Living on the Edge

A cautionary tale about ahead-of-the-pack treatment decisions

November 1, 1997 By Rick Loftus

I HIT EARLY, SOFT

I used to feel so smug about my treatment decisions. I was good at predicting treatment trends and was always a couple of years ahead of then-current guidelines. In 1989, when my CD4 cells were in the mid-300s, I started AZT—even though it was only approved for people whose counts had fallen below 200. By 1991, I was on double combo therapy—again, way ahead of the pack—and by 1993, I was on triple combo with a protease inhibitor)then highly experimental). I was aggressive, always hitting the virus with every drug I had. I figured it was best to wipe it out as quickly as possible before any real damage happened to my body.

Now I'm screwed. Because I didn't understand how resistance works, I now know I was jumping from one suboptimal treatment to the next. Each time, I made the virus stronger and reduced my future options. Today I've run through all the nucleoside analogues and three protease inhibitors. Nothing works for me. And while I still could use a nonnucleoside reverse-transcriptase inhibitor (NNRTI), I have nothing to take it with. Even drugs in the pipeline, like Glaxo's long-awaited 1592, probably won't work for me because of cross-resistance.

I made a simple mistake: I put too much weight on scientific theory and didn't spend enough time looking at the hard data about the drugs I was taking. I believed that an infectious disease should always be hit hard and early. What I didn't realize was that, while I was hitting early, I wasn't hitting hard. The drugs weren't powerful enough. By hitting early and soft, I was just creating a stronger virus.

I'm afraid that tens of thousands of people are about to make the same mistake I did. They'll overestimate the power of treatments they're on, and then when these fail, find out they're really in hot water. If the available triple combos deliver on their promise, then everything will be really great. Past experience, however, warns that the medical establishment and pharmaceutical industry have consistently overhyped the potency of drugs while ignoring dangerous side effects. I worry that in a couple of years, we'll discover that today's much-touted combos aren't all that effective, and then we'll wonder why we put so many people on treatments that didn't work, causing massive cross-resistance in the process.

The stakes are high. The protease inhibitors may turn out to be fully cross-resistant: After you've

failed one, none of the others will do any good. You probably only get one decent shot at combination therapy. Lots of people are gambling that the combo they're choosing today is the right one. If I could do it over, I'd take a more conservative approach. I'd wait until more is known about these drugs: Which is the most powerful, which has the least long-term toxicities, for how long are they able to suppress the virus? I'd wait to see if quadruple therapy becomes the standard of care.

There are risks to waiting. Each day off therapy allows the virus to multiple and CD4 cells to die. Your immune system gets generally weaker. Still, I'd be willing to trade 150 CD4 cells to know that the drugs I'm taking are going to work for the long term. I'd rather have my CD4 cells fall for a while but then, when I start therapy, have a drug combination that actually works for five or more years and if it fails, leaves me with other options.

Today, because of the choices I made a decade ago, I'm out of options. My CD4-cell count is 10 and my viral load around 500,000. While my health is pretty good, I feel like an accident waiting to happen. If my health begins slipping, I'll have nothing to grab on to. It's scary. I wish I'd been more skeptical back then. I wish the HIV community was more skeptical today.

—Stephen Gendin

Treatment

"Treatment failure." Growing numbers of PWAs are hearing that dreaded news. While studies are incomplete, experts estimate that between 25 percent and 45 percent of people starting on antiretroviral "triple cocktails" do not durably suppress their virus to undetectable levels. Reasons for this include HIV drugs resistance, drug malabsorption and "noncompliance"—that is, not taking the drugs correctly. At left, New York City AIDS activist Stephen Gendin describes his own experience with combination failure, and his fears that many other HIV positive will follow in his footsteps. The two pages that follow include a summary of Gendin's medical history and differing perspectives by two AIDS specialists on the lessons it may offer for PWAs facing risky treatment decisions today.

POZ asked two physicians with large, longtime HIV practices to offer their opinions on Stephen Gendin's treatment history and current situation. Dr. Calvin Cohen is the research director of the Community Research Initiative of New England in Boston. Dr. Michael Lange is the chief of the Division of Infectious Diseases at St. Luke's—Roosevelt Hospital in New York City. Both doctors refer to an article published by Dr. John Mellors of the University of Pittsburgh about the Multicenter AIDS Cohort Study (MACS), which has tracked 5,000 men with HIV since 1983 to determine what factors influence disease progression. Mellors' study found that untreated men with higher HIV viral loads had faster rates of progression to AIDS than those with lower viral loads.

HE DID HIS BEST

I think the main reason Stephen is in the situation he's in today is that he has a pretty aggressive virus, and we didn't know how to treat that—and didn't have the drugs we needed—back when he

was beginning treatment. In March 1993, his viral load was around 100,000, his CD4 cells around 200. The therapies available to him at the time weren't potent enough to fully suppress the virus, and the result was resistance to the drugs he tried. Today we have people with even lower CD4 cells and higher viral loads who do well when put on potent antiretroviral regimens. We can control their virus regrow their CD4 cells. Unfortunately, we learned how to best treat people with high viral loads—preventing resistance with powerful combinations—by making mistakes with people like Stephen.

Should Stephen have waited to do antiretrovirals? The problem with waiting is, we don't know what sort of rate of clinical progression he might have had. If Stephen had waited in 1993, he might have developed CMV retinitis and died in 1995. According to the MACS data, over the course of three years people with viral loads like Stephen's have an 85 percent chance of developing an AIDS illness, some of which are lethal. At least now he has a fighting chance—he's still here.

Certainly, though, Stephen's virus is harder to stop than that of others who waited. I emphatically agree with caution. Seemingly small differences in how drugs are used could make the difference between the potent long-term benefit and rapid failure. The problem is that with HIV, resistance develops quickly, is unforgiving, and appears to be irreversible. So there's no justification any more for dabbling with these drugs. Maybe not every doctor should be allowed to prescribe them. Every incorrect use risks a life lost. (In fact, several experts in the past year have promoted the idea of making HIV medicine a certified subspecialty requiring specific training in state-of-the-art AIDS practice.)

Who should wait now? People with the lowest viral loads should consider waiting for better drugs. If you have a viral load below 1,000, it would be easy to suppress with the current drugs, but there is no urgent need to do so. It's an individual decision. People can look at the MACS data, see what the average rate of disease progression was for someone with their viral load, and decide whether they're willing to wait. Someone with enough of a viral load that it scares them, and who is willing to take a regimen correctly—and that means taking a handful of pills a few times every day at the correct times—should be able to do combination therapy. If the virus rebounds, don't wait. Check the viral load again soon after and if it's still up, alter the regimen immediately if you have good alternatives. If you don't, it may be preferable to go off the meds completely until a new regimen likely to be effective is available. Staying on ineffective meds could lead to greater resistance and, ultimately, cross-resistance, greatly limiting your future choices.

As for Stephen: I would get him off all protease inhibitors and instead put him on as many nucleoside analogues—AZT, 3TC, ddI—as he can stand, as well as hydroxyurea. I would think twice about using 1592 (Glaxo's new nucleoside); it's unlikely to work on him due to cross-resistance. I would also put him on maximal preventive medicines against opportunistic infections, including oral ganciclovir to prevent CMV retinitis. We need to keep him well so that when the pipeline has two or three new drugs, we can put him on them.

While I understand Stephen's skepticism, I don't think we have as much to fear as used to. Of course, many of today's promising combos won't work for those like Stephen who are already

resistant to protease inhibitors, but they might for others. As Stephen put it, in previous days we didn't know how to hit HIV hard. That doesn't mean we don't know now. For people who need it, we should use it.

—Calvin Cohen, MD

HE HIT TOO SOON

Stephen obviously caught on to the theory of "hit early, hit hard." I was never a great believer in nucleoside monotherapy, and so I did not put my patients on nucleosides unless they were falling apart, with serious clinical problems. Triple therapy is certainly a great improvement over AZT monotherapy. However, I still don't believe you can eliminate this virus.

Nonetheless, if you decide to treat, I totally believe in triple therapy. If you don't achieve an undetectable viral load, you're not helping your patient. Everything going on before the era of triple therapy was essentially creating resistant virus.

As for rates of disease progression: You can average out the viral loads of people to find correlations with faster or slower rates, as Dr. John Mellors has done for the MACS participants. But those are averages; there are exceptions. I have plasma frozen on about 40 of many patients who were not in antiretroviral therapy going back six or seven years. Some had stable CD4 cells and relatively low viral loads. But some have had more than a 100-CD4 cell drop in a year, despite viral loads below 20,000. Conversely, some have viral loads above 100,000, but their CD4 counts don't drop. That's very rare, but it happens.

This is a complex disease; one should individualize therapy. In the euphoria of the success of triple therapy, some are saying that the moment you are infected, you should use it. But why use it when you've got 800 CD4 cells, as compared to 400 or 500 CD4 cells?

Dr. David Ho and Dr. Marty Markowitz have a hypothesis that aggressive combinations in the earliest stages of HIV infection may result in virus eradication in four to six years. It's all right to test this in small studies of acute infection. Due to phenomenal hype, however, people accept "hit early, hit hard" as already correct, and it is being applied to all patients. You can not extrapolate without data. Their hypothesis may not be correct.

The decision to take therapy is probably the most crucial decision a person with HIV can make. Staying "ahead of the pack" is how not to do it. I have a patient like Stephen, an MD who came to see me in August 1993, with tuberculosis and probably toxoplasmosis, CD4 cells below 20, not on antiretrovirals. He went on AZT, and in May 1995 his viral load was 500,000. We added 3TC in October 1995, and Crixivan in March 1996. Despite this, by October 1996, his viral load was two million and he was losing weight. He went on ritonavir-saquinavir, plus d4T, 3TC and nevirapine. After three months, he gained give pounds, and his CD4 count, which had never been above 20 since 1993, went from 16 to 106. His viral load was below 500. I don't know how to explain that. Should everybody go on five-drug therapy? I don't know. As for the decision not to do an NNRTI: Stephen's got nothing to lose. His current prognosis isn't good. He should try a combination with at least anecdotal evidence of pushing someone in his position below detectable virus levels.

We should get beyond the euphoria. Triple therapy is superior to anything we've had for the past 16 years. But we need to discover when best to start, and if partial suppression is acceptable. We also need more data on which regimens work for people whose viral loads have rebounded on protease inhibitors. It would be a shame to go backward, and wind up with a multiply resistant virus.

—Michael Lange, MD, FRCPC

Gendin's Treatment History

1988: In June, started dextran sulfate (an experimental antiretroviral).

1989: In February, stopped dextran sulfate and started AZT and high-dose acyclovir (Zovirax, an anti-herpes drug). In November, added hypericin (an experimental antiretroviral) and upped the acyclovir dose.

1990: Started naltrexone (an experimental immune-modulator) in February. He remains on naltrexone today.

1991: Stopped AZT and started underground ddC in January; later that year, added NAC (an antioxidant) and Tagament (an experimental immune-modulator). Still takes NAC.

1992: When ddC was approved, switched from underground product to approved dose. Later switched to ddI and started Bactrim. Still takes Bactrim.

1993: In March, stopped ddI and restarted AZT and ddC in combination with saquinavir in federal study.

1994: In November, stopped AZT and ddC and restarted ddI, while staying on saquinavir. Upped acyclovir dose further.

1995: Stopped ddI and started d4T as well as testosterone in February. In April, re-added ddI to d4T. In May, switched to AZT/3TC and started clarithromycin (a MAC-prevention drug). In September, started infusions of Cytolin (an experimental mouse-antibody immune modulator). In December, stopped all HIV meds and temporarily switched back to ddC monotherapy.

1996: In January, started regimen of d4T, 3TC, saquinavir. In May, added hydroxyurea (an anti-cancer drug and experimental antiretroviral) and substituted ritonavir for saquinavir. In August, started quadruple therapy by re-adding saquinavir. In October, switched to d4T/ddI/Viracept, while staying with hydroxyurea.

1997: In March, neurotherapy developed; stopped all HIV meds and started Elavil (antidepressant used to treat neuropathy). In May, resumed same meds, but with d4T at a lower dose.

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