Hip to the Future

The new side effect is bone death. Yes, the meds play a role. But dig deeper -- it might be immune recovery.

April 1, 2002 By Anne-christine d'Adesky

Eric Sawyer is a true AIDS veteran. At 48, the lanky, boyishly handsome New Yorker is an ACT UP poster boy still facing off with government officials and drug-company reps. But he's not exactly running around town. Sawyer has avascular necrosis, or AVN, a progressive bone disease caused by a cutoff of blood flow to a bone. The result is a dying hip bone, something that is forcing Sawyer -- and a growing number of other HIVers on HAART -- to resort to the once-unthinkable: hip-replacement surgery. Strikingly, many have even developed bilateral AVN -- both hips. And though AVN (also called osteonecrosis or aseptic necrosis) mainly targets HAARTers' hips, it can affect other joints in the body, like shoulders, elbows, knees and hands. "It's a scary thing to have to deal with," Sawyer says. "Even though I've been in a lot of pain for over a year, it took this long to get a diagnosis because nothing was turning up on the X-rays." Sawyer got the official word in mid-February after consulting with specialists about his upcoming surgery. Sighing, he adds, with typical understatement, "I'm not looking forward to this."

Like many AIDS vets, Sawyer has taken almost every combo of meds in his two-decade-long battle to stay ahead of the virus. It's been a rough ride. By now, he's burned through three triple-drug (HAART) regimens en route to his current salvage cocktail of five. The downside is side effects such as neuropathy (nerve damage), nausea and diarrhea -- which demand more daily pill-popping. But he's been largely spared more common side effects like protease paunch or other signs of metabolic or lipid abnormalities.

Sawyer's hip problem began three years ago with what he thought was a pulled groin and occasional clicking-and-locking in his right hip. One day he was playing baseball at a wedding beach party. "I was attempting to run the bases and, basically, had my hip pop out of joint and collapse," he recalls. "I fell on the ground." He was on crutches for a few weeks, but X-rays turned up only a little wear and tear. He had a little arthritis in some joints, possibly due to residual neuropathy. A series of X-rays and magnetic resonance imaging (MRI) scans showed some abnormalities in the right hip socket itself, and a bit of pointiness on the ball, like a bone spur. He started taking drugs to reduce inflammation in the joint as well as Cosamine DF to rebuild lost cartilage. "I've gone from having a thin, broken, deteriorating cartilage lining the hip to having absolutely none -- and bone rubbing on bone," Sawyer says. "At times, there is a really debilitating pain that makes me literally have to stop in my tracks." Bedridden at times, he's fallen into panic, isolation and depression over his worsening condition. Although "surgery sucks," as he puts it, it

also spells relief from pain.

Welcome to the HIV dollhouse. As Sawyer's story illustrates, something is indeed rotten in Denmark, and a range of bone problems must now be added to the list of serious complications of HIV therapy. But before you rush to heap blame on the meds, read on. No one knows the exact cause of AVN. There certainly appears to be a link to antiretrovirals, but it may be quite indirect -- for example, the result of the immune system's HAART-induced rebound. In non-HIVers, AVN is linked to a variety of diseases and events, including lupus, diabetes, alcohol abuse, pancreatitis, gout and a fatty liver. Since a fatty liver is a common side effect now seen in HIVers with lipodystrophy, there's a clue. But there are many others.

What can't be argued is the trend. "There is no question about it. We didn't see it before," says Philip Bauman, MD, an orthopedic surgeon at St. Luke's-Roosevelt Hospital in New York City who has replaced five HAART hips so far. "One of my associates also does hips, and we have an ongoing tally between 20 and 30 [at the hospital]. They are young -- in their 20s to 40s -- and on HAART." Compared to non-HIVers, for those on HAART, "it is usually a more severe form [of AVN] that doesn't get better with treatment."

Classically, AVN is caused by a lack of blood flow to the hipbone due to injury or a narrowing of blood vessels. The bone cells die, causing friction, inflammation, pain and a loss of mobility. To a lesser degree, the blood supply can also be limited in other joints, such as the humeral head of the shoulders or the femur of the knee.

Doctors have only just begun to distinguish HIV-related AVN cases from other bone disorders like osteopenia (mild bone loss) and osteoporosis (severe loss) seen in HIVers, including those on HAART [see "A Dangerous Age," *POZ* October 2001]. While he's keeping his eye on the osteopenia cases in HAART-takers, Bauman says that AVN is in a class by itself. "There are really two issues: AVN is the *death* of the bone. A separate issue is that the bone often gets *weaker*. I don't think the osteoporosis we see associated with this syndrome is part of the avascular problem or that osteoporosis will lead to avascular necrosis." Instead, he and other docs suspect that AVN is part of a unique syndrome, most likely related to the use of drug cocktails.

Today, frontline HIV docs estimate that as many as 10 percent of all people on HAART may have bone disease, but without hard data, that's just a guesstimate. How many have AVN isn't known, either. And because this syndrome can be asymptomatic for a long time and hard to spot on X-rays, the true scope of the problem may remain hidden. Often what singles out AVN from other bone problems is what literally tripped up Sawyer: sudden, excruciating pain.

"The pain is very obvious -- it's impressive pain," Bauman stresses. "But what's so *un*impressive are the X-rays initially. When someone comes in with severe pain in an otherwise-normal hip, that sets off a yellow light that makes me think about AVN. If someone is on HAART and has had some pre-existing problem that would make it more likely [for example, a protease paunch], I am even more suspicious."

So who's at risk of getting a bum hip? Based on interviews with several physicians, their patient

charts suggest that a growing percentage of AVN cases are, like Sawyer, PWA vets -- individuals who had lowered immunity before going on HAART and have taken HIV drugs for years and years. A good number also have lipodystrophy -- itself a confusing catch-all term for a variety of metabolic and lipid disorders that have put HAART-takers at risk for hepatitis and cardiac problems. Some also have osteopenia. But the lack of a good case definition may be impeding docs from spotting the problem, Bauman says.

Howard Grossman, MD, a well-known HIV specialist in New York City, has referred six HAART patients to surgeons for new hips due to AVN. “In a young population, that’s a fairly high number,” he says. While a small number of conference reports and newsletters have spotlighted bone problems in HIVers, he says, “I’m not sure that it’s reached most patients’ radars.”

Pediatric HAART cases also have doctors worrying: AVN is likely overlooked because bone scans aren’t routine in HIV care, as are, say, CD4-cell counts. Last year, an Italian team led by Allesandra Vigano, MD, reported that children with HIV on HAART had decreased bone-mineral density (BMD) levels compared to HIV negative kids. The BMD levels were even lower in those who also had lipodystrophy. Another researcher, Stephen Arpadi, MD, of St. Luke’s-Roosevelt, says that he doesn’t see *clinical* symptoms of decreased bone density in his pediatric patients on HAART, but when he uses lab-based measurements and scans, he sees evidence of a loss.

Last year, Arpadi also reported that the decline in BMD seems to worsen as kids get older and are on HAART longer. “Well over half of adult bone mass is acquired during adolescence,” he says. “While osteoporosis presents itself as a problem in later decades, its origins are clearly in the first two decades of life. So the concern is: Are we impeding normal bone mineralization or, worse, causing demineralization, which there is [so far] no evidence for? Are we going to see significant, premature, highly prevalent osteoporosis and related problems down the line?”

Arpadi isn’t waiting to find out. He plans to routinely monitor kids with HIV using bone scans, reviewing such markers as height, weight and signs of lipodystrophy for possible links. But his job is tough: Because all the children have been on HIV meds since birth -- and some in utero -- he can’t tease out a particular drug and drug class as the root of the problem. It’s also a “luxury,” as he puts it, for pediatric HIV docs to focus on potential long-term problems when they are scrambling to keep kids who are on meds happy and healthy. “I don’t mean to downplay bone problems,” Arpadi says, “but it’s hard to take my eyes off of the prize -- which is survival right now.”

That’s also true, of course, for many adults on HAART, who are downing the drugs to stay alive but increasingly must weigh the clear and present benefit of low or no viral load and CD4-cell rebounds against the scary prospect of irreversibly harming major organs such as the liver and heart -- and, now, bones. “It would be nice to have a choice,” Sawyer says of his salvage therapy. “But my options are frankly very limited.”

Two other groups of HAART-taking HIVers are also likely at higher risk for bone problems: post-menopausal women and men over 40, whose bones weaken as they age and their calcium levels

fall.

Grossman says that a big part of the problem is our lack of knowledge about the risk of AVN, period. "There was an article in *The New York Times* a few years ago about increased incidence of aseptic necrosis in the general population over 40," he says. "So there could always be something else [not related to HIV] going on, too."

Yet there's doubt in his voice. When pushed a little, he admits that HIV meds are likely involved in the bone deterioration. "There was a rise in AVN of the femoral heads [of the hip] before protease inhibitors [PIs]," he says, "but I definitely think it has accelerated since the PIs. I think it's a combination of the two." Still, he's very wary about "throwing out the baby with the bathwater," as he puts it, by scaring people into stopping lifesaving therapy. "I think it's related to specific drugs," Grossman says. "I don't think it happens with some of the triple nucleosides, for example." In his opinion, it's the "d" and "p" drugs -- ddI, ddC, d4T and the protease inhibitors -- that may be the culprit.

Some of Grossman's patients with bone problems also have lipodystrophy. Like other observers, he suspects that there's a link. "They tend to go hand in hand," he says. "But I don't know if they are *causally* related. I think similar drugs are causing similar problems. By staying away from certain drugs, I'm not seeing as many bone problems."

While HAART leaps out as one link, the lipodystrophy syndrome offers an important history lesson in not rushing to judgment about the root cause of a HAART side effect. When buffalo humps and sunken cheeks first turned up in patients taking protease inhibitors, activists and doctors (and *POZ*) were quick not only to finger these new drugs but to lump a myriad of symptoms into the lipo basket, making it hard to diagnose and treat specifics. That was definitely a mistake. Fat atrophy and high cholesterol levels for example, are complications of HAART, but losing your cheek fat and developing severe hepatitis are different clinical events and require different treatment. We also know that each drug class affects the heart, liver and other organs differently. The same may be true for bone problems. That means that managing AVN may look very different from managing osteoporosis. This time, docs suggest, let's try to keep things separate and not muddy the waters.

"This problem has been handled the same way as lipodystrophy in that the initial response was to blame all the antiretrovirals," says Donald Kotler, MD, who caught flack from activists for arguing that other drugs, not just protease inhibitors, might be contributing to lipodystrophy. "We are at such a disadvantage because of our lack of knowledge. The *infection* [immune deficiency] may be the culprit, as opposed to the *virus*. But, again, I don't know how longstanding HIV infection would do something on its own."

If HAART is the easy answer to the causal question, there's a breathtaking list of other contenders, each with some data to suggest a link, but no clear-cut cause-and-effect. There's HIV itself -- though the AVN cases are clearly showing up in people on HAART. There's the effect of drug therapy on a recovering immune system, which stimulates inflammation- causing immune-cell activity. There are metabolic problems that lead to a fatty liver. There are also decreased lactic-acid levels and mitochondrial toxicity. Some researchers have even speculated that prior use of

prednisone, a steroid used to treat *pneumocystis carinii* pneumonia in the early days of HIV, is a player.

In trying to untie this knot, Joseph Kovacs, MD, of the National Institutes of Health (NIH), did a review of AVN cases that was published last September. The NIH was unable to identify the drugs as a solo contender for AVN. Instead, its study cited such lifestyle factors as weight-lifting, body-building, and steroid and testosterone use as risks possibly linked to AVN.

Kotler, a leading lipo expert, is most intrigued by the theory that HAART-related immune recovery plays a part, since CD4-cell activation causes cytokine activity and subsequent inflammation that can, in an unfortunate irony, cause the bone to become acidic and lead to its breakdown. But he's not favoring it as the top candidate. Another lipo expert, Andrew Carr, MD, of Australia, is promoting a link between bone problems in the spine -- another site to watch -- and a condition called lactic acidemia.

Like Grossman, Kotler thinks that the way forward is for researchers to begin taking a harder look at AVN patients using some common comparative standards. "I haven't seen much research at all," Kotler says of the dearth of AVN/HAART studies. "If I was to recommend anything, it would be to scream at people to generate some data." Kotler says the bottom line is to learn from our recent mistakes in the lipo past. Instead of denying there's a problem, he suggests, let's treat AVN as a progressive trend that is likely to get worse over time, not better, and indeed may be worse than we know now. To his mind, there needs to be a shift in HIV management to anticipate these potential long-term complications.

But first we need to know exactly what the problem looks like. At the top of Kotler's wish list is a clinical database on AVN and other bone cases. He also calls for government or other leading agencies to back an agenda for basic and clinical research into the problem, matched by immediate funding for treatment trials. This would mean that we might get to test Grossman's theory that "p" and "d" drugs may be more toxic to bones, or that anti-inflammatory drugs can have an impact on the rate of bone death in the hip. (There should also be studies to see if any supplements help.)

In the absence of research, Grossman's policy is to assume that everyone on HAART is at risk for bone disease, so he's quick to order tests for lactic acid and bone scans. He urges patients to take the same precautions that are recommended for older people: regular exercise, a good diet rich in vitamin D and calcium, no smoking, limited alcohol. But he pooh-poohs megavitamins and calcium supplements because his patients with bad bones tend to have normal calcium levels. In cases of osteopenia, he prescribes Fosomax (alendronate sodium), a bone-builder. With AVN, when the hip is shot or the pain unbearable, he suggests new hips, confident that surgery generally provides patients like Eric Sawyer with relief from their suffering. "There are always healing issues, but people do very well," Grossman says.

What will all of this look like in 10 years? That depends on what happens today. In sounding the alarm, the hope is that HIVers on HAART will act now to save their bones in the future. That means

staying healthy, but also talking to your doc about your bones and the merits of an MRI bone scan if you've got other HAART side effects. As Emma Goldman would say, if I can't dance, it's not my revolution. So follow Eric Sawyer's lead and start making some noise.

NEED A NEW HIP? HERE'S HOW

For HIVers, early detection of bone loss using MRIs or DEXA bonescans is key: avascular necrosis (AVN) is often irreversible by the time an X-ray detects it. Usually, hip-replacement surgery is the lastresort, since it's intensive, expensive and time-consuming; plus, the risk of infection is greater for HIVers. Before replacing the whole joint, most doctors will try to save the bone using techniques like core decompression to increase the blood flow to the dying tissue.

When hip surgery is necessary, some surgeons use cement to implant the artificial ball-and-socket, while others employ a cement-free process. Recovery takes months, plenty of antibiotics and other drugs,plus physical therapy to help the hip stabilize, strengthen and heal.Post-surgery, the big issue is how well and how long the solid plasticim plant will hold. Hip implants are designed to last for years, but loosen in a little more than a third of all patients within a decade.

Down the line, a variety of problems can arise due to bone debris,inflammation and friction; sometimes, chronic pain persists. But not to fear: For the majority of patients, surgery is a success, providing an end to pain and a restored ability to move.

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