain are far too common in those with late-stage liver disease. The same general risk factors described above have also been shown to elevate risk in those with liver disease, and in some cases there may be a dual effect that heightens the risk. For example, chronic liver disease is known to accelerate hypogonadism with resulting reductions in serum testosterone. Since those living with HIV are already at risk for this, the coinfectd may be even more likely to develop this problem, making its potential contribution to bone loss even greater.

Osteonecrosis

Studies from several universities (including both Georgetown University and UC San Francisco) have indicated that protease inhibitors may contribute to osteonecrosis, the other bone problem now being seen in increasing numbers of people. In one study, researchers reported on 18 HIV+ people who had been diagnosed with avascular necrosis of the femoral head since 1991. Of these, 11 had been taking protease inhibitors, and only one had any of the usual (non-HIV-related) risk factors associated with the disease. In the seven people who were *not* receiving protease inhibitor therapy, six were found to have traditional (non-HIV-related) risk factors for the disease. The differences were statistically significant, clearly suggesting that protease inhibitors increase the risk for developing osteonecrosis. (Paiement GD, Biuiji A, Ries M. Association between chronic use of protease inhibitors and avascular necrosis of the femoral head. Annual Meeting of the American Orthopedic Association, Hot Springs, VA; June 17-20, 2000.)

Researchers have theorized that elevated blood fats, particularly the high triglyceride levels often caused by protease inhibitors but also caused by HIV itself, might be blocking blood supply to the bones, thus leading to the tissue death, but note that this is definitely still theory, not a proven fact. Even in HIV+ people not on HAART, triglycerides are often too high and might be a factor in the development of the bone problems. It is also possible that there might be some direct toxicity to bone cells from protease inhibitors.

Use of corticosteroid drugs is considered a major risk factor for osteonecrosis. These drugs are often used long-term for treatment of inflammation caused by diseases like rheumatoid arthritis or lupus, and short-term in the treatment of infections like *Pneumocystis carinii* pneumonia or PCP; long-term use is definitely a risk factor; whether short-term use might also increase the likelihood of developing osteonecrosis is unclear. Alcohol abuse, bone injury, bone infections, and scuba diving are additional risk factors because each of these can contribute to decreased blood supply to

the bone. Some HIV+ people develop Addison's disease, an adrenal gland condition that results in reduced production of the steroid hormone called cortisol. It is usually treated with low doses of hydrocortisone (30 mg or so daily), a dosage level that is not usually thought to cause avascular necrosis but might contribute.

The hip is usually the first place that osteonecrosis of bone shows up, but it may also develop in the shoulder, knee, or hand. Common early symptoms include pain in the hip joint or groin area which may radiate down the leg to the knee, and may in some cases be quite excruciating. Some people will develop stiffness in the hip area (often particularly noticeable upon awakening), occasional aching (especially after long periods of walking or standing), and/or a decreased range of motion.

What are the possible treatments?

Until all the possible contributing causes have been better pinned down, advice on avoiding these bone problems will not be perfect. However, there are several suggestions that may be helpful.

For osteopenia and osteoporosis, those things well-known to help prevent or reverse osteoporosis in general may certainly help. Included would be weight-bearing exercise, a nutrient-rich diet in order to ensure the presence of all the nutrients needed by bone to grow, and additional supplementation with calcium, magnesium, and vitamin D. The latter may be particularly important. A Norwegian study found that blood levels of vitamin D-3, the natural form, were below normal in more than half of the HIV+ people studied, and 18 of the 54 people had undetectable levels. In addition, hormone replacement therapy might be particularly important in postmenopausal women since they are known to be at particularly high risk for the development of osteoporosis.

For both men and women, checking levels of the hormone DHEA would be important since this hormone is important for bone health. If found to be deficient, appropriate replacement would be desirable. (For additional info, see the *NYBC Self-Care Guide*.)

The use of natural anti-inflammatory agents like omega-3 fatty acids and ginger might also be useful.

If osteonecrosis is detected early on, small holes can sometimes be drilled in the bone to increase blood flow and allow new blood vessels to grow (a process called core decompression surgery), thus helping to slow worsening and reduce pain. However, there are no known curative measures that will permanently prevent a downhill slide toward bone death.

If it's progressed too far in the hip bone, the only thing that works is hip replacement. This surgery is usually successful and can provide true relief for those in pain from the bone problems. However, any surgery has some risks, and hip replacement must often be repeated after a number of years.

While pointing out that there's nothing that's been proven by research to prevent worsening, HIV researcher Joseph Kovacs, MD, advises patients to avoid activities that could increase the pressure on the hip joint, including some weight lifting exercises, squats, running on concrete, and carrying heavy weight on the shoulders.

Key Treatments

Bone nutrients. Supplementing with calcium (1,000 mg daily for men, and 1,000-1500 mg for women), magnesium (500-600 mg; excess magnesium can cause loose stools so watch for this), and vitamin D (800 IU daily) may be important for the prevention of osteopenia and osteoporosis. As discussed above, deficiencies of these nutrients have been reported in HIV+ people, and long-term supplementation may be crucial for helping to prevent problems. Other nutrients involved in the production of bone tissue include boron, manganese, zinc, copper and silicon. A potent multiple vitamin/mineral supplement will usually contain these.

Supplementation with sulfur-containing substances can provide necessary building blocks for bone and connective tissue. Included are MSM (methylsulfonylmethane; doses of 2,000 mg daily might be appropriate), chondroitin sulfate and glucosamine sulfate (a combo formula containing both could be used in doses of one capsule, two or three times daily).

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*.

Diet. In those whose diets are not already optimal, dietary improvement is a must to provide all the building blocks for bone. In addition, since an acid-forming diet can cause bone loss, aiming for a diet high in fresh fruits and vegetables is important. The good diet described in *NYBC's Self Care Guide* would be a great beginning.

Exercise. Long known to help prevent osteoporosis, **weight-bearing exercise** (as simple as walking for at least 30 minutes several times each week) is a crucial component of any bone protection program. It cannot be said strongly enough: for those who care about their bone health, setting up a regular exercise program is hugely important. Just do it. (For more info, see *NYBC's Self Care Guide*.)

Hormone replacement therapy. It is clear that in postmenopausal women, hormone replacement therapy can help to prevent osteoporosis. Since HIV-positive women may go through menopause at much earlier than usual ages, the lack of appropriate hormones may ultimately contribute significantly to osteoporosis problems. The pros and cons of such replacement therapy should always be discussed with your physician as there are significant risks associated with its use, as well as possible benefits. Another hormone important to bone health is DHEA, often too low in both men and women living with HIV. So both men and women should be tested for hormone levels, including particularly the female hormones in women, and DHEA in both sexes. Where found to be deficient, appropriate replacement could be helpful in preventing bone problems. For details on hormones, see *NYBC's Self Care Guide*.

Nutraceuticals

One reason HIV and/or antivirals are suspected is due to the high incidence of osteopenia and osteonecrosis seen in children with HIV. Some nutrients and botanicals found in this formula are designed to provide a broad spectrum of support, nourishing and enhancing the body's ability to retain and rebuild bones. Double check other supplement intake to assure that you are not taking too much zinc (more than 150 mg/day), magnesium (1,000 mg) or copper (5 mg). Please note that this is a rather HIGH amount of vitamin K (80 mcg of the phylloquinone form considered to be a maximum daily intake). *Do not use with coumadin/warfarin*. The happy news is that a 2,000 mcg (2 mg) single dose of vitamin K was given orally to newborn Thai infants, preventing late hemorrhagic (bleeding) disease and causing no harm (*J. Pediatrics*, 1991;119(3):461-464).

Other important nutrients include vitamins C (ascorbic acid), D, K, B12, folic acid; the minerals calcium (Krebs cycle chelate/carbonate) (although the quantity is pretty low at 600 mg), magnesium, zinc, copper, sodium, boron, silicon, strontium and betaine hydrochloride along with a soy bean extract. It is not entirely clear why strontium is in this formula. Recent data suggest that in the elderly, high doses of vitamin D given four times a year helped reduce the risk of fracture; however, these were at 100,000 units each occasion which some feel is very risky and potentially toxic. It may be better simply to add a decent amount of calcium (1,000-1,500 mg) and vitamin D (800 to 1,200 IU) per day. You must, of course, take into account your gender, height, weight and age when considering the best dose for you.

Bone Up (Jarrow) contains **Microcrystalline Calcium Hydroxypatite (MCHA)** is a superior form of calcium derived from freeze-dried bone. It contains phosphorous in a natural 2:1 ratio as well as other natural bone assimilating constituents such as trace minerals and glycosaminoglycans, and matrix proteins such as collagen. MCHA is very well

absorbed and utilized. Also includes magnesium, boron, glucosamine, zinc, copper, manganese and Vitamins B12, folic acid, D (1,000 IU) and K (10 micrograms).

Glucosamine & Chondroitin. Glucosamine is an integral part of all connective tissue in the body, used in conjunction with chondroitin to offset the pain and inflammatory damage of arthritis and joint-related pain. Glucosamine is available in two forms: N acetyl-glucosamine and glucosamine sulfate; some suggest it may be better for absorption to use both. Some clinical studies have suggested that glucosamine sulfate may increase insulin resistance. If you are at risk for diabetes or are taking protease inhibitors and seeing signs of insulin resistance in your blood work, we recommend that you not use this product.

Ipriflavone. The use of ipriflavone, a soy-derived flavonoid (a nutrient), may help prevent bone resorption and stimulate bone production. In double-blind, placebo-controlled studies in non-HIV+ people it has been shown to increase bone density. Although studies have not been specifically done in HIV+ people, it might help in similar ways in those experiencing bone loss.

Marrow Plus. Some naturopathic physicians report good results using a Traditional Chinese Medicine called Marrow Plus in the treatment of bone pain. With more than a dozen patients on HAART who had developed an aching sort of bone pain, significant pain relief with the use of Marrow Plus. For several patients, the initial pain was significant enough to warrant discontinuation of the HAART meds. The use of Marrow Plus reduced the pain enough to allow these patients to remain on their meds. This product is a combination of codonopsis and supporting herbs. The standard dose is three to four capsules, three to four times daily.

MSM (methyl sulfonyl methane) is a sulfur donor that, in addition to its role in supporting sulfation, is an important component of protein and, thus, of muscle tissue. Researchers have reported that HIV+ people lose much more sulfur daily than is normal (possibly losing up to 10,000 mg daily, when 850 mg is thought to be normal) This high sulfur loss may mean inadequate amounts for conversion to proper maintenance levels of the sulfur amino acids methionine, cysteine, taurine and glutathione, as well as repair of muscle tissue, resulting in joint and muscle pain often experienced by HIV+ people. *However, data suggest that the primary source for the sulfur loss is CYSTEINE, which is why N-acetylcysteine (NAC) makes the most sense.* Some naturopathic physicians report very good results with aches and pains using 3 to 6 grams per day (3,000 to 6,000 mg) of MSM, taken in divided doses. Higher doses may be needed to replenish the sulfur amino acid pool.

Jarrow's BioSilicon. This concentrated form contains orthosilicic acid. It is said to be particularly helpful for maintaining good nails (split nails), bones, joints, hair and skin, as well as , potentially, blood vessels and the brain. Silicon is important for tissue strength and elasticity. One study showed considerably greater bioavailability for this product than placebo, horsetail extract or a colloidal gel. Silicon may help to reduce an excessive level of aluminum which some have connected to the development of Alzheimer's; however, this is contested and indeed, some even suspect that silicic acid may be a culprit in the development of Alzheimer's (*Lancet*, 1991;338:1386-7). People with low calcium or estrogen levels may have a low silicon level which may be correlated to heart disease. Children taking parenteral nutrition with bone disease were noted to have lower silicon levels (*J. Am. Col Nutr*, 1992;11(5):601/Abstract 5). By the way, beer contains lots of silicon!

NYBC and Other Nutraceuticals for Bone Health:

Bio-Silicon x 30ml	30 drops per day
Calcium Citrate + Magnesium 520mg x 250	2-3/d (0-1B, 1L, 1D)
Bone Up (Jarrow)	6/d (2B, 2L, 2D)
Vitamin D 1,000mg x 180	1/d (1B)
Glucosamine & Chondroitin 500mg/400mg x 120 500 mg of glucosamine and 400 mg of chondroitin, both in sulfate form.	4/d (1B, 1L, 2D)
Ipriflavone 300mg x 90	3/d (1B, 1L, 1D)
Magnesium Glycinate x 120	2/d (1B, 1D)
Marrow Plus x 750mg x 270	9-12+/d (3+B, 3+L, 3+D)
MSM 1,000mg x 180	2/d (1L, 1D)