HIV and Bone Health

Bones are the foundation of our bodies; without healthy bones, we can become vulnerable to poor overall health. People with HIV are susceptible to bone loss, and to a condition called osteoporosis that may lead to fractures. In addition, as people with HIV are living longer due to effective antiretroviral therapy, bone complications may worsen as a result of aging and long-term HIV disease. Aging, antiretroviral drugs, traditional bone loss risk factors, and lifestyle all contribute to bone deterioration in the setting of HIV.

As with many HIV complications, studies of bone loss have provided conflicting results, and some have been of inadequate size or unsound methodology. But more research is underway to determine how serious bone problems may be in the short and long term in order to better prevent, diagnose, and treat them in people with HIV.

Bone Biology

Bone is made primarily of collagen, a protein that provides a flexible “framework,” and calcium phosphate, a mineral compound that gives bone its strength and hardness. This combination allows bones to bend enough to withstand stress but also gives them the strength to support the body’s other tissues.

The skeleton is not a static or fixed structure, like a marble sculpture or the steel frame of a building. Bone is alive and continually rebuilding throughout life. Any load-bearing physical exercise, including everyday activities like walking just a few feet, creates wear and tear on our bones that is repaired through a normal process called bone remodeling.

The remodeling process involves bone resorption, in which bone cells called osteoclasts are attracted to areas needing repair and move in to sweep away the damaged bone. Another type of bone cell, called osteoblasts, performs bone formation, laying down new bone and repairing the gaps created by osteoclasts. Any imbalance between bone resorption and bone formation leads to loss of bone mineral density (BMD), also called bone loss, as well as diminished structural integrity, loss of load-bearing capacity, and a greater risk of fracture. The process of remodeling can be disrupted by drug treatments, deficiencies in vitamin D and calcium, hormone imbalances, and immune dysfunction.

Maintaining a healthy skeleton through bone remodeling could be considered the body’s natural preventive maintenance program. In the first year of life, a period of tremendously rapid growth, almost 100% of the skeleton is replaced through bone remodeling. In adults, remodeling progresses much more slowly, at approximately 10% per year. In women, the rate of bone remodeling increases with the onset of menopause—the transition period (usually between 45 and 55 years of age) when a woman’s body makes less of the hormones estrogen and progesterone, her ovaries stop producing eggs, and she gradually ceases to menstruate. Menopause is a natural biological process and not an illness, but the resulting decreased estrogen levels contribute to bone loss in postmenopausal women.

Bone Loss in People with HIV

Documented for at least two decades, bone loss is gaining recognition as a major complication in HIV disease. As Ighovwerha Ofotokun from Emory University said at the 2011 Conference on Retroviruses and Opportunistic...
Infections (CROI), “the public health implication of bone disease in HIV is grossly underestimated.”

HIV positive people are susceptible to the same bone problems as the general population. The most common of these are osteopenia and osteoporosis, both of which can put individuals at risk for fractures.

**Osteopenia and Osteoporosis**

Osteopenia is the condition of lower-than-normal bone mineral density (BMD) and is considered a precursor to osteoporosis, the more severe form of bone loss characterized by compromised bone strength. Osteoporosis puts people at greater risk for fragility fractures—breaks that occur as a result of normal activities, such as a fall from standing height or less. (Such fractures suggest skeletal weakness, because healthy bones typically do not break as a result of falling from so low a height.)

The gold standard for assessing osteopenia and osteoporosis is an imaging technique called dual-energy X-ray absorptiometry (DEXA). A DEXA scan uses X-rays to measure calcium and other bone minerals in a given area of bone, such as the hip, spine, wrist, heel, or finger. DEXA scans are non-invasive, painless, and take only a few minutes.

Most commonly, results from a DEXA scan are used to generate a T-score, which compares the bone mineral density detected by the scan with the average BMD of a healthy 30-year-old adult. An individual whose BMD perfectly matches this average would receive a T-score of zero. Differences between an individual’s BMD and this “norm” are expressed as standard deviations. The more standard deviations below zero, the lower the BMD and the higher the risk of fractures. The chart at right shows how the World Health Organization uses T-scores to define various bone density states.

Another type of score, the Z-score, compares an individual’s DEXA results to the average BMD of people matched by sex, age, weight, and ethnicity. A Z-score therefore shows how an individual’s BMD measures up to that of people at the same life stage and with similar risk factors for bone loss.

Bone loss appears to be common among people with HIV. For example, in a recent meta-analysis, Todd Brown of Johns Hopkins University (Johns Hopkins University) and Roula Qaqish of Abbott Laboratories noted reduced BMD in 67% of HIV positive study participants. Osteoporosis, the more advanced form of bone loss, was reported in 15% of participants with HIV—three times more than in HIV negative study participants. Several cross-sectional studies from as early as 2000 indicate that BMD is reduced by 2% to 6% within the first two years after initiation of antiretroviral treatment. This decrease is similar to that seen during the first two years of menopause in HIV negative women.

**Fractures**

According to studies reported at CROI in 2010 and 2011 and elsewhere, fractures are occurring in HIV positive people at rates 30% to 70% higher than in uninfected individuals. In 2008, Virginia Triant of Massachusetts General Hospital and colleagues compared fracture prevalence in HIV positive and HIV negative individuals in a large clinic setting. Overall, the fracture prevalence per 100 persons was 2.87 in the HIV positive group, compared with 1.77 in the HIV negative group—a highly statistically significant difference. Despite the fact that the study accounted for gender, age, and race but not other factors

**OTHER BONE CONDITIONS**

Two other bone problems sometimes seen with HIV have gained attention in the past several years: osteomalacia and avascular necrosis.

Osteomalacia is a skeletal disorder characterized by “softening” of the bones; the bones contain the usual amount of collagen but lack calcium due to insufficient vitamin D intake or the body’s inability to process and use vitamin D. (See “The Role of Calcium and Vitamin D,” page 33, for more on this vitamin deficiency.) The condition results in fracture-prone bones, muscle weakness, and bone pain, particularly in the hips.

Also known as osteonecrosis, avascular necrosis (AVN) is bone death caused by inadequate blood supply to the affected area. It occurs most commonly in the hip and shoulder. Risk factors include chronic inflammation, use of corticosteroids in the setting of immune reconstitution, and hypertriglyceridemia—all factors associated with HIV disease and/or its treatment—as well as alcohol dependence. Researchers with the Aquitaine Cohort, a group of HIV positive individuals in France, reported in 2005 that 12 cases of AVN were detected in a six-year period; these cases were strongly associated with heavy alcohol use and history of corticosteroid use.
such as smoking, antiretroviral use, or body mass index, the difference in fracture rates is compelling.

Two very recent studies, one conducted in the United States the other in Australia, both identified CD4 cell count—one of the primary markers used to measure immune health in HIV disease—as a factor in fracture risk for people living with HIV.

Benjamin Young of the Rocky Mountain Center for AIDS Research, Education, and Services in Denver and colleagues found that a nadir (lowest-ever) CD4 count below 200 cells/mm$^3$ was associated with higher fracture rates in members of the HIV Outpatient Study (HOPS); older age, substance use, hepatitis C virus (HCV) coinfection, and diabetes were also associated with increased fracture risk. When compared with annual fracture rates for the general U.S. population between 2000 and 2006, the fracture rates for HOPS participants were between 1.98 and 3.69 times higher.

Risk of fracture was also strongly associated with CD4 cell count in a retrospective study conducted by Michelle Young and colleagues. The researchers analyzed medical records from 2,424 HIV positive individuals treated for fracture between 1998 and 2009 at the Alfred Hospital in Melbourne, Australia. Each patient who had experienced a fracture was matched with two “case control” individuals of the same age, sex, and length of time since receiving an HIV diagnosis; these control individuals did not experience fractures during the study period.

The analysis included 73 cases of fragility fracture or “low-trauma” fracture (researchers excluded injuries caused by traumatic incidents, such as car accidents). DEXA scan results, available from more than half the fracture patients and just under a third of the controls, showed that the overwhelming majority (88%) of those who experienced fractures had low BMD; 32% had osteopenia and 56% had osteoporosis. Median CD4 cell counts were significantly lower in the fracture patients than in the matched controls (283 cells/mm$^3$ and 448 cells/mm$^3$, respectively), and further analysis revealed a statistically significant association between increased risk of fracture and a CD4 count below 200 cells/mm$^3$. The authors reported “no associations between fracture risk and viral load, [or] use of, class or duration of antiretroviral agent,” although use of corticosteroids and some anti-epileptic medications, both used to treat HIV-related conditions, was linked with fracture risk.

Another recent study offers a slightly different perspective. Michael Yin of Columbia University Medical Center in New York reported at CROI in 2011 on a study that examined the time between starting antiretroviral treatment and experiencing a fracture. The investigators tracked more than 3,410 HIV positive participants from multiple clinical trials for several years. The average age at study start was 39, most participants (83%) were male, half were white, and 6% were coinfected with HCV. Among the female participants, 19% self-identified as postmenopausal.

During the study period, 67 participants (2%) experienced fractures. The median time-to-first-fracture was 124 weeks—roughly two and a half years. In participants who were new to antiretroviral therapy, the risk of fractures was highest in the first two years of treatment. These findings provide support for the association between antiretroviral treatment initiation and short-term bone loss; however, the investigators did not see links between specific antiretroviral drugs or drug classes and fractures, and suggested that further study is needed in the area.

Fragility fractures are in most cases caused by falling, which itself becomes more common with advancing age. Fractures seen with osteoporosis in the general population most commonly occur in the spine, hip, and wrist. Fractures often lead to other health problems; for example, it has been estimated that hip fractures result in a 2.5-fold increase in future hip fractures and a 10% to 20% increase in mortality.

Researchers and activists are drawing attention to the fragility fracture risk that people face as they get older with HIV. Ofotokun stated at CROI 2011 that fractures “can be a cause of crippling morbidity. In one year following fracture surgery, mortality . . . can be as high as 30%, particularly in the elderly and immunocompromised individual.” Jules Levin, director of the National AIDS Treatment Advocacy Project, said in an interview, “I think a critical issue is, perhaps, what will actually happen to HIV positive people when they age into their 60s and 70s. How prevalent will fractures become and how serious will the impact be?” Levin continued, “We know in the general population that once an elderly person experi-

### ESTIMATING FRACTURE RISK

Fragility fracture risk can be calculated using an online computer assessment known as FRAX, a tool developed by the World Health Organization to evaluate risk of fracture in the general population.

FRAX calculations give the probability of a fracture within ten years, based on patient models, individual clinical risk factors, and bone mineral density at the femoral neck (a common fracture site at the top of the thigh bone, near the hip joint). FRAX is available at [www.shef.ac.uk/FRAX/index.jsp](http://www.shef.ac.uk/FRAX/index.jsp).
increases a fracture, mortality [risk] increases. I don’t think we are prepared for this at all.”

Causes of Bone Problems in HIV Disease

Fragility fractures are essentially the clinical manifestation of bone loss, so research findings on risk factors associated with fractures hint at the underlying causes of reduced BMD.

Osteoporosis typically occurs as a result of aging and/or menopause; this is termed primary osteoporosis. However, secondary osteoporosis may occur in association with chronic illnesses and other health conditions. Specific disease processes and medication have been shown to contribute to secondary osteoporosis. In the general population, 44% to 90% of men age 50 or older and postmenopausal women with low BMD have secondary causes of osteoporosis. In men, hypogonadism, alcoholism, and glucocorticoid exposure account for 40% to 60% of cases of secondary osteoporosis; in women, postmenopausal estrogen deficiency and glucocorticoid use account for 35% to 40% of cases.

Low bone density and secondary osteoporosis in HIV disease most likely have several underlying causes and involve a complex interaction between the virus itself, traditional bone loss risk factors (such as age, sex, and ethnicity), the consequences of chronic HIV infection (including inflammation and low body weight), high alcohol and tobacco use, low vitamin D levels, and antiretroviral therapy.

HIV-Related Conditions

There is a high prevalence of bone loss among HIV positive individuals who are not on antiretroviral treatment, suggesting the virus itself and HIV-associated inflammation influence bone remodeling and bone mass. HIV proteins have been shown to increase the activity of osteoclasts and promote the death of osteoblasts, thereby increasing bone resorption and decreasing bone formation. In addition, tumor necrosis factor alpha, a cytokine (chemical “messenger”) that is elevated in the setting of HIV, promotes osteoclast activity without simultaneously promoting bone formation.

Hypogonadism (decreased production of the sex hormone testosterone) is common in HIV positive men and is a risk factor for bone loss. Lipodystrophy (HIV- and treatment-related fat loss, particularly in the face, arms, legs, and buttocks) may contribute to bone loss through the complex signaling of fat cell hormones. As with the general population, visceral (belly) fat accumulation has also been associated with low BMD in HIV positive individuals; this is an area of ongoing research.

Low body weight is also associated with poorer bone health in the general population. A meta-analysis by Mark Bolland of the University of Auckland, New Zealand, and colleagues found that many of the cross-sectional studies of BMD may not account for the overall lower body weight frequently seen in people with HIV. His team reviewed the data from these studies and in fact did find lower body weight among the HIV positive participants, which may help account for the lower BMD reported in these studies.

Bone loss in young people is also a growing area of research. A key determinant of bone mass in adults is normal bone development during adolescence and early adulthood. Nearly every study in children who were born with HIV has reported lower-than-expected bone mass as well abnormal hormone and calcium levels. Bone abnormalities may be worse in young people using antiretroviral therapy, those with advanced disease, and pubertal males.

Antiretroviral Drugs

Antiretroviral therapy has received much attention as a potential cause of bone loss in HIV positive people, and there is some evidence to support its role, although the mechanisms are not fully understood and studies have produced mixed results. For example, a study published in 2008 involving 492 members of the Aquitaine Cohort found osteopenia in 54% and osteoporosis in 27% of participants, but the analysis did not show a significant relationship between bone loss and antiretroviral treatment. However, several recent studies have clearly linked one drug, tenofovir (Viread), with decreased BMD (although not with osteoporosis or fracture rates). Tenofovir is implicated in phosphorus imbalance and with impaired vitamin D metabolism, which in turn are related to bone loss.

In a late-breaking paper presented at CROI in 2011, Kathleen Mulligan of the University of California, San Francisco (UCSF), described results from a sub-study of iPrEx, the global trial of oral tenofovir plus emtricitabine (Emtriva)—the antiretroviral drugs combined in the frequently used Tru-
vada pill—to prevent HIV infection in gay men and transgender women. (To learn more about this groundbreaking study, see “The iPrEx Results: Lifting Hopes, Raising Questions” in the Summer/Fall 2010 issue of BETA.) The sub-study enrolled 503 participants (247 taking tenofovir/emtricitabine and 256 taking a placebo pill) at study sites in Brazil, Peru, South Africa, Thailand, and the United States.

DEXA scans of the hip and spine were performed at study entry and every six months thereafter. The researchers also saw a trend toward increased bone mineral density in the placebo arm and a decrease in the tenofovir/emtricitabine group, with a very small but statistically significant difference between the groups at week 24. (No differences between the groups in bone fractures were found, however.) These results, Mulligan and colleagues noted, suggest a link between tenofovir/emtricitabine use and bone loss in HIV negative people, although ongoing analysis is needed to see whether the small decline is clinically significant and whether it worsens, stays the same, or improves with time.

Clearly, there are bone density concerns that still need to be researched for those with HIV on treatment, and in HIV negative individuals now that tenofovir is showing promise for HIV prevention. Interestingly, 36% of participants in this iPrEx sub-study had low bone mineral density in the spine and 18% in the hip at study entry, before taking PrEP. The unexpected prevalence of low bone mineral density prior to starting the study drug warrants further attention; as Mulligan said in her presentation, “it is possible that low BMD seen in some people with HIV infection may have predated the acquisition of HIV.”

Also at CROI 2011, Albert Liu of the San Francisco Department of Public Health and UCSF presented data from a study of oral tenofovir as PrEP in HIV negative men. DEXA scans were performed on 184 participants (median age 40 years, 77% white) at study entry and two more times several months later. Over 24 months of follow-up, the researchers saw a statistically significant net decrease in average BMD in the hip and at the femoral neck (where the thigh bone narrows, near the hip joint) in the tenofovir-using participants compared with those taking placebo pills. These declines were greatest in the first 12 to 15 months of tenofovir use. In addition, BMD loss of at least 5% at the femoral neck was seen in 13% of tenofovir users, compared with only 6% of participants in the placebo group.

“Larger studies with longer follow-up are needed to determine the trajectory of these BMD changes and any association with clinical fractures,” Liu and colleagues concluded in their abstract. Fractures were reported during the follow-up period (six in the tenofovir group and four in the placebo group), but all were caused by traumatic injuries and were not related to tenofovir use.

In another presentation at CROI 2011, Mulligan reported findings from a study of bone mineral density in young men (age 14 to 25). The study included nearly 200 men who acquired HIV “behaviorally” (that is, they were not born with the virus and therefore have not had HIV all their lives) and 53 HIV negative controls. Of those living with HIV, 104 had never been on antiretroviral treatment. Twenty HIV positive men, 40 years old on average, started antiretroviral treatment for the first time in this study. The men gained an average of 120 CD4 cells/mm3 following treatment initiation. Dramatically elevated levels of bone resorption markers occurred immediately after the participants started treatment, peaked at week 12, and remained elevated at week 24.

The researchers found that average BMD was lower in the HIV positive participants taking antiretroviral drugs, particularly those whose treatment regimen included a protease inhibitor (PI), than in the HIV negative group. Of those on anti-HIV treatment, 70% were taking tenofovir; however, the researchers wrote that “the low bone mineral density in those on [antiretroviral therapy] could not be wholly attributed to tenofovir use.” While this study concerned bone loss rather than fractures, the researchers concluded that “impaired accrual of bone or actual bone loss during adolescence may confer additional risk of bone complications in later life.”

It is less clear whether protease inhibitors contribute to bone loss, although a study presented at the 2010 CROI by Grace McComsey of Case Western Reserve University compared regimens based on the PI atazanavir (Reyataz) and the non-nucleoside reverse transcriptase inhibitor efavirenz (Sustiva) and found greater loss in the spine (but not the hip) in those using the PI-based regimen.

Newer data presented at CROI 2011 showed that bone remodeling is disrupted early after starting antiretroviral treatment, after which bone loss stabilizes, persists, or even increases. Ighovwerha Ofotokun presented preliminary results from a small study that assessed the timing of BMD changes by tracking blood levels of certain cytokines and proteins that are known markers of bone resorption and formation. Their results suggest that immune reconstitution—which occurs when immune cells rebound as antiretroviral therapy begins to check HIV replication—plays a role in bone loss in HIV disease.

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Ofotokun and colleagues concluded that bone loss begins early after starting antiretroviral therapy and is spurred at least partly by immune reconstitution and the accompanying surge in CD4 cells.

These findings are consistent with results from another small study presented at CROI, which found that treatment initiation was associated with loss of bone mineral density,
particularly within the first year of treatment. Marit van Vonderen of Medical Center Leeuwarden in the Netherlands and colleagues saw greater BMD loss in participants who took a regimen of two nucleoside reverse transcriptase inhibitors, zidovudine (Retrovir) and lamivudine (Epivir), plus the PIs lopinavir/ritonavir (Kaletra) compared with those who took the non-nucleoside reverse transcriptase inhibitor nevirapine (Viramune) plus lopinavir/ritonavir.

Further analyses of data from these studies may help identify a “window period” after antiretroviral treatment initiation during which bone loss can be forestalled.

The Role of Calcium and Vitamin D

Calcium plays a crucial role in bone development and maintenance. Calcium interacts with phosphorus in the body to form calcium phosphate, the material that gives bones and teeth their hardness and strength.

More than 99% of the body’s calcium is found in the bones and teeth, but calcium also circulates in the bloodstream and is present in muscle and other tissue. Outside the skeleton, calcium is vital to proper muscle function, contraction and dilation of veins, transmission of nerve impulses, and other important functions throughout the body.

If these tissues do not get adequate calcium from the diet, they must “borrow” the mineral from the skeleton. This is accomplished through a complex process involving parathyroid hormone, the kidneys, and vitamin D.

Parathyroid hormone (PTH) has three major functions related to calcium and bone health. It stimulates the activity of osteoclasts, which resorb bone and free up calcium from the skeleton so it can be used elsewhere in the body; it prompts the kidneys to excrete (get rid of) phosphate, which changes the balance of calcium and phosphate in the body and liberates more calcium to circulate in the blood; and it triggers the production of an enzyme that converts vitamin D into a form that helps the small intestine absorb calcium from foods and supplements.

Levels of calcium in the blood regulate the secretion of parathyroid hormone. When serum calcium levels decrease and the body needs to free calcium from the bones, the parathyroid gland secretes the hormone; when serum calcium levels are high, secretion of PTH is inhibited.

Much attention has focused recently on the role of vitamin D in bone health in HIV disease. The term “vitamin D” actually refers to a group of fat-soluble vitamins, two of which are important to human health: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D2 is synthesized by plants, and vitamin D3 is synthesized by humans when the skin is exposed to ultraviolet-B (UVB) rays from sunlight. Very few foods naturally contain vitamin D; these include fatty fish (such as salmon and tuna), egg yolks, and beef liver. Other foods, such as milk and breakfast cereals, are commonly fortified with vitamin D.

In the body, the liver converts vitamin D into a substance called calcidiol, which in turn may then be converted into calcitriol, the biologically active form of vitamin D, in the kidneys or by cells in the immune system. When calcitriol is synthesized by immune system cells, it behaves as a cytokine, helping direct the body’s defenses against invading pathogens like bacteria and viruses. When calcitriol is instead synthesized in the kidneys, it helps regulate calcium and phosphate levels in the blood and thereby plays a role in bone mineralization, growth, and remodeling.

Low vitamin D levels are commonly reported in the setting of HIV; for example, a study described at the 2010 CROI found vitamin D insufficiency in 72% of HIV positive participants. However, low vitamin D levels are also common in the general population, with a handful of identifiable risk factors such as age, sun exposure, and ethnicity. For example, African Americans typically have lower vitamin D levels than white Americans, as the higher concentration of the pigment melanin in darker skin reduces the skin’s ability to generate vitamin D from exposure to sunlight (although it is not clear that lower vitamin D levels associated with darker skin have any clinical consequences).

A blood test for serum concentration of 25-hydroxyvitamin D, or 25(OH)D for short, is the standard test used to assess vitamin D levels. A 25(OH)D level of 30 ng/mL indicates vitamin D sufficiency, whereas a level between 21 and 29 ng/mL is indicative of insufficiency or deficiency.

In early 2011, Christine Dao of the U.S. Centers for Disease Control and Prevention and colleagues published results from an observational study of vitamin D levels in HIV positive individuals from four U.S. cities. In this study, 70% of the 672 participants had either insufficient or deficient levels of vitamin D, compared with 79% for adults in the U.S. general population. Low vitamin D levels were associated with traditional risk factors, such as darker skin, as well as kidney impairment and duration of exposure to efavirenz and tenofovir.

The U.S. Department of Agriculture offers a comprehensive list of foods that contain vitamin D, either naturally or through fortification, and how many International Units (IU) of the vitamin are found in a “common measure” of each food (for example, a three-ounce serving of canned tuna or a single egg). The list is available online at www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/SR23/nutrlist/sr23w324.pdf.
There is some cause for concern regarding the effects of antiretrovirals on vitamin D levels. The association between low vitamin D levels and exposure to efavirenz is thought to be related to this drug’s ability to stimulate the activity of cytochrome P450, an enzyme that plays an important role in how the body breaks down and uses the vitamin. In addition, because the kidneys help convert vitamin D into a form the body can use to grow and maintain healthy bones, kidney disease—which has been linked with tenofovir use in some individuals and is sometimes seen with HIV-related metabolic disorders—raises the risk of vitamin D deficiency and bone loss.

Findings on vitamin D levels and the use of other antiretrovirals have been mixed; more research is needed to identify the mechanisms through which these and other HIV drugs affect vitamin D metabolism in the body.

Screening Recommendations

Osteoporosis is both preventable and treatable, and the first step is screening for changes in bone density. However, there is conflicting opinion on whom to screen and how frequently.

The National Osteoporosis Foundation’s guidelines for the general population are to screen those with any indication of a fragility fracture, as well as women older than 65 years and men 70 and older. Yet guideline panels have not agreed on the best time to screen for bone problems in HIV positive individuals. Many researchers believe that, based on current evidence that HIV infection poses a risk for bone disease, people with HIV should be screened at a younger age.

McComsey and colleagues recommend DEXA scans for all HIV positive postmenopausal women and men 50 or older who have additional risk factors for osteopenia and osteoporosis. Other recommendations are to screen everyone living with HIV in order to have a baseline measurement of bone mineral density for this population. Unfortunately, DEXA scanning machines are not readily available at every health center, and the costs of scans may not be reimbursed by insurers if they are performed outside of accepted guidelines.

Lab tests can also help monitor bone health, although some are not routinely performed outside of research settings. These include tests that look at levels of calcium, phosphorus, and albumin in the blood, along with levels of vitamin D and PTH and markers of bone formation and bone resorption. Amounts of calcium and phosphorus excreted in urine and assessments of overall kidney health can help identify bone problems, as well. Screening for tenofovir-associated kidney toxicity can also help head off bone loss.

Treatment for Bone Loss

Pharmaceutical Interventions

Several pharmacologic interventions that are administered in the general population are also currently used for treatment of bone loss in the setting of HIV disease. One particular class of drugs, bisphosphonates, is the standard first-line therapy.

Bisphosphonates work by binding to the bone matrix—the material between bone cells—and preventing bone resorption by osteoclasts. Alendronate (Fosamax) is taken orally once weekly, whereas risedronate (Actonel, Atelvia) and ibandronate (Boniva) are taken orally once a month. Ibandronate is also available in an injectable form, administered once every three months. Zoledronate (Aclasta, Reclast, Zomera, Zometa) is an injectable bisphosphonate that can be administered once a year.

Four studies of alendronate in HIV positive individuals showed BMD increases with use of the drug compared with placebo, but the studies were small and the statistical significance limited. Similar results were obtained in two trials comparing once-yearly zoledronate against placebo. Hopefully, longer-term trials will move forward as HIV positive individuals are living decades longer.

Adverse effects reported with bisphosphonates include irritation of the esophagus and upset stomach. Osteonecrosis of the jaw has been reported, but it is extremely rare. Atrial fibrillation (abnormal heart rhythm) and esophageal cancers were reported in some trials but could not be associated directly with bisphosphonate use. Paradoxically, there are reports of chronic suppression of bone turnover, which may prevent the repair of damage to the bone architecture, eventually compromising bone strength and leading to fractures.

Nelson Watts and Dima Diab of the University of Cincinnati Bone Health and Osteoporosis Center reviewed clinical trial results and post-trial reports on bisphosphonates for osteoporosis treatment in the general population. According to their review, ten-year data on alendronate use in postmenopausal women showed continued increases in BMD and no increases in fracture rates. The authors explained that bisphosphonates accumulate in bone, creating a reservoir that continues to release the drugs for months or even years after treatment is halted. For example, studies with risedronate and alendronate suggested that the anti-fracture effect lasts for at least one or two years in individuals who stopped treatment after taking the drugs for three to five years. Given this persistent effect and the risk of long-term side-effects, the authors recommended a “drug holiday” after five to ten years of bisphosphonate treatment.

Other treatments are also available for bone loss. The hormone calcito-
Calcium RDA (mg/day) | Vitamin D RDA (mg/day)
--- | ---
1–3 years | 700 | 600
4–8 years | 1,000 | 600
9–18 years | 1,300 | 600
19–50 years | 1,000 | 600
51–70 years, men | 1,000 | 600
51–70 years, women | 1,200 | 600
> 70 years | 1,200 | 800

Adapted from the Institute of Medicine, Report Brief: Dietary Reference Intakes for Calcium and Vitamin D.
recommendations for vitamin D were based on conditions of minimal sun exposure, due to the wide variability in vitamin D synthesis from ultraviolet light and the risk of skin cancer. Although the committee did not include HIV as a factor in its recommendations, the guidelines may be considered sound for all, regardless of HIV status—although individuals are always wise to consult their HIV specialist or other primary care provider before starting any vitamin regimen.

**Guidelines for Good Bone Health and Disease Prevention**

There are many answers still to be uncovered by HIV-related bone loss research, but until the answers are clear, there are preventative measures that can be recommended today.

Exercise is a major component in preventing bone loss. Weight-bearing exercises are those in which bones and muscles work against gravity as the feet and legs bear the body’s weight. They include simple walking, jogging, Tai Chi, stair climbing, using elliptical machines, playing tennis, and even dancing. Muscle-strengthening exercise includes weight lifting and other resistance exercises.

Many HIV positive people are perfectly capable of vigorous exercise, but just about anyone can design an exercise routine that fits their abilities and contributes to better bone health. Regular weight-bearing and muscle-strengthening exercise can also improve agility, posture, balance, and strength, thereby reducing the risk for falls.

Preventing falls is something all older persons must consider. Strategies to prevent falls include vision and hearing correction, evaluation and treatment for any neurological problems, and reviewing medications for side effects, such as dizziness, that may cause falls.

Tobacco use impairs skeletal health and slows fracture healing (and is a known risk factor for cancer and heart disease) and should be avoided. (For more on the effects of tobacco in HIV disease, and for tips on quitting, see “Smoking and Your Health: How to Quit (And Why You Should)” in the Winter/Spring 2008 issue of BETA.)

Moderate alcohol use has not been associated with negative effects on bone health and may even be associated with a slightly higher bone density and lower risk of fracture in men and postmenopausal women, according to one recent study by researchers at Tufts University in Boston. However, more than three alcoholic drinks a day may be detrimental to bone health (and may increase the risk of falling).

Finally, following the IOM recommendations for calcium and vitamin D intake, taking care to regularly consume foods rich in calcium and vitamin D, and talking with health care providers about supplementation can go far to help HIV positive people maintain strong bones as they age—and at any life stage. The vast array of vitamin and mineral supplements on store shelves can be bewildering; consulting with medical professionals first can make that shopping trip easier, ensure that the supplements purchased are of good quality, and help individuals fit calcium and vitamin D supplements into their current anti-HIV treatment regimen and into their lifestyle.

**Conclusion**

Bone complications in people with HIV are of vital concern, and more studies are seeking to address this complex health issue. The need for accurate, scientifically derived information on bone loss prevention and treatment becomes more urgent as
people with HIV grow older. People living with the virus, researchers, and health care providers must be ready to tackle these issues as HIV moves into its fourth decade.

Although more studies of bone loss in HIV positive participants are needed, fortunately, it is already clear that simple prevention approaches based on exercise, lifestyle modifications, calcium-enriched diets, and vitamin D supplementation can be safe and effective strategies to improve bone health as people with HIV live into their older years.

Matt Sharp is a Person with AIDS, longtime HIV treatment advocate, and writer.

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