Honeymoon to HAARTache

May 1, 1999 By Linda Grinberg

After living in the shadow of death for over a decade, the AIDS community heralded the protease era with frenzied exuberance. Awakening from this interminable nightmare, those at the brink arose from their deathbeds to contemplate a future once again. Hopes were raised even higher when *eradication* became the media buzz after the 1996 World AIDS Conference in Vancouver. Reveling in renewed health, survivors toasted a new dawn with their protease cocktails. Death rates in the developed world were cut in half. Amid the celebration, the specter of long-term side effects was overlooked, as any side effect seemed preferable to death. But unbeknownst to us, a monster lay sleeping, about to rear its ugly head.

The honeymoon with HAART (highly active antiretroviral therapy) was tarnished as reports of bizarre side effects began accumulating (see "HAART Chart"). Though some of the side effects were seen in clinical trials prior to the approval of protease inhibitors (PIs), their incidence increased dramatically post-approval. Complaints of protease inhibitorassociated diarrhea, gas, nausea and heartburn -- euphemistically referred to as "ritonavir moments," though associated with all PIs -- were soon matched by stories of people on indinavir (Crixivan) winding up in the ER, waiting in agony for "kidney sludge" to pass. Those already suffering from the side effects of older antiretrovirals -- such as neuropathy, pancreatitis and anemia -- now faced the double whammy of protease side effects, too. Lab abnormalities (not just the usual elevated liver enzymes, but also pronounced increases in blood cholesterol and triglycerides) became routine. In time, more serious problems, including elevated blood sugar, diabetes and coronary artery disease, emerged.

But the phenomenon that came to overshadow all others, causing PWAs the most angst, is a host of inexplicable changes in body shape -- abdominal fat, fat loss in the limbs, humps on the upper back, facial thinning and wrinkling, breast enlargement and protruding veins -- sometimes accompanied by skin problems, from dryness to ingrown toenails. New catchwords entered the HIV lexicon: *crix belly, visceral fat, buffalo hump, truncal obesity* and *protease paunch*. Yet none of these terms fully capture the human misery.

"I look like a marshmallow on toothpicks," says Sally Brookins of Colorado Springs, Colorado. "I've got slabs of beef hanging out of my bra, and a whopping buffalo hump." Three years ago, Brookins helplessly watched her health plummet with her CD4 cell count. She knew all too well she was in the placebo arm of a PI study, and that her life was slipping away. In the nick of time, she was switched to ritonavir. Immediately, her health and CD4 count rebounded. "Despite all the side effects over the years, it's still worth it to me," she says. "Most of my friends are in graveyards and didn't get a chance to have long-term side effects." As with countless other PWAs, her protease

cocktail gave her back her life -- but not without a price.

Initially, many doctors downplayed their patients' concerns, discounting the effects as merely cosmetic. PI manufacturers tried to reassure the community that these symptoms were rare and unrelated to the drugs. Demands by treatment advocates for a systematic reporting mechanism fell on deaf ears. Even after the problems were first reported at an AIDS conference in September 1997, neither the pharmaceutical companies nor the National Institutes of Health (NIH) initiated research into causes or treatments. The Food and Drug Administration (FDA), responsible for warning the public of dangerous side effects, was silent.

Frustrated PWAs launched mailing lists in cyberspace to share horror stories and exchange anecdotal treatment information. Activists began pressuring government and industry to act. Only after reports of diabetes and three acute cases of heart disease did this new syndrome begin drawing official attention. Meanwhile, a few inspired researchers began studying this enigma, leading to several intriguing but conflicting theories about causality.

The manifestations of this emerging syndrome, commonly referred to as *lipodystrophy*, differ from person to person. Researchers have yet to agree upon a case definition. Reported incidence rates vary widely -- from 3 percent to 80 percent -- depending on which symptoms or measurements are used, but appear to be rising over time. Still, in this vast constellation of body shape distortions and metabolic abnormalities, there is general agreement that most symptoms fall into three main categories: *fat redistribution* (altered body shape); *insulin resistance* (increased blood sugar and glucose); and *lipid abnormalities* (increased triglycerides and cholesterol).

But controversy surrounds the cause of the syndrome. Several theories have piqued the interest of the research community. While experts recognized HIV-related metabolic disturbances prior to the widespread use of PIs, two compelling theories implicate PIs as key culprits. Others hypothesize that PIs may be just one piece of a complex puzzle that could include an underlying metabolic disorder, genetic and other risk factors, other antiretrovirals, or immune restoration itself. Undeniably, the deluge of side-effect reports since the approval of PIs is evidence of a linkage, whether direct or indirect.

Among the first to report on altered body composition was a team led by David Cooper, MD, and Andrew Carr, MD, of St. Vincent's Hospital and the University of New South Wales in Sydney, Australia. In early 1998, they reported that 64 percent of their PI-treated patients had noted changes in body shape, *regardless of CD4 count or viral load*, suggesting a PI connection. According to their provocative hypothesis, published in *The Lancet* last June, the region of the HIV protease enzyme to which PIs bind is structurally similar to regions on at least two human proteins involved in the breakdown of fats or lipids. They theorize that the drugs' inhibition of these two proteins may lead to increased death of fat cells in the extremities, impaired clearance of fats from the blood, and fat redistribution.

In February, researchers at Glaxo Wellcome offered another plausible hypothesis. Noting an absence of reports of fat redistribution in clinical trials of their newly approved PI, amprenavir

(Agenerase), Glaxo began probing the mechanism of action of all PIs. Lab experiments indicated that PIs were interfering with normal metabolic functions by two different mechanisms -- neither of which appeared to be induced by their drug. They discovered that ritonavir (Norvir), nelfinavir (Viracept) and saquinavir (Fortovase) inhibited the formation of fat cells, whereas indinavir interfered with signaling of retinoic acid (a vitamin A derivative), implicated in the Cooper-Carr model. Either mechanism could potentially cause fat redistribution and affect lipid and insulin levels.

Donald P. Kotler, MD, of St. Luke's/Roosevelt Hospital in New York City, a leading expert on HIV wasting, believes that the problem may be "multifactorial" and not necessarily related to PIs directly. Since recognition of this syndrome coincided with prevalent PI use, he believes researchers leaped to premature conclusions. In the pre-protease era, Kotler had observed body-composition and metabolic abnormalities, though infrequently. Even recently, some PWAs with buffalo hump -- including one of Carr's own patients -- were not taking PIs. Kotler theorizes that such alterations could be *exacerbated*, rather than directly caused, by PIs. He suspects that cortisol -- a hormone released in response to stress that is also important in fat metabolism -- may play a key role. Cortisol is implicated in Syndrome X, a non-HIV condition with symptoms strikingly similar to lipodystrophy. "Syndrome X is all around us," Kotler says. "I may have it. Why shouldn't some HIV-infected people have it, since it seems to accompany chronic stress?" But a study of lipodystrophy published last year in *The Lancet* found no correlation between buffalo hump and increased cortisol. Another anomaly, in contradiction to the Cooper-Carr findings, is Kotler's conclusion, based on retrospective analysis, that lower viral loads seem to predict greater fat redistribution.

While we wait for further research to unravel this mystery, growing numbers of PWAs struggle daily with the debilitating effects of the syndrome on both their bodies and their psyches. Lipodystrophy has devastated the quality of their lives -- limiting physical activity, lowering self-esteem and bringing fear, despondency, loneliness and isolation. "I look in the mirror and think I look like hell. It's all very depressing," says Sean Casey Venable of Lewes, Delaware. In a culture that prizes appearance, body shape distortions have driven some to retreat from social activities. Doug Smith of St. Petersburg, Florida, says, "I feel much less attractive, and therefore have given up dating and, for the most part, hoping for a partner." Adds Sally Brookins, "I'm now self-conscious about my body. I don't want to dress up and go places. And forget bathing suits. When I was young and saw old people with fat backs, I used to dread that happening to me, and now it has. I don't like what's happened to my body, but my husband would rather have me here, with globs of fat hanging off my back, than gone. The side effects are worth it. Protease inhibitors have kept me alive."

"I'd rather be alive with a paunch than dead and rotting in my grave," echoes Oakland, California, AIDS activist Jeff Getty. "Let's put this in perspective. We wouldn't even be here to complain without these drugs." Despite early warning signs of lipid increases in the clinical trials, the FDA was caught by surprise by the magnitude of this problem. As disconcerting as these side effects are, few would criticize the FDA's decision in granting accelerated approval, given the soaring death rate and absence of viable treatment options in the pre-protease era -- and the dramatic

benefits since. When assessing the risk/benefit ratio of drugs for life-threatening diseases, unknown side effects are balanced against the risk of disease progression or death. Inherent in fast-tracked drug approvals is the risk that unanticipated, long-term side effects may emerge after approval.

“Even though the onset of this syndrome might have occurred within the time limits of clinical trials, you don’t usually recognize something unusual until you see the most severe cases,” says Jeff Murray, MD, spokesperson for the FDA’s Antiviral Division. It took a cascade of complaints about lipodystrophy -- and more than two years after the drugs were marketed -- until “we realized that this was truly a problem, more frequent than we had thought.” Last June, Murray recounts, “after reviewing the case reports, we decided there was enough information to link an association to this new syndrome.” Under FDA prodding, the companies added “fat redistribution” to the list of side effects on package inserts. This action was taken without issuing a public health alert. “The FDA shouldn’t be satisfied with obscure warnings on a package insert that no one reads anyway,” says Dave Gilden, editor of GMHC’s *Treatment Issues*.

Some observers say the system broke down between accelerated and final approval, that the FDA abdicated its responsibility by neither monitoring emerging side effects nor requiring additional studies. Activists question whether the current system provides sufficient safeguards. As John James, editor of *AIDS Treatment News*, points out, “There is little incentive for sponsors to go looking for problems once they’ve obtained approval.” Accelerated approval is based on 24-week data demonstrating safety and efficacy. Final approval is based on 48-week data confirming sustained benefit. At the time of accelerated approval, the FDA outlines, and the sponsor commits to, specific post-marketing (Phase IV) studies. Once these commitments are made, Murray believes that it would be unfair to suddenly demand, midstream, additional studies and that the agency must operate on a “level playing field” -- even if toxicities emerge in the interim. But once final approval is granted, the FDA no longer has the legal authority to require additional studies. Pulling a drug off the market is its only recourse -- a drastic measure that would find little support. Therein lies the problem.

“It’s impossible for the FDA to have the foresight to mandate studies of side effects, prior to their emergence,” says Don Howard of ACT UP/Golden Gate, who has been closely monitoring the situation. “Patients in clinical trials could continue to be followed, emerging side effects could be identified and reported back to the FDA, and then further studies could be outlined,” he says. Gilden agrees, proposing “a longer interval between accelerated and final approval, during which time the FDA would reserve the right to demand additional studies if warranted. This would have no impact on the patient’s ability to access the drug or limit income from drug sales.”

Treatment advocates have been highly critical of the lack of a side-effect monitoring system, a flaw that hampers the agency’s ability to respond promptly and effectively to newly emerging toxicities and potential health problems. Howard calls the FDA’s failure to send out a broad alarm to doctors and patients “woefully irresponsible.” He adds, “No one took responsibility, there was no point person to alert people. The community was the first to raise the red flag.”

Spurred into action by the reluctance of industry and government to address this perplexing problem, the AIDS community mobilized. PWAs set up hotlines and e-mail lists (see "Fat Chat"), conducted surveys and held community forums and teleconferences, seeking to monitor the side effects and share slivers of available information. Advocates met with drug companies, the FDA and NIH, to demand action. Despite good intentions, these ad hoc efforts lacked overall coordination, but did succeed in shining a spotlight on the problem.

“We could always improve our post-marketing surveillance, but for the FDA to assume a more active role would require additional funding from Congress,” says Murray. “I think the system, even though not optimal, worked quite well.” As to whether in retrospect the agency might have handled this problem differently, he responds: “No, I don’t think so. In this case, we made the label changes when there was enough information to make the association with PIs. At that same time, we asked the sponsors to consider research, without being able to give them a clear direction on finding the mechanism. Even at this point, we don’t have any clear ideas.”

One effort to facilitate a research agenda was launched by the Forum for Collaborative HIV Research in Washington, DC. Culling advisers from academia, industry, government and the community, the Forum has held two meetings on lipodystrophy. The first was in September 1997, when there was no published data, only anecdotal reports. “What was accomplished at the first meeting was an agreement that this was important, needed a closer look, that we needed to figure out the cause and prevalence, and get a sense of how dangerous it was,” says Forum director David Barr. By the second meeting last October, prevalence studies were identified as the immediate research priority, resulting in a proposal for a NIH-funded, multi-center trial.

“The work of the Forum is laudable,” says Howard, who attended the last meeting. Attention was focused on how often fat redistribution occurs, he says, but tracking incidence is “only one-third of the problem.” He adds, “We need to spend an equal amount of time and energy understanding causality and treatments that people can use today.” Advocates cite the need for short studies on remedies already being tried in the community and a range of other treatment strategies (see "The Skinny on Lipo").

Several PI manufacturers have stated that they are sponsoring research, with studies planned or underway. However, Martin Delaney, founding director of Project Inform, says: “Neither industry nor government seems to be doing enough. In nearly three years, we still don’t have an agreed-upon case definition of lipodystrophy, its treatment, or any sense of its long-term consequences.”

The pace of research remains slow. Mechanism-of-action and prevalence studies are important, experts believe, but they’re only the tip of the iceberg. Various hypotheses about causation await further investigation, which may pave the way toward treatments and novel drug designs. Prevalence studies will compare data on various populations and disease stages. Prominent researchers believe a comprehensive research agenda should include studies to ascertain whether PIs are the direct cause of lipodystrophy, and to identify risk factors and long-term health consequences of the syndrome. A few clinical trials to explore reversibility of symptoms by studying patients stopping or switching to other PIs or PI-sparing regimens are in progress, but

more are needed. Determining whether nutrition, exercise, lipid-lowering drugs, human growth hormone and other interventions provide a clear benefit is considered a top priority by PWAs.

It’s time for innovative solutions. “A multidisciplinary task force is needed to create a coherent strategy that rises above the pressures of the marketplace and coordinates research efforts,” says GMHC’s Dave Gilden. “It will take guts and leadership, as well as funding, to get a true picture of the cause, prevalence and long-term implications of these toxicities.” Without decisive action, some PWAs face a future of prolonged HAARTache.

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