HIV and Your Whole Health

HIV and Your Bones

Osteoporosis and osteopenia are familiar terms to many older adults. A diagnosis of osteoporosis, a serious loss of bone mass, can bring on a lot of anxiety, as it generally means that a person’s bones have become weaker and are more likely to break. And while a diagnosis of osteopenia—a less serious loss of bone—does not mean the same thing as an osteoporosis diagnosis, it can be of concern just the same. Unfortunately, many HIV-positive people—many of whom are younger than those who typically experience weakening bones—are learning that they, too, have osteopenia or osteoporosis.

The increased rates of osteopenia and osteoporosis among HIV-positive people is a concern, however, we’ve come to understand that osteoporosis in young or middle-aged HIV-positive people is not quite the same as a diagnosis of osteoporosis in older adults. As research continues, we are learning more about osteopenia and osteoporosis in HIV—including their possible causes—and the ways in which to slow (or reverse) their progression.

What is bone?

Bone is living tissue that is in a constant state of regeneration, much like the kidneys, heart, and other organs of the body.

Bone consists of two important components: collagen and mineral. Bone is mostly made up of collagen. Collagen provides a soft framework and gives bones necessary flexibility. The mineral component includes calcium and phosphate and hardens the collagen framework. Bones must maintain a balance of collagen and mineral so that they are strong, yet flexible enough, to withstand stress.

We reach our peak bone mass around the age of 30. However, our bones are changing constantly throughout our lives. This process is known as “remodeling” and there are two important types of bone cells to be familiar with: osteoclasts and osteoblasts. Osteoclasts are responsible for removing old or worn bone, which can leave cavities (lacunas). The removal of bone, and the creation of lacunas, is known as bone resorption. It is the job of the osteoblasts to fill these lacunas with new collagen and mineral, a process known as bone formation.

Just as healthy bone structure requires adequate amounts of collagen and mineral, there must also be a healthy balance of bone resorption and formation. If the amount of new bone deposited by osteoblasts equals the amount of bone taken away by osteoclasts, the bones stay strong.
However, after we reach our peak bone mass, the balance tends to shift, with more bone being taken away than deposited.

What is osteoporosis?
Osteoporosis—which means “porous bone”—is a disease characterized by low bone mass and structural deterioration of bone tissue. This can cause the bones to become fragile and, as a result, increase the risk of fracture. With osteoporosis, the greatest risk of fracture involves the wrist, hip, or spine. However, virtually any bone in the body is more likely to fracture in someone who has osteoporosis.

Osteoporosis is the result of too much bone resorption and not enough bone formation, a process that is discussed in the previous section. Both collagen and mineral are depleted in osteoporosis, which can compromise both the flexibility and hardness of bone.

Osteoporosis is a common problem in the United States. Approximately 10 million Americans are living with osteoporosis, approximately 70 to 80 percent of whom are women. It is responsible for more than 1.5 million fractures annually, including 300,000 hip fractures, 700,000 spine (vertebrae) fractures, 250,000 wrist fractures, and more than 300,000 fractures of other bones.

Generally, osteoporosis is less common in men than in women. This is true for several reasons. First, men have larger skeletons, meaning that they can usually afford to lose more bone before their bone strength becomes compromised. Second, their bone loss tends to start later in life and progresses more slowly. Third, they do not experience the rapid bone loss that affects women when their estrogen production drops as a result of menopause. However, despite these differences, men are still at risk for osteoporosis.

Technically speaking, there are two different types of osteoporosis: primary and secondary. Primary osteoporosis can occur in both men and women at any age, but usually follows menopause in women and occurs later in life in men. Secondary osteoporosis can occur in people who either take medications or suffer from diseases that can cause decreased bone density.

Osteoporosis is known as a silent disease, as it does not usually cause any symptoms. Many people do not find out that they have osteoporosis until they have suffered a bone fracture.

While osteoporosis is certainly an important predictor of fracture risk, it is not the only factor to consider. Fracture risk also depends on the likelihood of a serious fall or injury, which increases with age. For example, a younger man or woman with osteoporosis—someone with greater muscle mass, strength, dexterity, and coordination—is less likely to experience a serious fall of injury than an elderly man or woman. In turn, a younger person with osteoporosis is less likely to experience a bone fracture than an older person with osteoporosis. This is very important to consider when thinking about osteoporosis in relatively young, relatively fit HIV-positive people.

How is it diagnosed?
Bone mineral density (BMD) tests are the only way to detect osteoporosis. These tests are painless
and noninvasive, and they are very helpful in terms of measuring bone strength. There are a number of tests available: central machines, which measure BMD in the hip, wrist, spine, or total body; and peripheral machines, which measure BMD in the finger, hand, forearm, heel, or shin bone.

The most widely used and best understood BMD test is DEXA (Dual Energy X-ray Absorptiometry). DEXA measures BMD of the spine, hip, or total body. While radiation is used to conduct a DEXA scan, it involves approximately a tenth of the radiation required for a single chest x-ray. To conduct this test, the patient rests on a padded table. A large mechanical arm moves over the body, with a total body scan taking approximately 20 minutes to complete.

Results of BMD tests are usually expressed as “T-scores.” A T-score involves a statistical term called “standard deviation,” a measurement of how far something is away from what is considered “normal.” With respect to BMD testing, “normal” has been defined as the average BMD of healthy, young controls (representing peak bone density). If you are a female undergoing BMD testing, your bone density will be compared to that of a population of young, healthy women; if you are a male undergoing BMD testing, your bone density will be compared to that of young, healthy men. A T-score is the number of standard deviations below (or above) these “normal” cases:

- Normal bone: T-score better than -1.
- Osteopenia: T-score between -1 and -2.5 (discussed in the next section)
- Osteoporosis: T-score less than -2.5

BMD testing will also produce what is known as a “Z-score.” This compares the BMD of the person being evaluated with the average BMD of people of the same age and sex. However, when it comes to diagnosing osteoporosis, the T-score is of the most importance.

At the present time, there are competing views on when to screen for bone problems in people with HIV. A 2009 set of recommendations by the Infectious Diseases Society of America (IDSA) suggests screening HIV-positive men and women who are over 50, but only if they have another risk factor, such as a previous fragility fracture or the use of medications known to cause bone loss. A more recently published set of recommendations suggests that all HIV-positive men and women aged 50 and older should receive bone scans.

What is osteopenia?
A common misconception is that osteopenia is the same as osteoporosis. While both conditions mean that bone density is less than that of normal bone, only osteoporosis is associated with a significantly increased risk of bone fracture.

Whereas a diagnosis of osteoporosis reflects bone disease, a diagnosis of osteopenia is primarily meant to draw attention to decreasing bone density that might eventually progress to osteoporosis and the importance of maintaining bone health. Most experts agree that osteopenia
is not a cause for alarm and does not usually need to be treated, with the exception of more attention being paid to calcium and vitamin D intake (if deficiencies can be documented via a blood test), along with exercise.

While it is true that men and women diagnosed with osteopenia are at a higher risk of developing osteoporosis over a five- to ten-year period, only a percentage of people with osteopenia will eventually develop osteoporosis and experience a serious fracture.

What are the risk factors for osteoporosis?
There are a number of factors that can increase the risk of osteoporosis. These risk factors include:

- **Age:** The older you are, the greater the risk of osteoporosis.
- **Gender:** Osteoporosis is more likely to occur in women than in men.
- **Race:** Caucasians and Asians are more likely to develop osteoporosis. However, this is not to say that African Americans and Latinos are not at risk for this disease.
- **Bone Structure and Body Weight:** Small-boned and thin women and men are at a higher risk for osteoporosis.
- **Menopause/Menstrual History:** Normal or early menopause (brought about naturally or because of surgery) increases the risk of developing osteoporosis. In addition, women who stop menstruating before menopause because of conditions such as anorexia or bulimia, or because of excessive physical exercise, may also lose bone tissue and develop osteoporosis.
- **Low testosterone levels:** Low testosterone levels (hypogonadism) in men have been associated with decreased bone density and strength. Low testosterone is a relatively common problem in HIV-positive men.
- **Lifestyle:** Cigarette smoking, drinking too much alcohol, consuming an inadequate amount of calcium, or getting little or no weight-bearing exercise, increases the chances of developing osteoporosis.

HIV—and the medications used to treat it—are also believed to be risk factors for osteoporosis as well. This is reviewed in much greater detail in the next section.

What is the connection between HIV and osteoporosis?
Studies have documented that osteopenia and osteoporosis are more common among HIV-positive people, compared to HIV-negative individuals of the same sex and age. However, the reasons for
Is HIV infection itself to blame? Possibly. A number of potential connections between HIV and bone loss are being studied. For example, HIV infection can increase certain proteins in the body—including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-a)—that may also be responsible for accelerated bone loss. It’s also possible that the constant level of T-cell activation in the body may have an effect on bones. Some researchers have also speculated that HIV’s ability to infect cells in the bone marrow may be to blame.

It’s also possible that the medications used to treat HIV may have a negative effect on bone health. There have been studies linking **protease inhibitors** (PIs) and **nucleoside/nucleotide reverse transcriptase inhibitors** (NRTIs) to decreased BMD in HIV-positive people. Some research suggests that protease inhibitors can impair the way the body utilizes vitamin D, which is essential to bone health. There has also been research suggesting that the mitochondrial toxicity caused by some NRTIs can impair the function of osteoblasts. Additionally, there has been research linking body-shape changes (lipodystrophy)—which can be caused by PIs and NRTIs—to decreased bone density. A majority of studies now find that the use of ARV medications typically results in a 2 to 6 percent bone loss within the first two years after starting treatment—about the same as that seen in women after the onset of menopause. Fortunately, longer-term use of ARVs does not appear to cause chronic and progressive bone loss beyond the first two years of treatment.

One thing is certain: the risk of osteopenia/osteoporosis increases with the length of time someone has been living with HIV. Moreover, HIV-positive people who have other risk factors for osteopenia/osteoporosis, may be at an increased risk for these bone problems.

What about prevention and treatment?
At the present time, there is no way to cure osteoporosis. However, there are ways to help prevent it and treat it. It is generally agreed that all HIV-positive people can reduce their risk of developing osteoporosis through the following strategies:

**Calcium and vitamin D intake:** While calcium alone cannot prevent or cure osteoporosis, it plays an important role in maintaining bone health. According to the National Academy of Sciences, adults between 19 and 50 years of age should be receiving approximately 1,000 mg of calcium a day; adults 51 years of age and older should be receiving approximately 1,200 mg of calcium a day. Yet surveys have shown that many Americans are not consuming enough calcium to maintain bone health; studies have also shown that HIV-positive people of all ages are lacking in calcium intake.

Foods rich in calcium include milk, cheese, tofu, and broccoli. Other foods, including orange juice, are often calcium enriched, meaning that calcium has been added by the manufacturer. For people who are unable to consume enough calcium-rich foods, calcium supplements can be purchased through grocery stores, pharmacies, and health food shops. Be sure to discuss any supplements you buy—or plan to buy—with your doctor.

**Vitamin D** is also important, as it helps the small intestine to absorb calcium. It also slows the
removal of calcium from the body by the kidneys. In other words, calcium and vitamin D work together to help maintain bone health. Vitamin D is manufactured in the skin following direct exposure to sunlight. Many people are able to get enough sun exposure in their day-to-day lives and do not need vitamin D supplementation. However, for certain individuals—including older adults, people with HIV, and people who go without direct sun exposure for extended periods of time—vitamin D supplementation is important. The major food sources of vitamin D are vitamin D-fortified dairy products, egg yolks, saltwater fish, and liver. Oral vitamin D tablets are also available, but it is important to be careful with these, as high doses of vitamin D can be harmful. Many calcium supplements also include vitamin D, and will say “calcium plus” of “calcium +D” on the label.

Exercise: Like muscle, bone is living tissue that becomes bigger, denser, and strong with consistent exercise. To maintain and increase bone density and strength, both weight-bearing exercises and resistance exercises are helpful. Weight-bearing exercises include activities that force your muscles and bones to work against gravity—such as running, jogging, walking, and stair climbing—in which the feet and legs bear the weight of the body. Resistance exercises—including weight lifting and various stretching routines—draw upon muscle strength to strengthen muscles and bones. For best results, it’s probably best to work with a physical therapist or a certified trainer to determine the best exercises for maintaining bone health.

Lifestyle changes: Maintaining a normal body mass index (body weight proportional to height and frame size) and avoiding tobacco and alcohol use are key factors to consider.

Be careful with certain prescription drugs: Certain medications, especially if they are used at high doses or for long periods of time, can increase bone loss. For people with osteopenia or osteoporosis, stopping (or switching) certain drugs—including corticosteroids (e.g., prednisone and cortisone), phenobarbital, pentamidine, and ketoconazole—should be discussed with a health care provider.

As for ARVs, it’s still not clear which ones are most to blame for the increased rates of osteopenia and osteoporosis in HIV-positive people. In turn, there are no recommendations regarding which ARVs should be avoided or switched in HIV-positive people at risk for decreased bone density. In fact, studies evaluating the effects of switching from a PI-based regimen to an NNRTI-based regimen have not consistently found any positive effects on BMD in HIV-positive people. One particular drug, tenofovir (found in Viread, Truvada, Atripla and Complera), might increase the risk for bone loss. However, no studies have found increases in fractures from its use. Nevertheless, some people might wish to avoid it if they have had previous fractures or been diagnosed with osteoporosis.

Antiresorptive Medications: There are two distinct phases that contribute to bone remodeling: bone resorption and bone formation. In osteopenia and osteoporosis, the rate of bone resorption is higher than the rate of bone formation, leading to decreased bone density and strength. A number of prescription drugs approved by the U.S. Food and Drug Administration slow bone resorption, meaning that they can slow—and possibly halt—the decline in bone density and strength.
It is important to note that most of these agents have only been studied in post-menopausal women experiencing significant bone loss or older men with a secondary osteoporosis (e.g., corticosteroid use). Very little is known about the use of these agents in women who are still menstruating or younger men. Even less is known about their use to manage osteopenia or osteoporosis in HIV-positive people.

Antiresorptive medications are almost always used in combination with calcium and vitamin D supplementation to maximize the effects of treatment.

Bisphosphonates:

- Fosamax (alendronate): Alendronate is approved for both the prevention (5 mg every day or 35 mg once a week) and treatment (10 mg every day or 70 mg once a week) of postmenopausal osteoporosis. Alendronate is also approved for treatment of osteoporosis in men and women as a result of long-term corticosteroid use. Alendronate has been shown in clinical trials to reduce the risk of spine, hip, and wrist fractures. Studies have confirmed that the drug is useful for increasing bone density in HIV-positive people with osteoporosis.

- Boniva (ibandronate): Ibandronate is approved for the prevention and treatment of postmenopausal osteoporosis. The dose is one tablet (150 mg), once a month, taken on the same day each month. Ibandronate has been shown in clinical trials to reduce the risk of spine fractures. No clinical trials of ibandronate in HIV-positive people with osteopenia/osteoporosis have been conducted.

- Actonel (risedronate): Risedronate is approved for the prevention and treatment of postmenopausal osteoporosis. It can be taken daily (5 mg) or weekly (35 mg). It is also approved for use by men and women to prevent and/or treat corticosteroid-associated osteoporosis. In clinical trials, risedronate has been shown to reduce the risk of spine and other bone fractures. No clinical trials of risedronate in HIV-positive people with osteopenia/osteoporosis have been conducted.

Bisphosphonates are poorly absorbed. In turn, they must be taken on an empty stomach. Alendronate and risedronate should be taken first thing in the morning, at least 30 minutes before eating or drinking anything other than water. Ibandronate should also be taken first thing in the morning, at least 60 minutes before eating or drinking anything other than water.
These medications can cause heartburn and erosion of the esophagus. In turn, it is best to remain upright – either sitting or standing (for at least 30 to 60 minutes)—after taking these medications; they should not be taken immediately before bedtime. It might also be best to take these medications 30 to 60 minutes before taking other medications, such as anti-HIV drugs.

These medications could, theoretically cause jaw bone erosion and, paradoxically, weaker bones if taken over long periods. Thus far, however, studies of up to 10 years duration in HIV-negative women have shown extremely low rates of jaw problems and no additional fracture risk. Whether the same will be true in people with HIV, who might have to continue taking bisphosphonates for life, remains to be studied.

Hormone Therapy:

- Miacalcin (calcitonin): Calcitonin is a hormone that suppresses bone resorption and slows the removal of calcium and phosphorous by the kidneys. It has only been studied in, and approved for, postmenopausal women with osteoporosis. It is not known if calcitonin is safe or effective for the prevention or treatment of osteoporosis in HIV-positive men or premenopausal women.

- Estrogen: Synthetic estrogen, which mimics the activity of the natural female sex hormone, is approved for the prevention and treatment of osteoporosis in postmenopausal women. It is not used for the prevention or treatment of osteoporosis in men and is not recommended for premenopausal women. It is usually taken as a pill or administered via a patch applied to the skin. After the onset of menopause, estrogen therapy can increase the risk of endometrial cancer (cancer of the uterine wall).

- Prempro: A medication that contains both estrogen and progesterone, it has been shown to reduce the risk of hip and other fractures. However, even if estrogen and progesterone are used together, there is still an increased risk of breast cancer, strokes, and heart attacks. In turn, the U.S. Food and Drug Administration recommends using other osteoporosis medications to prevent/treat osteoporosis and, if estrogen/progesterone therapy is used, the lowest possible doses should be considered.

- Testosterone: Testosterone therapy may be a useful hormone therapy to slow or reverse decreased bone density and strength in men, including HIV-positive men. In one study reported
in 2001, a team of researchers randomized 51 HIV-positive men with osteopenia and muscle wasting to receive either testosterone (200 mg a week) or placebo for three months. At the end of the study, the men who received testosterone had significant improvements in their spinal BMDs, compared to the men who received placebo. The researchers cautioned that additional studies are needed to assess the effectiveness of testosterone therapy in HIV-positive men with decreased bone density.

Selective Estrogen Receptor Modulators (SERMs): SERMs are a new class of drugs that have been developed to provide the benefits of estrogen therapy, without the usual side effects of estrogen therapy. SERMs produce estrogen-like signals when they land on receptors of cells in the body, including osteoclasts. And because SERMs do not cause cells in certain tissues—such as breast and uterine tissue—to divide, the risk of breast and endometrial cancer using these drugs is reduced.

- Evista (raloxifene) is the only approved SERM for the prevention and treatment of postmenopausal osteoporosis. The dose is 60 mg a day. It is not approved for men or premenopausal women. In clinical trials, raloxifene reduced the risk of spine fractures in postmenopausal women with decreased bone density and strength. It is not yet known if raloxifene reduces the risk of hip and other non-spine fractures. Much like estrogen therapy, SERMs may only be useful for postmenopausal women with decreased bone density; it is not known if this drug will be useful for the prevention or treatment of osteoporosis in premenopausal HIV-positive women.

Bone-Forming Medications: While bisphosphonates, calcitonin, hormone therapy, and SERMs have been shown to reduce bone resorption, one class of drugs has been shown to actually help build new bone.

- Parathyroid Hormone is the primary regulatory of calcium and phosphate metabolism in bones. Forteo (teriparatide), a form of parathyroid hormone, has been shown in studies to increase bone density and strength. It is approved for the treatment of osteoporosis in postmenopausal women. It is also approved to increase bone density in men with primary osteoporosis, or osteoporosis caused by low testosterone levels. Parathyroid hormone levels can be measured with a blood test. In postmenopausal women participating in clinical trials, teriparatide reduced
the risk of fracture of the spine, hip, foot, ribs and wrist. In men, teriparatide reduced the risk of a spinal fracture; more data from studies are needed to determine the effects of this drug on the risk of fractures involving other bones in the body.

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