Osteopenia, Osteoporosis, and Other Bone Problems in HIV-Infected Individuals

Pablo Tebas, MD
Assistant Professor of Medicine
Washington University School of Medicine, St. Louis, Missouri

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SUMMARY BY TIM HORN
EDITED BY JOHN BILEZIKIAN, MD, AND MARC HELLERSTEIN, MD

OVER THE PAST FEW YEARS, A TREMENDOUS amount of attention has been paid to emerging metabolic complications in HIV-infected patients, particularly those receiving highly active antiretroviral therapy (HAART). *The PRN Notebook* has reported on many of these complications in past issues: insulin resistance and glucose intolerance (June 2001), coronary heart disease risk (June 2001), mitochondrial toxicities (June 2000), and fat redistribution (March 2000; September 1998). There is now growing concern regarding another metabolic problem occurring in HIV-positive patients: decreased bone density.

Like other metabolic complications, it is not entirely clear whether low bone density—more specifically, osteopenia and osteoporosis—in people living with HIV is related to advancing age, HIV infection itself, HAART, or perhaps a combination of all three. Fortunately, data regarding the epidemiology, pathogenesis, and etiology of bone density loss as it relates to HIV continue to emerge at an appreciable rate.

Osteoporosis and Osteopenia

BONE IS COMPOSED OF BOTH AN ORGANIC component consisting of collagen, which gives bone its flexibility, and a mineral component that includes calcium salts and phosphate salts, which combine to form hydroxypatite crystals and add hardness to the collagen matrix. Osteopenia and osteoporosis are characterized by a loss of both collagen and mineral—the collagen-calcium ratio is almost always normal in individuals with either of these two bone disorders—which compromises bone strength and can lead to an increased risk of fracture. Conversely, in osteomalacia (rickets in children), there is defective or inadequate bone calcification while the collagen matrix remains largely intact.

Clinically speaking, osteoporosis can be characterized as either primary or secondary. Primary osteoporosis can occur in both sexes at all ages but often follows menopause in women and occurs later in life in men. In contrast, secondary osteoporosis is a result of medications, other conditions, or diseases. Examples include hypogonadism, hyperthyroidism, celiac disease, and as discussed in this article, the possibility of either direct or indirect effects of HIV.

There is no way to accurately measure overall bone strength. However, bone mineral density (BMD) is widely accepted as a proxy measure, given that it accounts for approximately 70% of bone strength. BMD measurements have been shown to correlate strongly with the load-bearing capacity of the hip and spine and with the risk of fracture. As explained by Dr. Tebas, patients with osteopenia have a twofold increase in their risk for fracture compared to patients with normal BMD. For patients with osteoporosis, there is a fourfold to fivefold increase in risk for fracture. And for patients with osteoporosis and a history of a fracture, the risk of another fracture occurring is increased 20-fold.

While decreased BMD is certainly an important predictor of fracture risk, it is not the only parameter to consider. Fracture risk is also associated with a history of falls, low physical function such as slow gait speed and decreased quadriceps strength, impaired cognition and vision, and the presence of environmental hazards (e.g., icy sidewalk conditions).

Evaluating BMD

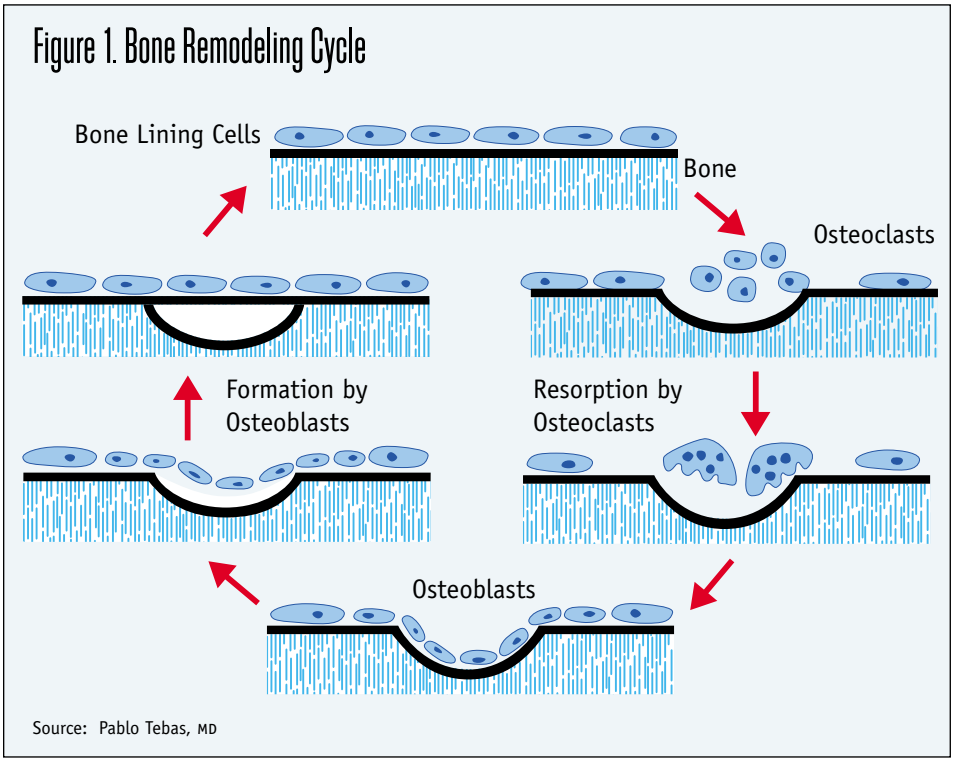
BMD IS OFTEN REPORTED AS A T-SCORE, which is equivalent to the number of standard deviations (SD) below a reference population of young healthy adults of the same sex and race as the subject. The T-score has also been used by the World Health Organization (WHO) to define osteoporosis. For example, a value for BMD within one SD (T-score > –1) of the young adult reference would be considered normal. Patients with a value for BMD more than one SD but less than 2.5 SD below the young adult mean (T-score < –1 and > –2.5) are said to have osteopenia. The WHO operationally defines osteoporosis as a BMD value 2.5 SD below the young adult mean (T-score < –2.5).

An alternative to the T-score is the Z-score, which compares the BMD to an age-, sex-, and race-matched population. However, Z-scores are not typically used to define osteoporosis, since they would not reflect the increasing prevalence of osteoporosis with age. For example, elderly patients may have a Z-score of zero, based on comparison to their own age group, but may very well have a T-score that would put them in the osteoporotic category. However, a Z-score lower than expected can alert clinicians to possible secondary causes of osteoporosis, including the possibility of HIV-associated osteoporosis independent of the effect of aging. A Z-score greater than 2 SD below age-matched controls confers a diagnosis of osteoporosis.

Although T-scores were based original-

ly on assessment of BMD at the hip by dual-energy X-ray absorptiometry (DEXA), they have been applied to define diagnostic thresholds at other skeletal sites and for other technologies. Experts have expressed concern that this approach may not produce comparable data between sites and techniques. Of the various sampling sites, measurements of BMD made at the hip predict hip fracture better than measurements made at other sites, whereas BMD measurement at the spine predicts spine fracture better than measures at other sites.

According to a recent report drafted by the National Institutes of Health, newer measures of bone strength, such as ultrasound, are being evaluated for potential use in the clinical setting (National Institutes of Health, 2000). Recent prospective studies using quantitative ultrasound (QUS) of the heel have predicted hip fracture and all nonvertebral fractures nearly as well as DEXA at the femoral neck. QUS and DEXA at the femoral neck provide independent information about fracture risk, and both of these tests predict hip fracture risk better than DEXA at the lumbar spine.



During bone resorption, osteoclasts attach to the mineralized bone matrix and excavate pockets, or lacunae, on the bone surface, releasing bone collagen and mineral. During bone formation, osteoblasts are recruited to the newly resorbed areas on the bone where they deposit new collagen. When the normal balance of resorption and formation is disturbed—becomes uncoupled—collagen and calcium loss can occur.

Bone Turnover

GROWTH IN BONE SIZE AND STRENGTH OCCURS during childhood, but bone accumulation is not completed until the third decade of life, after the cessation of linear growth. Even after bone accumulation has ended, there is a constant state of remodeling, with repeated cycles of resorption, followed by deposition of new bone.

Bone remodeling involves the coupled action of osteoclasts and osteoblasts. The osteoclasts resorb bone to release necessary calcium and collagen metabolites. Once bone has been taken up by osteoclasts, a pocket, or lacuna, is formed. It is up to the osteoblasts to deposit new bone to gradually fill the lacuna.

Generally speaking, loss of bone density can occur in two ways: increased resorption and decreased formation. The first involves excessively deep lacunae created by osteoclasts, which cannot be adequately filled by osteoblasts. The second involves diminished osteoblast function, such that a normal sized lacuna is not filled. In other words, when the normal balance of resorption and formation is disturbed—becomes uncoupled—collagen and calcium loss can occur.

In the research setting, bone remodeling can be assessed using surrogate markers of bone turnover in the blood or urine. These markers include bone-specific alkaline phosphatase and osteocalcin, which are indices of bone formation. There are also urinary levels of pyridinolines and deoxypyridinolines and serum and urine levels of type I collagen telopeptides (CTX and NTX), which are indices of bone resorption. The level of these markers may identify changes in bone remodeling within a relatively short time—several days to months—before changes in bone density can be detected. It is important to realize, however, that marker levels cannot predict fracture risk and are only weakly associated with changes in bone mass. Therefore, they are of limited utility in the clinical evaluation of individual patients.

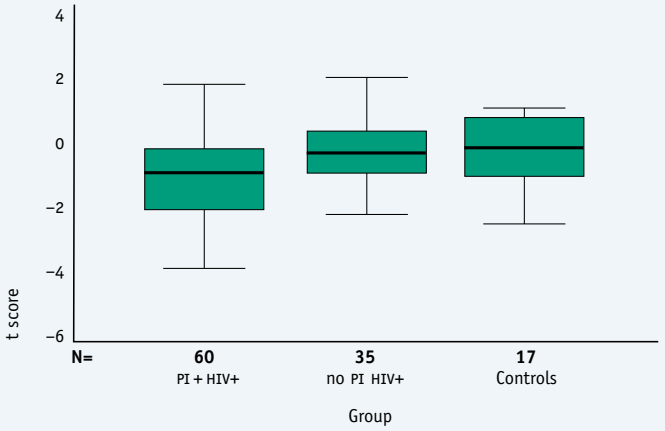
Bone Density in HIV

PRIOR TO THE WIDESPREAD USE OF HAART, studies indicated that bone metabolism was altered, albeit minimally, in HIV-infected individuals. In one analysis, 45 HIV-infected patients had statistically significant lower lumbar spine BMD scores than did HIV-negative controls (Paton, 1997). However, body and hip BMD scores were similar in both groups, and none of the patients had BMD scores associated with osteoporosis. "The general theme that we saw before the availability of HAART was that HIV infection itself decreased bone mineral density by a little bit," Dr. Tebas commented. "Patients with advanced HIV disease tended to have lower-than-normal bone mineral density, but much more along the lines of osteopenia, not osteoporosis."

At the 8th Conference on Retroviruses and Opportunistic Infections (CROI), a team of investigators from Gilead Sciences reported preliminary data from a BMD substudy being conducted as a part of GS-99-903, a phase III clinical trial comparing tenofovir DF (Viread) to stavudine (Zerit), both in combination with efavirenz (Sustiva) and lamivudine (Epivir) in antiretroviral-naive patients (McGowan, 2001). "When tenofovir was being studied in dogs, the drug was associated with some bone loss," Dr. Tebas said. "The FDA required Gilead to look at BMD in patients participating in this trial."

DEXA scans of the lumbar spine and proximal femur were performed in all patients participating in the substudy. Two

Figure 2. Decreased BMD T-Scores: Lumbar Spine



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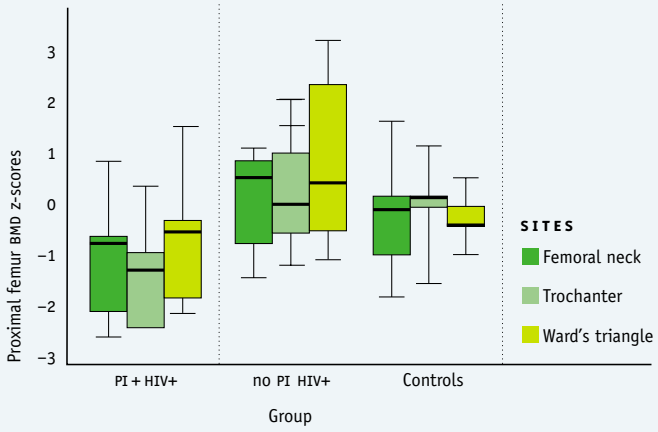
Lumbar spine bone mineral density (BMD) T-scores for 112 men evaluated by Dr. Tebas and his colleagues at the Washington University School of Medicine. The box represents the interquartile range, the thick line the median and the thin lines the range of the T-scores. The median lumbar spine BMD (P=0.002) and the T-score for the HIV-positive patients on protease inhibitors (HIV+ PI+) group (P=0.02) were lower than the other two groups. The controls were healthy, HIV-negative subjects; the non PI HIV+ group included HIV-positive patients not taking protease inhibitors.

Figure 3. Decreased BMD Z-Scores: Proximal Femur



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HIV-positive patients taking protease inhibitors (HIV+ PI+) had significantly lower BMD Z-scores in the neck (P = 0.08), trochanteric (P = 0.01), and Ward's triangle (P = 0.09) regions of the proximal femur than the other two groups. The controls were healthy, HIV-negative subjects; the non PI HIV+ group included HIV-positive patients not taking protease inhibitors.

baseline measurements were performed at both anatomical sites, and measurements will be repeated at six-month intervals. In the first 151patients evaluated thus far, the mean baseline lumbar BMD was 1.0686 g/cm^2, with a mean T score of -0.0786 and a Z score of 0.0238. According to the WHO definitions described above, 24% of patients were classified as osteopenic and 2% as osteoporotic. "Again, we see a sizeable population of patients with osteopenia," explained Dr. Tebas. "Theoretically, as bone mineral density is normally distributed, approximately 16% of the individuals should be osteopenic; this study indicates a slightly higher rate."

Dr. Tebas' interest in BMD, as it relates to HIV, arose by happenstance. "We'd been doing evaluations of patients with fat abnormalities, using DEXA, and some of our research nurses noticed that a number of patients had low bone mineral density. We decided to take a closer look at all of our patients who had undergone DEXA scanning."

Dr. Tebas and his colleagues at Washington University performed a cross-sectional analysis of whole-body, lumbar spine, and proximal femur bone mineral density in 112 male subjects (Tebas, 2000). Data involving 60 HIV-positive men receiving a protease inhibitor-based regimen, along with 30 HIV-positive men receiving a non-protease inhibitor-based regimen and 17 HIV-negative controls, were presented by Dr. Tebas at the PRN meeting.

Among HIV-positive men receiving a PI-based regimen, the median T-score was –1.005 and the median Z-score was –0.923. As for the HIV-positive men receiving non-PI-based regimens, the median T-score and Z-score were both –0.382; among the 17 controls, the scores were –0.227 and 0.145, respectively. "Our HIV-positive patients receiving a protease inhibitor had the highest rate of osteopenia, around 50%," added Dr. Tebas. "Osteopenia was seen in 23% of our HIV-positive patients not receiving a PI-based regimen and 29% of our HIV-negative controls."

The cross-sectional analysis echoed a number of other studies in showing that patients receiving protease inhibitors had greater central and appendicular adipose tissue ratios than the other two groups. However, there was no relationship between the central to appendicular fat ratio and lumbar spine or proximal femur BMD, suggesting that osteoporosis and body fat redistribution are independent side effects of HAART.

"We are not blaming the protease inhibitors," Dr. Tebas cautioned. "It may be an indirect consequence of HAART therapy. That is, several years of HAART may accelerate the typical loss of bone mineral that occurs with advancing age."

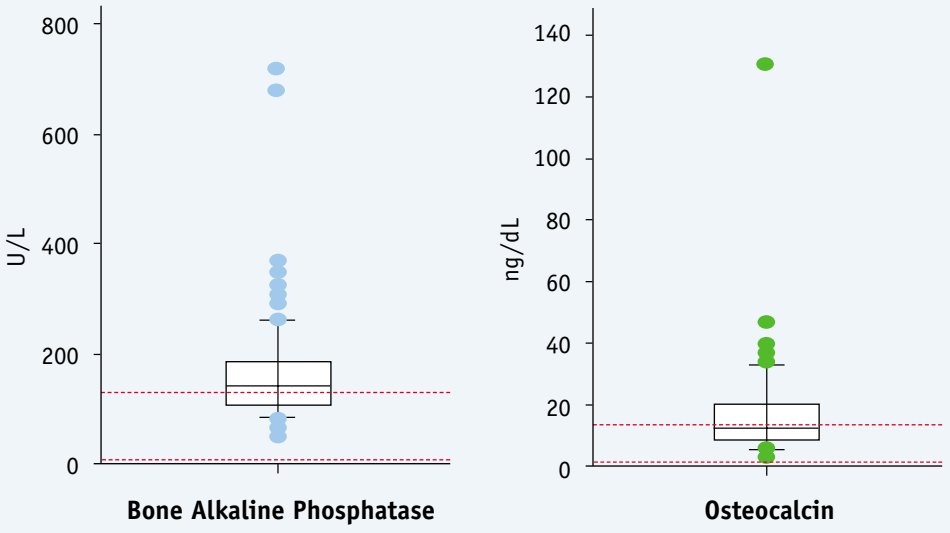
Dr. Tebas' team has also looked at specific markers of bone turnover in a cohort of 73 patients receiving protease inhibitor-based regimens (Tebas, 2000). Approximately 5% of the patients included in the analysis had osteoporosis; 40% had osteopenia and 55% had normal BMD. Key blood values included alkaline phosphatase and osteocalcin, two markers of bone formation. The urine analysis included the markers pyridinoline and deoxypyridinoline, both of which are associated with bone resorption.

As shown in Figure 4, markers of bone formation appeared to be higher than average in the cohort. "What was really interesting to me were the elevated alkaline phosphatase levels," Dr. Tebas pointed out. "Normally, we associate this with liver function. But it turns out that alkaline phosphatase can also come from bone and elevated levels should not be automatically attributed to ongoing liver damage." As for bone resorption, Dr. Tebas and his team found that patients in this cohort, on average, had higher levels of urine pyridinoline.

Dr. Tebas also reported correlations between lumbar spine T-scores and serum

alkaline phosphatase and urine pyridinoline levels. "This was a surprising finding," he said. "These markers have been looked at in the past, particularly in elderly patients to help determine how fast bone mineral would be lost. Given that such correlations weren't found before, it was surprising to us to find them in our cohort of HIV-infected patients." Dr. Tebas did not speculate, however, on how these markers might be used in clinical practice.

"It is important to recognize that our findings, thus far, have been from cross-sectional studies," Dr. Tebas reiterated. "Even though we found associations between HIV, protease inhibitor use, and bone mineral loss, we cannot attribute these findings to be causative of osteopenia or osteoporosis. These data simply imply that additional studies are necessary."



In a cohort of 73 patients undergoing therapy with protease inhibitors, Dr. Tebas and his colleagues reported elevated serum levels of alkaline phosphatase and osteocalcin, two markers of bone formation. Elevated alkaline phosphatase and urine pyridinoline (not shown), a marker of bone resorption, correlated with decreased BMD T-scores in this cohort of patients. The red horizontal lines represent the reference ranges for alkaline phosphatase and osteocalcin; the blue and green dots represent the serum levels of both markers in each of the patients included in the analysis.

Etiology of Bone Density Loss in HIV

JUST AS THE CONNECTION BETWEEN HIV INfection and/or antiretroviral drugs remains uncertain in the development of osteopenia and osteoporosis, it is also unclear how these factors might lead to such complications. However, theories abound, a handful of which were described by Dr. Tebas.

Testosterone deficiency, including levels at or below the low end of the reference range, is an underlying cause of secondary osteoporosis and a relatively common problem in HIV-infected men, especially those with advanced HIV disease. These established facts led Dr. Tebas and his team to hypothesize that hypogonadism, as a consequence of HIV infection, is a cause of osteoporosis. However, an analysis of 52 patients receiving a protease inhibitor-based regimen proved otherwise. Of the 52 patients, approximately half had T-scores consistent with osteoporosis and three had testosterone levels below 200 ng/dL. Only one of the patients with osteoporosis had hypogonadism, whereas the other three patients with hypogonadism had healthy BMD as determined by DEXA scanning. "We really don't think it's hypogonadism," Dr. Tebas bluntly concluded.

A second etiologic possibility raised by Dr. Tebas is a deficiency in vitamin D metabolism, possibly caused by protease inhibitors. The primary function of vitamin D is to increase calcium absorption from the digestive tract and promote normal bone formation and mineralization.

In the skin, previtamin D_3 is synthesized photochemically from 7-dehydrocholesterol and is slowly isomerized to vitamin D_3. In the liver, vitamin D_3 is converted to $25(OH)D_3$, the major circulating form. It passes through the enterohepatic circulation and is reabsorbed from the gut. Principally in the kidneys, it is further hydroxylated to the much more metabolically active form, $1,25(OH)_2D_3$ (1,25-dihydroxycholecalciferol, calcitriol, vitamin D hormone). The critical 1-hydroxylation of $25(OH)D_3$ is strongly stimulated by parathyroid hormone (PTH) and, independently of PTH, by hypophosphatemia.

As explained by Dr. Tebas, the enzymes involved in hydroxylation of vitamin D are cytochrome P450 enzymes. "It's fairly obvious what this means," he commented. "If the protease inhibitors we're using are P450 inhibitors, it's quite possible that they are also inhibiting the enzymes involved in vitamin D metabolism."

To test this hypothesis, Dr. Tebas teamed up with Adriana Dusso, PhD, and other colleagues at Washington University; their findings were first reported at the Second International Workshop on Adverse Drug Reactions and Lipodystrophy, held last fall in Toronto (Dusso, 2000). *In vitro* experiments pairing the protease inhibitors indinavir (Crixivan), ritonavir (Norvir), and nelfinavir (Viracept) with human monocyte-macrophage THP-1 cells expressing 1α-hydroxylase, an enzyme that is identical to the renal enzyme response for the formation of $25(OH)D_3$, were performed. According to Dr. Tebas, the rates of conversion of tritiated-$25(OH)D_3$ to $1,25(OH)_2D_3$ were reduced 79% in cells incubated with ritonavir, 66% in cells challenged with indinavir, and 31% in cells challenged using nelfinavir.

"When we used interferon-gamma to stimulate the THP-1 cells to produce 1α-hydroxylase," he added, "there was an even greater level of vitamin D_3 metabolism with these protease inhibitors."

While these data are certainly interesting, Dr. Tebas stressed that they should not yet be considered clinically significant, nor should they be interpreted to mean that clinicians should begin monitoring $1,25(OH)_2D_3$ levels in their HIV-positive patients. "Our study does not mean that we should start treating patients with high-dose vitamin D. This *in vitro* study suggests that we should pursue this further, but

WHAT ABOUT AVASCULAR NECROSIS?

Osteoporosis is not the only bone-related complication being seen in HIV-positive patients. There is also avascular necrosis, a condition that has been reported in a growing number of patients in recent years. As with osteoporosis, however, it is still unclear to what extent avascular necrosis is related to either HIV infection or its treatment.

Avascular necrosis—sometimes referred to as osteonecrosis, aseptic necrosis, and ischemic bone necrosis—results from either direct or indirect damage to the vascular supply to the bones. Without an adequate blood supply, the bone tissue dies and causes the bone to collapse. If the process involves the bones near a joint, it often leads to collapse of the joint surface.

Although it can happen in any bone, avascular necrosis most commonly affects the femoral head and the humeral head and can also affect the scaphoid, lunate, and femoral condyles. In the general population, avascular necrosis usually affects people between 30 and 50 years of age, and more than 10,000 people are diagnosed with this condition each year.

It is still unclear to what extent avascular necrosis is related to HIV disease. According to one report at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, HIV-positive patients have a risk of avascular necrosis that is 58 times higher than those in the general population (Scribner, 2000). There has also been one report linking avascular necrosis to protease inhibitor use (Hodak, 1999) and at least two reports that failed to confirm such an association (Masur, 2000; Glesby 2000).

While it is still not clear what role, if any, either HIV or HIV-related treatment plays in the development of avascular necrosis, it is clear that a number of the established risk factors for osteonecrosis are familiar tunes in HIV disease. These risk factors include a history of corticosteroid use, alcohol abuse, smoking, hypercholesterolemia, chronic pancreatitis, and hypertriglyceridemia—many of which are primary adverse effects of highly active antiretroviral therapy. As with the study of osteoporosis, more research is definitely needed to elucidate the pathogenesis and etiology of avascular necrosis in HIV-infected patients.

A diagnosis of avascular necrosis is made using either CT or MRI scanning. While X rays may be useful in patients with advancing avascular necrosis, they are not particularly useful in the diagnosis of the condition in the earliest stages.

Early-stage avascular necrosis can be reversed or its progression halted by correcting the suspected underlying problem. For example, a patient with hyperlipidemia, perhaps from the use of a protease inhibitor-based regimen, may benefit from a switch in antiretroviral treatment and/or adjunctive lipid-lowering drug therapy. Also, pain-relieving medications may be needed, and weight-bearing (hip) or lifting/carrying (shoulder) may need to be limited while maintaining good range of motion through physical therapy. If progression of the osteonecrosis continues, or if it is already advanced at the time of diagnosis, an orthopedic surgeon may be consulted for vascular grafts, core decompressions, or prosthetic replacement of the affected joint. *prn*

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we don't know what we'll find *in vivo*. In fact, our patients, for the most part, have normal serum vitamin D_3 and $1,25(OH)_2D_3$ levels. So it's not at all clear what's going on in terms of vitamin D metabolism."

Might protease inhibitors have more of a direct effect on either osteoblast or osteoclast function in regulating bone density? According to Dr. Michael Wang, another colleague of Dr. Tebas at Washington University, it is possible that they do. According to *in vitro* and *in vivo* data reported by Dr. Wang at the 8th CROI, indinavir (5 mg/mL) inhibited *in vitro* bone nodule formation without cell toxicity, while ritonavir and nelfinavir had no inhibitor effect. In murine osteoblastic cells treated with indinavir, there was a dose-dependent decrease in alkaline phosphatase, which, as discussed above, is a marker of osteoblast differentiation.

To test the effect of indinavir on bone *in vivo*, Dr. Wang's team injected indinavir intraperitoneally into mice for two weeks and assayed for the potential of bone marrow stromal cells to differentiate into osteoblasts *ex vivo*. They found a tenfold decrease in osteoblast colony forming units with indinavir.

Opposite inhibitory effects were observed when the drugs were tested with osteoclasts. Ritonavir reversibly suppressed osteoclast differentiation with an inhibitory dose 50% of 10mg/mL. When the drug was applied to mature osteoclasts on bone slices, the cells failed to resorb bone even though the number of osteoclasts did not change. This inhibition held true *in vivo*, as systemic ritonavir administration to mice blocks parathyroid hormone-induced osteoclastogenesis. Interestingly, these inhibitory effects were not observed with indinavir.

"This study was really quite interesting," Dr. Tebas recalled. "Even though indinavir and ritonavir target the same viral enzyme, they have opposite effects on osteoblasts and osteoclasts. We definitely need additional studies to determine what this might mean."

Other etiologic possibilities included el-

POSSIBLE TREATMENTS FOR OSTEOPOROSIS

While not specifically discussed by Dr. Tebas, there are a number of treatments currently approved for the treatment of osteoporosis. These treatments, for the most part, are approved for osteoporosis in postmenopausal women (primary osteoporosis) and, in some cases, bone loss associated with glucocorticosteroid use in both men and women (secondary osteoporosis). Clinical trials evaluating these therapies in either HIV-infected men or women have not yet been conducted.

Hormone Replacement Therapy

Estrogen replacement therapy (ERT) is approved by the U.S. Food and Drug Adminstration (FDA) for the prevention and management of osteoporosis. Observational studies of ERT have indicated a 50% to 80% decrease in vertebral fractures and a 25% decrease in nonvertebral fractures with five years of use and an anticipated 50% to 75% decrease in all fractures with 10 or more years of use. However, very little is known about the safety or efficacy of ERT for the management of secondary osteoporosis in premenopausal women. Thus it is difficult to say what role, if any, ERT might play in the majority of HIV-positive women (or men) with decreased bone metabolism.

Testosterone replacement therapy has been validated as a treatment for hypogonadism in both HIV-positive and HIV-negative men. As discussed in this article, however, the role of HIV-associated hypogonadism in the development of osteopenia or osteoporosis remains questionable. Similarly, there are no data from clinical trials evaluating the potential role of testosterone replacement therapy in HIV-positive men dealing with either of these two bone disorders.

Bisphosphonates

Alendronate (Fosamax) and risedronate (Actonel) are approved for both the prevention and treatment of osteoporosis in postmenopausal women and both men and women with secondary osteoporosis associated with long-term glucocorticosteroid use. Side effects associated with the bisphosphonates are uncommon but may include abdominal or musculoskeletal pain, nausea, heartburn, or irritation of the esophagus. Both alendronate and risedronate must be taken on an empty stomach.

Raloxifene (Evista)

Like ERT, raloxifene is approved for the prevention and treatment of osteoporosis in postmenopausal women. It is from a new class of drugs called Selective Estrogen Receptor Modulators (SERMs) and has been shown to increase bone mass and after three years of therapy to reduce the risk of spine fractures by about 50%. While SERMs have been shown to mimic the positive effects—and mimimize the potential disadgantages—of ERT, it is still not clear what benefits they offer premenopausal women, including those living with HIV.

Calcitonin (Miacalcin)

Calcitonin is a naturally occurring hormone involved in calcium regulation and bone metabolism. In postmenopausal women, it has been shown to reduce the risk of vertebral fractures by approximately 40%—a lower efficacy rate than those typically seen using ERT, bisphosphonates, or SERMs. Calcitonin cannot be taken orally but is available as an injection (50 IU to 100 IU QD) or nasal spray (200 IU QD). With respect to adverse events, injectable calcitonin may cause an allergic reaction, flushing of the face and hands, urinary frequency, nausea, and a skin rash. The only side effect reported with nasal calcitonin is nasal irritation. prn

evated leptin levels. According to a paper in *Science* by Dr. Patricia Lucy and her colleagues at Baylor College of Medicine, leptin-deficient mice have surprisingly high BMD in comparison to control mice (Lucy, 2000). "In humans, leptin levels increase when fat mass is increased," pointed out Dr. Tebas. "In patients with lipodystrophy, there is an increase in fat mass and an increase in leptin. This increase in leptin might be associated with a decrease in bone density."

In closing his talk, Dr. Tebas made it clear that he and his colleagues at Washington University will be pursuing a great deal of research on bone density in the near future. "We'll be doing histomorphometry studies, as we should be able to learn a lot more from looking at our patients' actual bones. We'll also be participating in longitudinal studies and, of course, looking at potential therapeutic interventions." prn

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