The Clock Watchers

With their multidrug resistance and dwindling T cells, HIVers desperate for “salvage therapy" remind us that in the absence of a cure, we’re all playing for time.

October 1, 2003 By Tim Murphy

In a fluttery, stuttery falsetto that swoops between rage and hilarity, Michael Barry, 43, reads aloud a note he wrote recently to his doctors, family and the world: “Do not resuscitate. I’m ready to die.” In this age of potent HAART cocktails, undetectable viral load and buoyant projections that many HIVers will live to ripest old age, he knows this isn’t the sort of thing a forward-looking HIV positive American is supposed to say. But Barry, diagnosed 18 years ago, has good reason: He hasn’t had more than 20 T cells since 1996. And today, from his parents’ home outside Orlando, Florida, he adds, “I’m one happy T cell.” That’s after nearly a year on both the recently FDA-approved Fuzeon (T-20) and the experimental protease inhibitor tipranavir, a combination that has wrought what his doctor, Gerald Pierone, MD, calls “near miraculous” results in many other patients. When it comes to “salvage therapy” — a term that emerged among HIV doctors in the late 1990s to describe new options for patients with failing regimens — Barry has missed out.

Barry has been on nearly every HIV med, and tests show dense resistance to all of them. Besides tipranavir and the laborious Fuzeon injections, he takes 37 pills every morning, including Epivir (3TC) and Viread (tenofovir); Valcyte to suppress his CMV; other opportunistic infection–fighting meds including Bactrim, Flagyl and Levaquin, plus Mycelex and Diflucan for thrush; and Neurontin for neuropathy (“I’m holding the phone right now and my fingers are totally numb”). The whole process, he says, takes two hours.

Cut to New York City, where poet Tory Dent, 45, has dumped her triple-protease cocktail of ritonavir-boosted Crixivan (indinavir) and Fortovase (saquinavir)—which she’d hoped would trump her heavy cross-protease resistance. She started it over a year ago, when her T cells hovered at 100 and she feared a return of the CMV that had impaired her eyesight in 2000. Stabilized, she went off to an artists colony to work on the successor to her poetry volumes *What Silence Equals* and *HIV, Mon Amour.* Then her viral load came bounding back. “We upped the Crixivan, but it didn’t do any good,” she says in the girlish voice that belies her 15 years with HIV. “I’m only on [infection-preventing] drugs right now.” She has 24 T cells. “My viral load is probably 500,000,” Dent adds. “At this point, I’m so bored with it.”

Meanwhile, just outside Washington, DC, Norfleet Person, 41, diagnosed with HIV in 1996, has put crack, crime and prison behind him—but not the massive drug resistance his patchwork adherence caused. The Army-trained former computer technician still downs a daily cocktail of Kaletra

(lopinavir/ritonavir), Fortovase and Epivir, but his viral load holds steady at one million, his T cells at zero. A stint in the Fuzeon trial "might have raised my CD4s from seven to 40," he says, "but the pain in the injection site is terrible. I could barely walk." Person spends his days watching *Judge Judy*, occasionally visiting his sister or mother, and hoping that "something new [in treatment] will come out." But he expects to die soon from AIDS, just as his lover, James, did in 1994. "I'm like, it's gonna happen—no way around it."

And down in Houston, Sharon Wagner, 45, a former substitute teacher diagnosed with HIV in 1987, awaits her latest lab results. The last ones weren't good, even two months after she entered a trial for tipranavir. Her viral load had actually risen from about 181,000 to nearly half a million, and her T cells had plunged from 63 to 29. A devout Christian, she says she's still "happy-go-lucky." Yet she adds, "God always gives me more than I can handle, and I wish he wouldn't trust me with so much. I don't pray for patience anymore."

She says she's never enjoyed viral suppression and "good numbers," even in the protease age. "Why can't these meds work on me when I see people [on HIV meds] being able to maintain?" she asks. "We're just the people who are grasping at straws, trying to tie a knot and hang on."

THE SPOILERS

Seven years after the AIDS death rate plummeted in the U.S., Barry, Dent, Person and Wagner are among that unlucky minority of positive Americans who aren't just "living with HIV." With their single- or double-digit CD4 counts, opportunistic infections and pooped-out meds, they've got good old-fashioned AIDS. True, we now know that nearly every HIVer will develop some resistance to some meds—and that resulting low levels of detectable virus needn't mean HAART "failure," especially in patients with a long treatment history. Recent research even suggests that some forms of drug resistance could actually be useful, sapping HIV's overall "fitness." Such findings have led some patients to sit tight on seemingly failing regimens rather than jump to second or third options.

But folks like these four used up *all* their options a long time ago. And while many of us can just pop our one-a-day combo and get on with our lives, they exist in a kind of purgatory, spoilers at the HAART-cocktail party. A. Mathivannan, MD, of DC's Whitman-Walker Clinic, says that of his 450 patients, Person is one of the five or 10 in final jeopardy—and that having little to offer them "doesn't make me feel good." Virginia Cafaro, MD, a longtime San Francisco HIV doc, says treating such patients is "like having flashbacks to what we'd hoped were days gone by." But perhaps it's the patients who feel most out of step with the times. Dent says that when she was admitted in 2001 to the same hospital she'd been in six years before, "there was no AIDS ward anymore. I was put in with surgical patients. Now, if I tell people I have AIDS, they don't understand."

Or perhaps we camera-ready, rock-climbing HIVers simply refuse to understand. Cafaro calls HIV's neediest cases "the ever-present reminder that we do not have a cure." After all, treatment options are limited, and none works forever. With their scary infections and desperate hopes pinned on pharma's Next Big Thing, the badly failing won't let us forget that we're all measuring our existence in life-years per regimen — that we're all, to various extents, watching the clock.

MONOTHERAPY BLUES

How did it get so bad for such folks? Most are alumni of AIDS' Dark Ages, diagnosed in the 1980s and treated with a strategy that makes current doctors cringe: *Sequential monotherapy*. This prescribed one antiretroviral at a time, a sure-fire route to drug resistance. For countless HIVers, early NRTIs (nukes) like AZT (Retrovir) and ddI (Videx) lost their potency before they could be teamed up with the NNRTI (non-nuke) Viramune (nevirapine) or the first protease inhibitors to smack HIV down hard. And that initial half-attack paved the way for resistance to every new med doctors could add to the pack.

What's more, in those early years of HAART, not only did the "hit early, hit hard" strategy reign, but an undetectable virus was the single-minded goal. To achieve it, some doctors switched patients hastily from one drug to another, dealing treatment cards with little regard for future options. "There are many patients where we wish we could have played it differently with 20/20 hindsight," says Shannon Schrader, MD, who took on Wagner only after another doctor had burned her through several protease inhibitors.

By 1998, so many HIVers needed rescuing that activists formed the Coalition for Salvage Therapy (CST). The group pushed to get such patients into trials for Kaletra and Viread, which eventually helped stabilize many HIVers. Wagner and Person weren't among them. Dent, on the other hand, watched her T cells leap from 40 to 365 after one month on Kaletra. But a year later, she was breaking out in shingles, one of many latent infections that often surface in HIVers when their immune systems kick back in. Plus, she recalls, "My cholesterol and glucose got really high. I developed serious lipodystrophy—my legs were emaciated." The drug that had finally made her HIV undetectable was all but killing her. She ditched it in October 2001, then landed in the hospital after her virus roared back. "It's never been easy," she sighs.

THE PIPELINE PARADOX

For Dent, Wagner, Person and Barry, these missteps can't be undone. "The important issue for these poor souls is the [drug development] pipeline," says longtime activist and CST cofounder Lynda Dee. Peering into the pipeline, however, it's hard to tell whether this is the best or worst of times for the neediest HIVers. Yes, the horizon is encouragingly crowded: In addition to tipranavir and a few other new protease inhibitors, there's a handful of second-generation NRTIs (nukes) and NNRTIs (non-nukes) for HIVers who are resistant to the current crop, plus an exciting new class of drugs called entry inhibitors (see "I Wanna New Drug"). Moreover, the FDA's fast-track process for HIV meds means bringing new drugs to market takes "half the time it used to," as Dee puts it.

But with blockbusters like Combivir (AZT/3TC) and Kaletra approaching annual sales of $1 billion, manufacturers may be more concerned with getting folks on meds they already offer than nurturing new ones that may not yield profits for a decade. "In the first half of the 1990s, almost every company had an AIDS research program," recalls Martin Delaney of the treatment-activist group Project Inform. "Whoever conquered that disease—it was a pharmaceutical's dream." Now, he says, "there's only four or five companies left doing AIDS, and they've pulled back. Put yourself in a CEO's shoes: Do you go to a disease like AIDS that already has many drugs out and public

pressure to all but give them away in Africa? In the richer countries, there's a limited market — and each [new drug] is just a competitor."

A spate of pharmaceutical mergers also hasn't helped. A story in the June 2003 *amfAR Treatment Insider* argued that when Bristol-Myers Squibb (BMS) bought DuPont two years ago, it severed DuPont's full pipeline of new HIV drugs. Dee says that Agouron is "where they were a year ago" with its non-nuke capravirine because, after the company was acquired by the giant Pfizer, "nobody knows whose secretary is whose." And Delaney calls tipranavir's development "the slowest I can remember," blaming the time lost during the sale of its maker, Pharmacia, to Boehringer-Ingelheim.

The industry rejects those claims: BMS rep David Rosen says the company's non-nuke development "remains active," while Pfizer researcher Rick Pesano, MD, PhD, says that capravirine trials are "moving forward." But Boehringer's Douglas Mayers, MD, concedes: "Whenever you transfer a drug from one company to another, you're going to lose a year or so."

ALL IN THE TIMING

But to clock watchers, a year may make all the difference—and few drugs will be available, even in early trials, for at least several months. Some patients are holding out for T-1249 (whose current trials include only those who developed resistance in Fuzeon trials) and for tipranavir, which looks promising for folks with protease resistance. Its final trials began enrolling in February, and Mayers says Boehringer hopes to show data for FDA approval by early next year.

The world of clinical trials — with their countless eligibility criteria, consent forms and blood draws—is one that drug-needy HIVers know well. As much as companies would like to enroll treatment virgins with zero resistance, they know, in Dee's words, that "the best way to prove your drug is through experienced patients." And yet those most in need, with the heaviest resistance, are often locked out, for fear that, tested in them, new drugs won't yield impressive outcomes. "You might not like to hear this," says Aaron Diamond AIDS Research Center's Martin Markowitz, MD, who often consults on salvage cases, "but if you're developing a drug, and you give it to too many people who are in really bad shape, you're never going to get it approved."

That's why early activists lobbied for expanded-access programs, which get free drugs to needy patients who don't qualify for clinical trials. Drug-maker Gilead put heavy restrictions on its expanded access for Viread until CST protested. A new group, AIDS Treatment Activists Coalition (ATAC), has since supplanted the now-disbanded CST, but Dee says "it's exactly the same people doing the same work." One of its recent coups for the salvage crowd? Getting Boehringer to double this year's expanded-access slots for tipranavir from 300 to 600 (see "Stayin' Alive").

Yet even with early access, a dilemma endures: HIVers often slap promising new drugs onto a burnt-out regimen—with little result. The CST persuaded the FDA to allow a failing patient two or more study drugs simultaneously, and, slowly but surely, rival drug companies may be coming around to the idea as well. Mayers says that Boehringer is "exploring" such partnerships, though he declined to name with whom. "I'm sure it will be done," he adds. "The FDA has encouraged us."

Still, every drug is on its own schedule, and nabbing two or more at the same time is tough. So should patients get what they can from a new drug, or hold off until they can pair it with another? "In an ideal world, you'd wait," says Pierone, Barry's doctor. "But there are people who just don't have the luxury."

MAKING DO

"Sometimes I think I got AIDS because I can handle it," says Annette Lizzul, 40, a salvage success story. Diagnosed with HIV 18 years ago, the never-say-die New Jersey resident was in bad shape when she came to Aaron Diamond's Markowitz in 1999. "She had multi-class drug failure, T cells around zero, a viral load around 3 million and active CMV disease," says Markowitz, who didn't nail her lucky combo until Kaletra and Viread became available a few years later. "We combined a dual protease inhibitor with Viread, and the best possible nuke was ddI [Videx], and I threw in 3TC [Epivir] because [it may] maintain the M184V mutation that keeps the virus less fit." Lizzul remembers it this way: "He said, 'I'm gonna put you on so many drugs, you're gonna puke, but whatever side effects you have we'll take care of.'"

Two years later, Lizzul is holding steady on the same combo, her viral load undetectable and CD4s just breaking 600, the highest they've been in 15 years. It hasn't been easy—she says lipodystrophy has left her with "twig legs"—but she's feeling good enough to hold a part-time job at the Hyacinth AIDS Foundation. She's considering moving out of her parents' house and maybe even meeting a man. "My goal is to get on *Oprah*," she laughs.

Lizzul was salvaged by what's variously called mega-HAART, giga-HAART or "kitchen sink" therapy—giving patients "as many drugs as they can tolerate," as Markowitz puts it, and sitting pretty until something better comes along. Other salvage patients are hoping to buy time with a "partial treatment interruption"—subtracting the protease inhibitors, say, and leaving the nukes, banking that some nuke mutations can weaken the virus. The jury is still out on whether a *complete* break can prime patients for better results when they restart—and such breaks have their risks. "Generally, I hesitate to discontinue meds on people who have multidrug-resistant virus because they're the ones who do poorly off drugs," Markowitz says.

NOT JUST NUMBERS

If such last-resort options feel like a crapshoot, that's because they are. Even a salvage pro like Markowitz chalks up Lizzul's eleventh-hour turnaround to "the luck of the draw." Dent and her doctor, hoping for similar luck, plan to team up Fuzeon and the new protease inhibitor Reyataz. Mathivannan wants to get Person on expanded-access tipranavir. Pierone plots to put Barry into early trials for protease inhibitor TMC 114. And Wagner is torn: Should she try to get Fuzeon through Texas ADAP—or say to hell with all her meds?

The T cells of these four people total 54. Their remaining days may be as precariously numbered if science, commerce and time don't converge in just the right way. Then again, HIVers with only a handful of T cells have gotten along for years on infection-preventing meds and what seemed like a lousy combo — or none at all. And though they're bitter over the countless heartbreaking lab

reports, their lives haven't stopped for numbers. In one breath, Norfleet Person says he's ready to die, and, in the next, voices anger at his mother's reaction to news that he had no more T cells: "She said, 'Oh, well.' I wanted her to ask questions: *Will your numbers change? Is there something I can do for you? Will you get better?*" Michael Barry says, "I pray for ending life. I know that sounds pathetic, but my quality of life — it's hard." Yet he traveled recently, neuropathy and all, to San Francisco for a peace march, to DC to protest for more AIDS funding ("I think what keeps me living is fighting the government") and to Fort Lauderdale to celebrate his 43rd birthday with his friend Chas ("We rented a Mustang convertible"). Tory Dent is leaving for a vacation in San Francisco with her husband, Sean, 10 years her junior, whom she met a decade ago. The last entry in her nearly completed volume is a love poem to him.

Sharon Wagner, particularly, will not stop for scary numbers—not with a daughter in college, a grandchild and a new boyfriend, Jimmy, she met through an online dating service for HIVers. Recently, she interviewed at a Houston nonprofit for part-time work. "It made me feel good to get dressed in a suit, high heels and pantyhose," she says. "The woman there knows my illness, and it was so comforting. I really want this job."

Two weeks later, she learned that her viral load had risen again—and that she'd gotten the job. "It's tiring to plan for life and death at the same time," she says. "I feel like I shouldn't plan for life, but I need to, because if I am going to live, I don't want to have had that wasted space."

STAYIN' ALIVE: A GAME PLAN

Think you've hit the end of the road? Here's a step-by-step survival guide:

1. TAKE A DEEP BREATH You're not going anywhere soon. Some HIVers with few or no T cells have lived for years without illness just by taking anti-infection meds like Bactrim. Go to www.aidsmeds.com, click "Lessons," then "Opportunistic Infections (OIs)" for a complete rundown.

2. DEMAND TOP CARE Doc says you're out of luck? Don't stand for it. Call your local AIDS group, the American Academy of HIV Medicine (866.241.9601) and the National Institutes of Health (800.HIV.0440) and tell them you need cutting-edge care. Often, it's at a university or research hospital.

3. GET IN THE LOOP Go to www.aidsinfo.nih.gov/clinical_trials/,click "Treatment Experienced/Failure" and search for trials or expanded-access programs that may be right for you (do your best with the medical jargon). If there's a trial site near you, dial the number. It just might save your life.

4. FIGHT FOR YOUR LIFE The veteran fighters of AIDS Treatment Activists Coalition, many of them HIV positive, need fresh faces and voices to help push Uncle Sam and Big Pharma for new therapies (and, hello, a cure). Learn what they're about and find out how to join up at www.atac-usa.org.

5. DON'T DO IT ALONE Seek the support of a shrink, HIVer group, whatever you can find. Most of

all? “Never take no for an answer,” urges Sharon Wagner. Poet Tory Dent puts it plainly: “Justhang in there.”

I WANNA NEW DRUG!

Could these contenders offer the neediest HIVers new hope?

TIPRANAVIR *(Boehringer-Ingelheim)*
An all-new protease inhibitor (PI)

What’s the hope?
It promises punch in patients with PI resistance.

How can you get it?
Two Phase III trials and an open-label safety study are now enrolling. Search “tipranavir” at www.clinicaltrials.gov or call 800.344.4095 x6215.

CAPRAVIRINE *(Agouron/Pfizer)*
A second-generation NNRTI (non-nuke)

What’s the hope?
It could aid HIVers with Sustiva-Viramune cross-resistance.

How can you get it?
Two trials are now enrolling. Search “capravirine” at www.clinicaltrials.gov or call 858.622.8035 for details.

PRO 542 *(Progenics)*
One of a new class of drugs called entry inhibitors

What’s the hope?
A once-weekly injection could seriously whack HIV—without the side effects of today’s drugs.

How can you get it?
A trial for HIVers with failing regimens is enrolling. Search “PRO 542” at www.clinicaltrials.gov for details.

And periodically visit www.clinicaltrials.gov to search trials for new drugs like NNRTI **TMC 125**; PI **TMC 114**; and entry inhibitors **SCH-C** and **TNX-355**. (PS. Drugs get snazzy names only after they’re approved.)

© 2026 Smart + Strong All Rights Reserved.
http://beta.docker.poz.com/article/The-Clock-Watchers-671-5895