What Would You Do to Cure HIV?

Research geared toward curing HIV is experiencing a resurgence. With new enthusiasm and increased funding, researchers are beginning to plot new interventions to bombard the virus in unusual ways. The first round of studies is bound to carry serious health risks, however, and many will fail. The big unanswered questions are whether HIV-positive people will volunteer for these trials—and if so, whether the FDA and other regulators will let them.

May 25, 2011 By David Evans

In February 2007, a high-stakes experiment involving a single person with HIV and leukemia got under way in Berlin. To cure his cancer, the "guinea pig" in the study, an American named Timothy Brown (but known in the press as "the Berlin Patient") had to undergo a stem cell transplant, wiping out his immune system and replacing it with the stem cells from a donor. What made this a groundbreaking case is that Brown agreed to receive HIV-resistant stem cells. The goal was ambitious: to cure Brown's cancer and to help him grow a new immune system impervious to HIV infection, all the while subjecting him to unpleasant side effects and a risk of serious treatment-related illness or death.

It's one thing to let a person like Brown—who would have died without a stem cell transplant—take such a risk, and quite another to let an HIV-positive person with a near-normal lifespan thanks to antiretroviral (ARV) therapy do the same. Yet allowing people who are otherwise healthy to enter potentially risky studies is exactly what may be needed to move cure research forward. Whether research regulators will allow such studies to proceed is another story.

Philip Dickey, a 44-year-old HIV-positive man from Miami, says he'd be willing to do so if the right experiment came along, and he's the kind of guy whom many medical ethics committees would fight to keep out of a risky study. He's only been HIV-positive since September 2008, and though his CD4 cells dipped below 500 just one time, he's been taking ARVs for several years with few negative consequences. He feels, however, that it's almost an obligation for some people to put their well-being on the line so that other people may one day live free of HIV.

"The benefits I have in my life today are because people took risks," Dickey says. "Sometimes you do things because you know that it's going to be a part of helping other people."

Not everyone will be as willing as Dickey to put the greater needs of society above their own, but prominent San Francisco AIDS researcher Jacob Lalezari, MD, says that there are plenty who will—and who already do.

“I can’t tell you how many people I’ve enrolled in studies over the years, who enrolled knowing full well that they were taking some risks, knowing full well that they would derive no benefit, and knowing full well that they might be dead before any conclusion was drawn from the study,” he remarks.

The big question then, as AIDS cure research takes its biggest steps forward in decades, might not be whether healthier people with HIV will put their lives on the line, but whether the groups that regulate AIDS research will let them.

Adventures in Cure Research

Until recently, researchers who chose to pursue cure-oriented research were considered naive and misguided by more conservative scientists. That all changed, however, with the case of Timothy Brown. Brown has been off all ARV therapy since he received his first round of donor stem cells, which carried a unique mutation making them naturally resistant to HIV infection. After undergoing two rounds of stem cell transplants (both from the same donor), he has his leukemia finally in remission, and at this point, experts can’t find HIV in his body no matter how hard they look.

Cure research has experienced a resurgence now that we know it is possible to take a person chronically infected with HIV and perform an intervention that leaves him or her able to either eliminate or at least control HIV without the need for lifelong ARV therapy.

Simply because there’s growing interest in trying to eradicate HIV, however, doesn’t necessarily mean that such experiments will proceed quickly and easily. Just ask David Margolis, MD, from the University of North Carolina at Chapel Hill. Margolis—who was at the forefront of believers in the possibility of HIV eradication—has spent much of the last couple of years getting a cure-related study off the ground.

Margolis wants to test the potential of a cancer drug called Zolinza (vorinostat, SAHA) to reduce the reservoir of infected, but sleeping, cells that are typically out of reach of ARV drugs. When he initially proposed doing the Zolinza study, he first had to persuade the drug’s maker, Merck, to allow him to study it for HIV, and not cancer, for which it has been approved. Pharmaceutical companies are notoriously shy of ceding control of their products in this way, but Merck agreed.

With Merck on board, Margolis also had to convince funders that the study had enough merit to deserve the money. His highest hurdle, however, and one he originally failed to overcome was convincing the FDA that the drug was safe enough to study in people with HIV who were otherwise fairly healthy.

Margolis says he fully supports the ethical requirement that researchers must do everything possible to minimize risks to those who choose to participate in trials. What’s more, he is sympathetic to the challenges faced by the FDA, which is dually charged with protecting the public while also hastening the speed of drug development.

“Their first job is to protect patients, and their other job is to not end up on the front page of *The*

New York Times [in a scandal]," he comments.

In Margolis's case, the FDA had applied the brakes on his study because the results of laboratory tests indicated that Zolinza, while a treatment for some types of cancer, had the potential to lead to other types of cancer, at least in cell cultures. These results, along with unknown safety variables, delayed movement on Margolis's study for over a year. Though Margolis eventually prevailed, the FDA's hand-wringing frustrated Margolis, who along with Zolinza's inventor, felt the cancer risks were being overstated.

Margolis worries about how regulators are viewing the risks they'll allow participants to take in such cure-oriented studies. "Are we drawing the line in the right place: Is it too conservative, or too risky?" he asks.

Jonathan Jay, JD, a bioethicist at the Henry M. Jackson Foundation in Rockville, Maryland, who consults on ethical issues as a contractor with the Division of AIDS at NIH, concedes that ethics committees and regulators—such as the FDA, institutional review boards (IRBs) and data and safety monitoring boards (DSMBs)—do run the risk of slowing down important research.

"I agree that the particular procedures involved in ethics review and in regulatory approval may not be as efficiently designed to reach those goals as they could be," he says, noting that the goal is to protect study participants without unduly bogging down or roadblocking research that could ultimately save lives. "It's definitely a valid complaint, but it would be a big mistake to swing too far in the opposite direction."

To do so, suggests Jay, would be unethical, and the ethics have never been more complicated since the first U.S. AIDS cases were described in 1981.

It is challenging enough to define the appropriate balance between risk and benefits when the people being studied are quite ill. When the study participants are doing well, however, the ethical considerations become quite murky.

Untangling the Ethical Web

To untangle the ethics of a study, researchers and regulators are always faced with a long list of questions. They must look at whether a study is well designed and whether the treatment or procedure being evaluated is likely to improve the standard of care or lead to significant advances in the field. Researchers must also document that they've done everything possible to minimize risks to the participants. Researchers also need to prove they will do everything they can to ensure that potential volunteers fully understand their risks before consenting to participate. This last piece, informed consent, is the real linchpin in deciding the ethics of a trial.

Another ethical consideration is a person's motivation for joining a study. Only recently, for example, have ethicists begun to grow comfortable with people taking risks purely for altruistic reasons. While no longer the case, it wasn't so long ago that people who wished to donate a kidney to a stranger were rarely allowed to do so. Ethicists worried that altruism itself couldn't

adequately explain why a person would take such a big risk and experience such pain and discomfort for a person they didn't even know.

Confusing matters is the fact that ethical questions such as these are based on unknown variables. The reason we conduct clinical trials in the first place is to determine whether a new treatment or procedure works or is safe. And it is Phase I studies that potentially carry the most weighty ethical concerns, given that very little is known at this stage in the research process about a treatment's effectiveness or safety in human subjects.

Yet that's where we are with cure-related studies, solidly stuck in the early Phase I experimental process. That's why researchers and regulators are having these difficult discussions about when or whether to allow healthier people to enter these studies, where the risks are potentially high and the possible benefits are anything but guaranteed.

For cure research, Jay says, "There are lots of reasons to be concerned that even someone who says all the right things about wanting to help others and understanding that there's no benefit to him or herself, there might be reason to wonder if that's a subject who understandably holds out hope—maybe a sort of irrational hope—that the intervention might in fact help them a lot."

Jay's concern is backed up by Margolis, who says that it is especially true when people think they are in a study where curing HIV is the ultimate goal. "The cure thing is a very slippery slope," Margolis says. Even when you tell potential participants there's no chance they'll be cured as a result of participating in a study, and even when the participants insist they understand this, Margolis says, "when they find out the results later they are disappointed that they weren't cured."

"Not all of them," he adds, "but some of them."

"Researchers and ethicists tend to prefer using sicker patients for high risk research, though this raises questions about informed consent," Jay says, explaining that whether to use sicker people or better-empowered people is a deep ethical question that HIV cure stakeholders need to address—sicker people have less to lose health-wise, but healthier, better-empowered people might tend to make more well-informed and freer choices.

Jeff Gamel, who found out he had HIV in 1985, would likely fall into the camp of people who are sicker. The 49-year-old Alabaman, who currently lives in Birmingham and has been plagued with health problems for years, is very well informed. He says he'd be in a good place to judge risks but has become more leery than he once was about participating in a study.

"Right now, I'm at a point in my life that I wouldn't take as many risks as I would have a few years ago," Gamel reasons. "I've had so much damage done to my body already, from years of medication."

Still, Gamel says if the study were the right one and he felt the risks weren't too high, he'd sign up.

Risk Versus Reward

The potential risks from cure-oriented research should not be understated. In Brown's case, for example, high doses of multiple chemotherapeutic drugs needed to be administered to obliterate his immune system and then allow the donated HIV-resistant stem cells to take root and proliferate. In effect, Brown was at significant risk for life-threatening infections, serious liver damage, debilitating damage to the mucosal lining of the mouth and throat, and rejection of the donated cells—to name a few possible complications.

Strategies that don't require chemotherapy ablation also carry potential risks. Lalezari and his colleagues are conducting a study in patients with advanced HIV infection in which some of their CD4 cells are painlessly removed, genetically modified and reinfused. A collaborating team of researchers is using the same technology to alter the stem cells of people who require a stem cell transplant to treat their cancer. The researchers hope to artificially make a person's CD4 cells as resistant to infection as Brown's have become.

Things have proceeded well enough so far that the next of these studies will possibly be open to people living with HIV but who've never taken ARV drugs before. While none of the studies conducted thus far has even hinted that the gene-modified cells could be dangerous, Margolis says there's still room for concern.

Margolis says it would be puzzling if people didn't carry at least some concern about gene therapies, where strings of DNA are sliced and diced. "I will bet you that [there will be] a couple of snips at various places in the genome [where there shouldn't be cuts]," explains Margolis. "It doesn't have to happen often, but if it happens at the wrong place at the wrong time, that's [problematic]."

Another route Margolis and others are pursuing is to eventually wage a full-scale assault on HIV—purging it from inside the cells where it currently hides out and then beating it down with potent ARV therapy. To do this, however, it might ultimately be necessary to wake up latently infected cells to such a degree that it could have consequences—very serious consequences—including inflammatory damage in the brain and other organs.

Either approach, however, will eventually have to be studied in people who are doing well on ARVs, and these studies will often require them to stop taking HIV therapy. Though the most forward thinking researchers are beginning to describe when and how it might be ethical to ask someone to take an HIV treatment interruption, many researchers—and, more importantly, regulators—remember the disastrous results of some previous treatment interruption studies.

I'd Like to Be a Prophet

Activists and researchers have begun engaging the FDA and asking for its views on the risks for cure-oriented studies. What's more, at a meeting held recently in Baltimore to discuss these issues, a group of researchers, activists and ethicists charted out the key ethical questions that will need to be answered—and the regulatory processes that will need to be improved so that cure research can move forward as quickly, but safely, as possible.

Stephen LeBlanc, an activist with the AIDS Policy Project, was at the Baltimore meeting, and he's concerned about the potential roadblocks. He and other activists have been working diligently for the past couple of years to move cure-related research forward as quickly as possible.

"The community needs to stay involved as the research gets bigger," LeBlanc urges, "because [regulators] and funders—who are going to have to give approval for this research to move forward—haven't been part of these discussions yet, and they're going to need to hear from people with HIV that this research is important and critical and that people are going to want to participate in it."

According to Lalezari and Margolis, recruiting people with HIV into these studies is not likely to be a huge challenge, but it will take diligence to make sure the right people are chosen for studies, and that researchers are vigilant in protecting them from risk by ensuring that they know those risks.

Matt Williams falls somewhere between Dickey and Gamel in terms of his willingness to participate in a study. The 47-year-old from Brighton, England, learned of his HIV status in 2003. Though Williams has participated in at least one study over the years, he says it was very low risk.

He says he is more of a "Phase II guy" than someone who'd stick his neck out on a really early study, but he would consider entering a Phase I study if some of the smartest activists he knows felt the treatment had promise and the risk wasn't too high. Like Dickey and Gamel, he too feels the desire to make a contribution to his HIV-positive peers.

When asked about the source of his altruism, he says, "I am reminded of the end of *Angels in America*, a quote, 'We are not prophets' or something like that. But it would be exciting and humbling to be a prophet in a small way, to have taken part in the trial that led to a cure."

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