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## As AIDS Drugs Fail Thousands, 'Salvage' Is Key

By Marilyn Chase

STEVE KOVACEV, a sinewy 52-year-old from Truro, Mass., has run the Boston Marathon and sailed in the Transpacific Yacht Race from Los Angeles to Honolulu. Neither event comes close to his current competition: a race for his life.

Mr. Kovacev has AIDS. He has used all the drugs available to fight HIV, the virus that causes the disease, but now almost all regimens have lost strength, and his virus is on the upswing. His plight places him in an unenviable class: the estimated 40,000 U.S. AIDS patients whose illness isn't responding to treatment. As a last-ditch effort, some of these people -- Mr. Kovacev included -- are turning to a regimen known among AIDS patients and doctors as salvage therapy.

In general, salvage therapy refers to any treatment devised by a doctor to save a patient when all other options have failed. There isn't a single recipe for salvage. Some AIDS physicians return to older drugs to wring out a last drop of efficacy, while others bid for access to experimental agents in a desperate attempt to bring the spiraling virus under control.

Today there are about one million people living with HIV in the U.S., with about 40,000 new infections a year. In 2004, the most recent year for which statistics are available, 15,798 people died from AIDS, down sharply, thanks to new AIDS drugs, from 51,000 in 1995. Hepatitis and drug toxicity contribute to deaths among HIV patients. Because of salvage therapy, most patients with drug-resistant virus are, for now, hanging on.

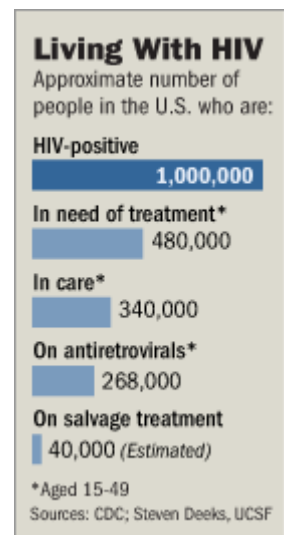
Even with optimal treatment, Daniel Kuritzkes, associate professor of medicine at Harvard Medical School, says, "we've only changed the slope of the disease progression, not halted it altogether, and eventually they do run out of options."

Nearly two dozen AIDS treatments are currently on the market. But as the epidemic turns 25, many long-term patients have been driven by the mutating virus to keep

switching regimens until all have failed. Of the 40,000 patients who aren't responding to even the latest high-power medication, "20,000 are in dire need," says Houston AIDS-treatment activist (and AIDS patient) Nelson Vergel. "I call them the invisibles, because they are too tired and too sick to fight for their rights."

Mr. Kovacev believes he contracted HIV in the early 1980s from his partner, who died in 1990. In 1996, illness forced him to begin antiviral cocktail treatment for AIDS. He "got very sick last fall and went on a new regimen -- one of the last available," combining the injectable drug Fuzeon with two antiviral pills, says his doctor, Stephen Boswell of the Fenway Community Health Clinic in Boston.

Over the years, Mr. Kovacev has survived bouts of an intestinal parasite that left him wasted, a virus that nearly blinded him, and painful neuropathy that required morphine. But he rallied to



run the 2006 Boston Marathon last month as an unregistered disabled runner. He finished the race -- his 13th marathon -- in six hours and 41 minutes.

Dr. Boswell cites Mr. Kovacev's "voracious will to live" and athleticism for his survival. Mr. Kovacev swears by nutrition and Dr. Boswell's vigilance in tailoring 10 successive AIDS cocktails.

Mr. Kovacev hates the term "salvage therapy." "Salvage sounds like you're dredging a shipwreck," he says.

Mr. Vergel seems resigned to the term. "Salvage isn't a science. Salvage is an art," says the Houston activist, who has taken all 22 approved AIDS drug products.

Many patients now in salvage have, like Messrs. Kovacev and Vergel, lived with HIV for over two decades. Some like Mr. Vergel took the first antiviral, AZT, approved in 1987, and swapped in each new product until protease inhibitors in 1996 heralded the era of modern drug cocktails.

At San Francisco General Hospital, physician Steven Deeks is studying 300 salvage patients, many of whom started on AIDS drugs in the early 1990s. Many considered aggressive switching as the best practice at the time, and the patients quickly switched to each new product like DDI and 3TC.

By the 1996 debut of protease-inhibitor drugs, which are now anchors of modern cocktail therapy, such patients "already had high-level resistance," Dr. Deeks says. It now appears that rapid switching of single drugs had fueled the development of resistant virus.

Dr. Deeks, an associate professor of medicine at the University of California at San Francisco, warns that people on cocktails who still swap in the latest new drug one at a time are perpetuating the problem. "We need to stop switching so aggressively," he says. "We need to hold still until we have a number of new families of drugs."

Salvage therapy is "a huge issue," says Harvard Medical School Professor Jerome Groopman. "You've got these patients who did well and you're excited for them. Then you get back with them and they have 12 mutations. You're desperately searching. They're hanging on by a thread."

Dr. Deeks urges resurrecting old drugs like AZT or 3TC as stopgaps to stabilize patients until two or three novel drugs can be combined in an all-new cocktail.

Once doctors get access to two or three novel drugs, they can concoct the first all-new cocktail many patients have had in several years. Raining multiple blows on HIV gives a chance even patients with multidrug-resistant virus can lower the level of HIV in the blood to the limits of detection, Harvard's Dr. Kuritzkes says.

Experimental drugs furthest along in the new product pipeline include: the new protease inhibitor TMC114 from Johnson & Johnson's Tibotec unit; new integrase inhibitors from Merck & Co. and Gilead Sciences Inc.; new entry inhibitor drugs that block the CCR5 co-receptor from Pfizer Inc. and Schering-Plough Corp.; and Tanox Inc.'s IV monoclonal antibody to block the virus's entry through the CD4 receptor on human immune cells.

"I'm excited," Mr. Vergel says. But he adds, "I want people to wait. Don't blow your options by adding [one drug] to a failing regimen."

For those who can wait, Mr. Vergel says the new drug pipeline may yield products this summer and next spring. "I am just concerned that so many patients who need help now may not see the good days coming ahead," he says.

