Pipeline Problems

In the past month, two companies shelved their once-promising experimental HIV drugs, citing the challenging nature of bringing a profitable product to market. Has the overwhelming success of modern-day HIV drugs jeopardized the future of new HIV treatment options?

June 22, 2010 By David Evans

Since Matt Sharp first learned that he was HIV positive in 1988, life has been about trying to stay one step ahead of the virus. Like many, he started each new HIV drug only to have it eventually fail, followed by a wait for the next one to be available through a clinical trial, expanded access program or U.S. Food and Drug Administration (FDA) approval. That's just the way it was—trying to outrun HIV and to hold on until science and the pharmaceutical industry developed the next best thing. There were no other options.

The last three years, however, have been kinder to Sharp. In the space of about a year and a half, from June 2006 through January 2008, four new antiretroviral (ARV) treatments were approved, all of them with the potential to work against even the most drug-resistant HIV. After Sharp started a regimen with one of these new treatments, his virus became undetectable for the first time ever. His CD4 cells, which had been depressed for years, started to inch back up, and he continues to do well today.

Sharp is not alone in his Lazarus effect. Thousands of people with multidrug resistant virus, many of whom were once quite sick, have been able to push their viral loads to undetectable levels and restore their health with the newest antiretrovirals, often in combination with each other. But what happens if their HIV accumulates additional mutations and breaks through? Unfortunately, the number of promising agents waiting in the wings for people with drug resistant virus is dwindling.

Two companies, Avexa and Myriad Genetics, suspended development of their experimental ARV treatments over the past month. From press statements, it appears that both companies determined that their drugs—apricitabine (a nucleoside reverse transcriptase inhibitor) and bevirimat (a maturation inhibitor)—could not be brought profitably to market. While neither drug was perfect, or had a certain shot at FDA approval, some activists and researchers see their failure as evidence of a paradox—that today's highly effective drugs are hurting the development of tomorrow's promising agents.

"The very incentives that got industry involved to develop HIV drugs are now working against us," says Jay Lalezari, MD, the director of clinical research at Quest Clinical Research in San Francisco,

who specializes in the study of drugs for people with multiple drug resistance. “But, you know, money is a driver, and you don’t expect these companies to do it for nothing,” he laments.

“It’s getting harder and harder to hit a homerun with a new HIV drug,” says Bob Huff, a longtime HIV treatment activist from San Diego. “The current drugs are very good, and most doctors and patients are fairly satisfied…. The incentive for companies to invest in developing new HIV drugs is not strong right now.”

“It’s disconcerting,” Sharp agrees. “In terms of practical issues around drug development, we do need to put our heads together and strategize about fixing the things that are broken.”

Sharp is working with Huff and Nelson Vergel, an activist from Houston, to help identify novel ways for people who’ve run out of treatment options to get their hands on multiple experimental agents at one time. The three are also looking at creative ways for companies to get drugs approved that might only benefit treatment-experienced people, a market that is increasingly small and potentially less profitable than ever before.

Sharp, Huff and Vergel express concern about options for people who have already become resistant to current meds. With apricitabine and bevirimat now out of the picture, it only leaves a couple of drugs in an advanced state of development for people with multi-drug-resistant virus. Given the uncertain nature of drug development, however, those drugs could also tank or be delayed, and it could be quite a while before something new is approved.

Sharp is not hopeless, however, and cautions that, “There’s no reason to panic. I definitely don’t think this is the end of the world.”

Lalezari agrees that things are not so bleak, at least not yet. He points out that a number of his patients are still doing well clinically, despite going for many years with very low CD4 counts and detectable virus. He stresses that it is possible to pick a regimen and stick with it for a long time, even if your viral load remains detectable. He encourages people to sit tight on such a regimen and to “try to keep this détente with the virus, and we’ll see if gene therapies or other immune therapies can be brought to bear in the future.”

Vergel is another veteran of the treatment wars and knows what it’s like to face uncertainty. He says that if his current drug regimen fails, he’s not sure what he’ll turn to. He’s not despairing, however, because he feels that he and other activists are making progress with the FDA in figuring out how to make new treatment options available, even when the traditional avenues of approval are a challenge.

In the meantime, he distills his own positive outlook for the many hundreds of people with HIV he interacts with each year through his Internet and public speaking activities. As he sums it up: “You have to give them hope.”

A Good News, Bad News Story

“The bigger picture with HIV therapeutics is a good news, bad news story,” says Paul Sax, MD, clinical director of the HIV program at Brigham and Women’s Hospital in Boston. “The good news is that HIV treatment success is so high now. The bad news,” he adds, is that “the motivation to develop new drugs, especially drugs to treat resistant virus, has ironically never been lower. There’s this small group of people who have no options even with those newer drugs, and for them, the situation is very discouraging.”

Treatment success has made developing a new drug targeted toward drug-resistant virus problematic in several ways. First, we can no longer simply pit a new drug against a placebo, with no other active drugs to back it up. A number of studies have found that when people take only one active drug at a time, they quickly develop resistance to that drug. For this reason, federal treatment guidelines recommend waiting to start a new treatment, if possible, until two or three active drugs can be combined into a new regimen.

While combining two or three active agents is good for study participants, it’s a headache for trial designers. This is because the difference between an experimental drug and a placebo are much smaller and more difficult to measure if their impact is masked by the potency of other powerful drugs.

Sax points to the failure of the drug vicriviroc to demonstrate efficacy over a placebo in treatment experienced participants as a perfect example of this dynamic at work. “The vicriviroc study had the old study design,” Sax explains, “which was [a background regimen chosen by drug resistance tests] plus or minus the [vicriviroc], and they didn’t see any benefit, unless you [only looked at people taking] one other active drug.”

To detect such slight differences you have to either recruit only people with one or fewer active treatments available or design trials with twice as many people. The first option goes against the grain of treatment guidelines, and Sax thinks that the challenging and slow recruitment for a number of recent studies targeting treatment-experienced patients makes it quite unattractive to the companies. Even more unattractive, however, is the second option which almost doubles the cost of the trial.

Vergel has been working with Lalezari and Steve Deeks, MD, professor of medicine at the University of California at San Francisco, to estimate the number of people in the United States with resistance to all of the existing drugs—the kind of people that Sax says would be a challenge to recruit.

Vergel estimates that there are at least 1,500 such individuals, but that number is not growing rapidly. While this may be good news from a public health perspective, it is bad news for people with highly drug-resistant HIV who are depending on the pharmaceutical industry to develop new treatment options. Corporate board members and shareholders demand the highest profit possible with the least expense. With clinical trials potentially getting more expensive and harder to recruit, and the market size staying small, it’s getting very difficult to meet those demands.

“We’re up against the fact that drug development is about making a profit,” Sharp says, “and unfortunately that’s what we have to deal with.”

What the Future Holds

Sharp, who works frequently with Vergel on treatment advocacy projects, says that there *are* promising treatments further back in the pipeline, and that still other more innovative types of treatment are finally reaching the point where they can move in to clinical trials designed to prove efficacy and safety. What’s more, Sharp remains devoted to advocacy related to eradication: the elimination of HIV from the body.

Lynda Dee, a veteran treatment activist and the president of AIDS Action Baltimore, confirms Sharp’s experience: “Activists have met with companies over the last year, and some have said that they have internal programs looking at new drugs and eradication,” she says. “I’m hopeful that this discontinuation of the development of [apricitabine and bevirimat] doesn’t mean that all of the industry has turned tail and left the HIV field.”

Lalezari thinks that an entry inhibitor from TaiMed Biologics, an integrase inhibitor from ViiV Healthcare, and an attachment inhibitor from Bristol-Myers Squibb might have a shot further down the road. He’s less sanguine than Sharp or Dee about the prospects for antiretroviral drug development in general, given the challenges involved. “I think we could enter a period where there’s an abrupt end to HIV drug development,” he asserts. “That’s not to say that there aren’t new modalities of interest…but in terms of new direct-acting antivirals, it’s going to be very difficult,” he predicts.

Protecting Your Options

Are we on the verge of returning to the days when the best that a long-term survivor could do was guard against opportunistic infections and pray to survive long enough to benefit from the next drugs to come out of the pipeline?

Perhaps not, according to Lalezari. “The thing about the treatment-experienced population, which is astonishing, is that I have a whole bunch of people that I have been following for a number of years now, who are doing just fine. They have detectable virus, and their [CD4] cells are less than 20, but their health is just great, which is not explained in my understanding of the universe.”

Sax stresses that going off treatment would be a lot worse than staying on a failing regimen. “You know, all attempts of treatment interruptions of people with drug resistant virus met with bad outcomes,” he says, “So one thing for sure, is that people should stay on something. The question of what is more difficult. It’s never been well studied.”

In the end, what’s at stake is whether new drug development can stay ahead of HIV-positive people’s needs for new treatment options. Vergel points out that those who’ve yet to develop drug resistance can preserve their future options by finding a tolerable effective treatment and adhering to it religiously. In this regard, the possibility of a dry spell in new drug approvals could encourage people not to take for granted that new options will inevitably keep coming down the

pike. “Fear,” Vergel says, “can be a good motivator” by way of emphasizing the importance of treatment adherence.

For people who’ve run out of new options, there is still reason for hope. It is possible to stay clinically healthy despite a failing ARV regimen, as Sax and Lalezari point out, and there are ways to minimize the risk of developing resistance to the experimental agents that might come later. Vergel tries to remind people of that and tells them “to not come from a place of despair.”

Sax thinks it will be helpful for researchers and health care providers to pool together their knowledge and resources to figure out the best care models for people who’ve run out of treatment options, arguing that since few providers have large numbers of such individuals it is difficult to become an “expert” in treating them. He thinks that activists and groups such as the Forum for Collaborative HIV Research in Washington, DC, can aid in that process.

Despite the challenges involved in developing the next generation of HIV therapies, Sax believes in remaining optimistic, especially with his patients who’ve run out of options. He tells them: “Press on. Drug development has helped us in the past. We hope it does again in the future.”

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