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The Ones HIV Left in Limbo

Salvage therapy is the last resort of a largely unknown and unlucky minority who began treatment before multidrug 'cocktails.'

By James Ricci

Times Staff Writer

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SAN FRANCISCO — In a consultation room at San Francisco General Hospital, Warren Ratcliffe rolls up the leg of his jeans to display an anachronism. Purplish brown, leech-shaped splotches cover his left shin and calf.

They exist also, he says, on his stomach and chest, and he fears they might appear on his hands and face, where clothing won't obscure them.

Kaposi's sarcoma, once the familiar and portentous calling card of the deadly AIDS epidemic, has all but disappeared over the last decade, during which multidrug "cocktail" therapy has drained HIV of much of its ferocity and returned many patients to normal lives.

The markings on Ratcliffe's skin, however, tell of a grim exception.

For an estimated 40,000 Americans such as Ratcliffe, the newer treatments have not subdued the disease. Most members of that group had the bad fortune of being diagnosed with HIV when single-drug treatment — or monotherapy — was all that was available.

Monotherapy gave the virus only one obstacle to mutate past, and as researchers later discovered, resistance to the drug often developed. Multidrug therapy, which was initiated in 1996 and usually consists of three medications, usually presents the virus with a virtually insurmountable mutational challenge.

But longtime monotherapy patients are an unfortunate exception. Because the drug they have taken is one of the three types used in the multidrug cocktails, if their virus has already become resistant, it can more easily become resistant to other drugs in the mix too.

That leaves veterans of monotherapy playing a fearsome waiting game, trying to stay alive long enough for new drugs — which their infection might not be resistant to — to become available while their doctors repeatedly improvise with existing medications to slow their progress toward death.

This little-known corner of HIV medicine is called salvage therapy, the last resort of this unlucky minority.

Warren Ratcliffe's arduous journey through disease and treatment illustrates the plight of those who wind up in salvage therapy.

A 58-year-old native of Mississippi, he settled in San Francisco after serving four years in the Navy during the Vietnam War. He thinks he was infected in 1976.

The disease lay dormant for a dozen years, but in 1988 he took an HIV test and was found to have the virus. Ratcliffe was immediately put on AZT, a drug that is in one of the three major classes of current HIV medications.

Although he had stomach problems with AZT, he had no symptoms of the disease itself for three more years, and his infection-fighting T-cells were, at 400 per milliliter of blood, near normal numbers — a sign that his immune system was operating effectively.

In 1991, however, a dermatologist discovered a lesion from Kaposi's sarcoma on the back of his right leg — proof that the AZT was no longer working.

Ratcliffe was then put on daily alpha interferon injections that had him "feeling like I'd been run over by a bus, and it backed up and ran over me again. Basically I had one day a week — maybe two — when I felt human."

What ensued over the following years was a cascade of medications sequentially and in combinations, none of which succeeded in knocking the virus down to undetectable levels. Two experimental drugs Ratcliffe has taken as part of clinical trials have failed.

Now his salvage therapy regimen reads like a pharmaceutical catalog: Neupogen (three injections a week to boost his white blood cell count); Fuzeon (two injections a day to help prevent the virus from fusing with normal cells); Crixivan (two pills a day; a protease inhibitor that interferes with HIV's replication process); Kaletra (three capsules twice a day; another protease inhibitor); Viread, Epzicom and Zerit (one pill a day each to interfere with the virus' ability to make DNA); Zithromax (one pill a week to prevent opportunistic infections); and Bactrim (one pill a day to combat infections).

Despite all this, his T-cell count is down to 37. Anything below 200 is considered an indicator of full-blown AIDS. His weight is low, and he sometimes has difficulty giving himself injections because of a lack of fat beneath the skin.

"I've had every drug out there and the virus keeps building resistance to them," Ratcliffe said. "My problem is, I need three new drugs.... So, we try to maintain until there are additional drugs available and I can take more than one at a time."

Through sleeplessness and constant bone pain, Ratcliffe is still able to attend to errands and other aspects of normal life, thanks in large part, he says, to the support of his partner, who is also a veteran of monotherapy but whose virus has been suppressed to undetectable levels by multidrug treatment.

Ratcliffe says the fact he is still alive is due to the level of HIV expertise among doctors in San Francisco, and especially to the talent of Dr. Steven Deeks, possibly the world's leading authority

on salvage therapy.

Deeks has shown that drug-resistant HIV strains are less "fit" than original "wild-type" viruses and do their damage more haltingly, especially when up against numerous drugs in a salvage-therapy regimen.

"The basic principle of therapy is that one should have three fully effective drugs in any new regimen. But this is rarely possible in heavily pretreated patients," Deeks said.

"Hence, we often try to get two fully effective options and combine this with other 'partially effective' options. The need to add up all of these partially effective options is why many salvage regimens contain five or more drugs."

Salvage therapy is a machine of many moving parts. Matters are complicated by the fact that a patient's resistance to a given drug often means resistance to all the other drugs in its class.

"Salvage therapy in this point of time is an art," said Jeff Sheehy, communications director for the AIDS Research Institute at UC San Francisco, where Deeks is an associate professor of medicine. "It's almost like Steve Deeks is a magician. He's like a wizard concocting potions You have to understand the meds, the side effects, the resistance profiles of each drug and the resistance profile of the virus in the individual you're treating."

Like Ratcliffe, Mark McClelland credits salvage therapy with keeping him alive. Despite low T-cell counts, he is able to exercise regularly and practice yoga. His apparent good health belies a history of high hope and bitter disappointment with HIV treatments.

McClelland, a 44-year-old former healthcare policy analyst, tested positive for HIV in 1990 and immediately was placed on AZT, then on another AZT-class drug he found more tolerable. Six years later, he went on a three-drug regimen and his T-cells jumped from 12 to 250 in two weeks. "I felt great," he said. "I had normal energy and I even considered going back to work. I did some traveling."

After about eight months, however, he began to decline again.

In 1998, he was placed on a new four-drug regimen that succeeded in suppressing his virus to undetectable levels. After two years, however, the drugs became toxic to his liver and he was put on an altered regimen to which his virus quickly became resistant.

His two brushes with success took their psychological toll. "You think, 'Hey, maybe this is it. Maybe I'm going to be OK,'" he said.

"So, there's a letdown. I mean, there are people who went on three-drug therapy the same time I did and they've been doing great ever since, which is not a happy comparison for me."

Now McClelland takes six drugs of various classes. Although his T-cell count has dipped as low as 4, he says, "I'm clinically stable, have good energy, am not getting any infections."

Like everyone connected with salvage therapy, McClelland keeps a vigilant eye on the drug pipeline, waiting for at least two new ones that he is not resistant to and that can be combined. The temptation is to leap on each drug as it emerges, but that carries a greater risk of developing resistance to it.

Two new drugs from one pharmaceutical company are being combined in clinical trials. Further back in the pipeline is an entirely new class of drugs called integrase inhibitors. Together, these developments might offer the chance of a new three-drug combination in a couple years. Another intriguing new class called R-5 drugs is already being tested, but has run into problems with liver toxicity.

Of concern to Deeks and his colleagues is the fact that drug-resistant strains of HIV increasingly are showing up in newly infected patients. In San Francisco, recent studies indicate that between 5% and 27% of new cases involve HIV strains that are resistant to at least one of the three classes typically used in multidrug therapy. In one study, about 13% were resistant to two of the classes.

This, Deeks says, shows the importance of testing new patients for drug resistance, which is routinely done in San Francisco but not elsewhere and is not covered by medical insurance. "It says something about our health system that insurance will cover \$30,000 to \$40,000 a year worth of medications but will not spend a few hundred dollars for a resistance test to tell us which drugs to use," he said.

Knowing which drugs new patients are resistant to is critical. It enables doctors to avoid including them in multidrug regimens, which would predestine failure and speed patients into salvage therapy and the harrowing wait for medical science to catch up before it's too late.

That wait, McClelland says, has to be managed with the proper attitude. "One of the main life lessons is not to give in to anxiety, but to live in the moment, to enjoy being healthy today," he said.

After discussing his case, Ratcliffe puts on his jacket and slips his backpack over a shoulder. As he leaves, he says to a visitor: "I never thought I would live this long with this disease. I hope you can come back five years from now and interview me."