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Survivor

Treatment Advocate Nelson Vergel Wants the Experimental Drug Pipeline Opened Up for Patients Like Himself Who Are in Need of Salvage Therapy

By Benjamin Ryan

Nelson Vergel is trapped in medical limbo. The 46-year-old treatment advocate expects to remain there for the next two or three years unless he can successfully use his activist chops to change the drug research system. In doing so, he hopes to allow thousands of other HIVers like himself to cut to the front of the antiretroviral waiting line. Vergel is one of those unlucky guys known as salvage patients--those who, during their long history with the virus, have knocked down every available anti-HIV medication like so many dominoes, developing increasing genetic resistance as their treatment options dwindle toward zero. His goal: to get access to experimental meds in clinical trials for salvage patients.

Opinions differ widely on the prevalence of people like Vergel, but studies have shown that 14% to 20% of medicated HIVers who have a detectable viral load are resistant to three of the four current classes of antiretrovirals. (Testing for drug resistance cannot be performed on patients with an undetectable viral load, so it is impossible to get exact figures on the HIV-positive population as a whole.)

"I hate when people say, 'Well, you know, salvage therapy is not a big problem. All those people have died off. Everybody's kind of stable,'" Vergel says of attitudes he's encountered in his efforts to get people on board with his mission. "Where do they live?"

The imminent release of Aptivus (tipranavir), a new protease inhibitor, gives Vergel

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little hope. As an advocate for patients who need salvage therapy, he knows that adding a single new drug to a failing regimen--known as sequential monotherapy--is a surefire way to develop resistance to that medication. The best way for multidrug-resistant HIVers to achieve an undetectable viral load, which will in turn help them avoid further drug resistance, is to begin two or three new drugs at once.

Such an opportunity is unlikely until 2007 or 2008, when a revolution in HIV treatment could occur: up to nine novel therapies hitting the market at once. Some of these drugs will belong to new classes, attacking the virus in unique ways and thus reducing the likelihood that HIVers will have existing cross-resistance to them. However, until these drugs are green-lighted by the Food and Drug Administration, they will be available only to patients lucky enough to gain entry to clinical trials.

"I really hope that in four years we do not need to worry about salvage therapy," Vergel says, "but right now we do. We are the patients who need these new drugs the most."

Health Concerns

Salvage patients are often left out of drug trials because pharmaceutical companies typically specify exclusions that make patients in late-stage disease ineligible: those with extensive liver damage, diabetes, hepatitis C coinfection, or T-cell counts below 50.

An even more important concern for salvage patients is that no pharmaceutical company has ever studied an antiretroviral in combination with another experimental agent. For someone like Vergel, entry into such a trial would be ideal, since he would be able to take two or more new therapies at once. So he has been traveling around the country, meeting with pharmaceutical representatives and urging them to develop research models that would allow such combinations, even if that means incorporating one or more drugs from other companies.

"I have my own interest as a patient," Vergel says of the passion behind his activism, but he adds, "I have met people everywhere I go who want this really badly and are desperate."

He has the FDA on his side. The agency has supported such research models for several years, but no one has risen to the challenge--yet.

One pharmaceutical company, Tibotec, is set to be the first to perform such research. It has a nonnucleoside (TMC-125) in phase IIb trials and a protease inhibitor (TMC-114) in phase III. Motivated both by hopes of helping desperate patients and of finding a marketable combination therapy, Tibotec is designing a phase III trial that will administer both drugs to patients.

Other companies are generally receptive to the idea of studying combinations of experimental drugs, but they must worry about the details of designing successful trials that will both protect the safety of patients and get the drug to market as quickly as possible.

Martin Delaney, founding director of Project Inform, says, "In many cases the companies are reluctant" to do this kind of research, "because they fear that they will get blamed for the other [company's drug's] toxicity."

The Risks Involved

Patient safety is a key issue that gives drug companies pause. Researchers are wary

of potential drug interactions when combining two drugs they do not yet fully understand. These interactions are especially risky in salvage-therapy patients, whose often damaged bodies are already highly sensitive.

Timing is another problem. To avoid slowing down respective approval processes, the drugs need to be in the same stage of development. Although there are currently nine drugs belonging to four classes in phase II trials, they are each moving along at their own pace.

Pharmaceutical companies also worry that increasing the complexity of studies would slow down research. Scientists strive to reduce the number of variables when studying how drugs work. So it may be counterproductive to research two new agents at once, especially when corresponding study subjects are likely to have a range of medical complications and medications beyond the purview of the study.

“A program like that may be compassionate for the short term, in terms of helping people right now who need it,” says Michael J. Abrams, CEO of drugmaker AnorMed Inc. “But it potentially is not compassionate in the long term. If it slows down or even causes a problem that prevents the drug from being approved, then it is going to deny the access to a much larger group that is going to need it eventually.”

AnorMed is developing antiretrovirals called coreceptor antagonists, which block HIV's ability to latch onto coreceptors R5 and X4 on the CD4-cell molecule. Each drug blocks only one coreceptor, so research suggests that it would be best to take the drugs in combination. Consequently, Abrams says he is interested in conducting combination research.

Companies researching protease inhibitors or nucleoside and nonnucleoside analogs are less interested in teasing apart how the drugs function in combination since there is already a wealth of information about how these drugs work.

Beyond the Bottom Line

Still, Richard Levy, MD, senior vice president of drug development at Incyte, whose Reverset nuke is in phase II trials, says people should not view pharmaceutical companies as Big Brother organizations worried only about profits. “I do not think that companies do not want to help. The question is,” he says, “how can they help best?” He believes that whenever possible patients participating in clinical trials should be given the most potent possible multidrug regimen.

Vergel, with support from other less-vocal quarters, argues that studies can be designed to include a subset of salvage patients. The data gathered would not necessarily be pivotal for the FDA's approval but could bring greater insight to the subtleties of a drug's usage, information pharmaceutical companies could use in their marketing.

“It can be only a win-win for the company and patients,” says Rob Camp, the antiretroviral project director with Treatment Action Group, an AIDS activist coalition. “Since most drugs today need to show some added value--usually in the resistance, adherence, price, or side effects areas--putting two new agents together makes nothing but sense as long as some basic interactions and safety guidelines have been looked at.”

Meanwhile, Vergel has no plans to halt his efforts, even if not everyone is on board. He believes he is making headway. “I am hopeful,” he says. “I just thought I was

going to have more people working with me” to achieve the goal.

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