

Illustrations by Matt Hansen

Hopeful act:

A rebel transplants organs from HIV-positive donors

By Sara Reardon

David thought he would spend the rest of his life in and out of hospitals. A 45-year-old auditor in South Africa, he had developed severe anemia seven years earlier due to kidney failure. His illness forced him to quit his job and travel to the hospital for dialysis three times per week. What he needed was a new kidney, he says, “but at that time, no one would transplant with my condition.” That condition was HIV infection, of which South Africa has more cases than any other country in the world. The prevailing sentiment held that a person like David would soon die of AIDS, and using an organ on him would be a waste.

David (whose name has been changed to protect his privacy) was one of the lucky ones, as he was among the 20% of South Africans who have private health insurance and therefore could at least receive dialysis. Until 2009, most people with both HIV and kidney disease were caught in a cruel paradox: the South African healthcare system would only cover dialysis as an interim measure until a patient could receive a kidney transplant. Because they were automatically ineligible for

transplants, HIV-positive patients were simply sent away to die.

In 2008, after several years of treatment, David got a call from a surgeon at his local hospital. Would David be willing, his doctor asked, to take part in a radical and potentially risky treatment that could grant him a new kidney? “It was the opportunity of a lifetime,” he says. “I was very eager.”

David traveled to Groote Schuur Hospital in Cape Town, one of South Africa’s largest hospitals and the site where the world’s first heart transplant took place in 1967. There, he and a group of other HIV-positive individuals in need of kidneys met with a young transplant surgeon named Elmi Muller from the University of Cape Town, who described her plan. Muller had long been frustrated by what she saw as a colossal waste of organs from HIV-positive donors. Although collecting them was not specifically illegal in South Africa as it is in many countries, fears of contracting the disease from an organ transplant and a general stigma against HIV-positive people made the practice taboo. At the same time that Muller

was turning down HIV-positive patients for dialysis, she was throwing away organs from young, otherwise healthy donors with HIV. And HIV-positive patients are particularly in need of new organs: the virus often infects renal cells and produces toxic proteins, eventually breaking the kidney down and causing kidney disease in up to 30% of people living with HIV¹.

Matching these HIV-infected donors with HIV-infected recipients seemed as though it could be a powerful combination, albeit risky and unprecedented. “I felt that in my personal situation, where these patients didn’t have much option, there was not so much to lose,” Muller says.

David and the others gathered in the hospital that day in 2008 eventually became the first of 29 HIV-positive people to receive kidneys from deceased donors also infected with the virus to date, and there are 55 more recipients on the waiting list. Muller gives the patients immunosuppressant drugs, which thus far have not proven to hinder their HIV treatment. So far, only three have rejected the organ. Muller

is the first person in the world known to have purposely transplanted an HIV-infected organ.

Muller's patients and the data she is collecting from them provide evidence valuable far beyond her home turf. In the US, as in South Africa, waiting lists for organs are lengthy, with more than 100,000 people in the US waiting for kidneys alone. Transplant surgeons are enticed by the prospect of adding hundreds of organs per year to the pool. Last November, the US Department of Health and Human Services (HHS) overturned a 1988 law that prohibited collecting HIV-infected organs and will now permit clinical trials of 'positive-to-positive' transplants. There are plenty of questions about such transplants, such as the risk of spreading a drug-resistant strain of HIV, the safest way to suppress the immune response of an already-immunosuppressed person, and whether reservoirs of virus that remain in the donated kidney will eventually destroy the organ. The answers, researchers say, may lead to improved immunosuppression tactics for transplants and even shed light on the nature of HIV itself.

Breaking the ban

An estimated 12,000 people in the US contracted HIV from transfusions between 1978 and 1984², leaving the public terrified. In reaction, the US passed a blanket ban on organ collection from HIV-positive donors in 1988.

But by the late 1990s, screening procedures for HIV had become accurate enough to eliminate this worry. At the same time, the advent of effective antiretroviral drugs meant that HIV-infected people could expect to live to a relatively old age—and also develop all the disorders that come with growing old. Instead of suffering from sarcomas and other AIDS-associated diseases, people began to see their HIV-positive friends dying from liver and kidney diseases, says Peter Stock, a transplant surgeon at the University of California, San Francisco (UCSF). "The transplant community was slower in recognizing it had become a chronic disease," he says. The situation was exacerbated by the fact that no insurance agencies would cover organ transplants into HIV-infected individuals.

But the number of people waiting for organ donations was growing each year: by 2000, some 74,000 people in the US were waiting for donors, according to the Organ Procurement and Transplantation Network (OPTN) in Washington, DC, which tracks transplantations and manages policies for the HHS. With such a long waiting list, the reasoning went, transplanting a healthy organ into someone with a fatal viral infection would be denying that organ to someone who could live a long

life. Additionally, doctors worried that since these the immune systems of HIV-infected individuals were already compromised, further immunosuppression with drugs could be dangerous.

Stock wanted to at least explore the possibility that such transplants would succeed. In 1999, with the help of AIDS lobby groups and lesbian, gay, bisexual and transgender (LGBT) activists, he and his colleagues successfully lobbied the state of California to grant Stock's team \$3 million for a pilot study of transplanting uninfected livers and kidneys into HIV-positive recipients. The 37 patients from this study and a subsequent one appeared to do well overall and were only slightly more likely to reject organs than HIV-negative recipients were³. But the grassroots effort provided enough preliminary evidence for Stock to receive a \$25 million grant from the US National Institute of Allergy and Infectious Diseases (NIAID) in 2003 to transplant livers and kidneys into 275 HIV-positive patients.

Shortly after the NIAID trial began, Stock received a letter from Cape Town. Elmi Muller had been following his work with interest; the promising results from UCSF provided fodder for an experiment she had wanted to try for some time—namely, using organs from HIV-positive donors. The two met in 2007 when Stock traveled to South Africa to present at a conference, and together they designed a protocol for transplanting kidneys into HIV-positive patients from deceased infected donors.

In 2008, Muller transplanted David and another patient with the two kidneys from a single HIV-positive donor. But almost immediately, her practice attracted attention from the South African Department of Health, which balked at paying for this unconventional treatment.

Additionally, Muller says, there was concern about the ethics of the study, which Muller had not set up as a regimented clinical trial in order to treat patients more quickly.

UCT initiated a disciplinary proceeding against Muller in October 2008. But within a few weeks, she received a call about a second HIV-positive donor whose kidneys matched two of her patients, a young man and a mother who had been turned down for dialysis. They were essentially on their deathbeds, and Muller felt the opportunity that the new donor provided was too good to pass up. "I gave them

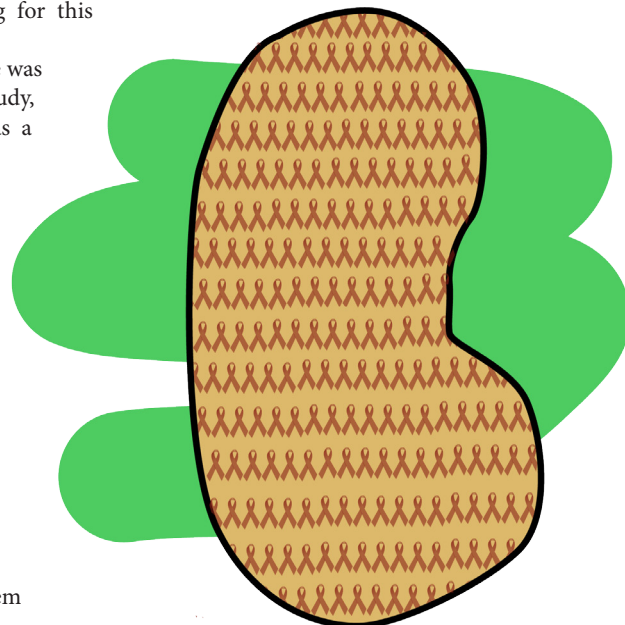
the kidneys—there was not another option," she says. Both patients survived, but Muller's defiance left her one step away from being fired from UCT. "I created problems for myself by going ahead," she admits. Her study was shut down for nearly a year while the government investigated both UCT and Muller.

Eventually, after much paperwork, the health department backed down and allowed the transplants to continue under the auspices of a clinical trial. In 2010, Muller's team published her first round of results showing that these first four patients thrived two years after the surgery. (As a secondary result in 2009, because HIV-positive people could now receive transplants, the South African Department of Health changed its policies to allow dialysis for HIV-positive patients.)

Legal changes

By 2010, US insurance companies had realized that HIV had morphed from a fatal infection to a manageable condition, and many had begun covering transplants, which had been otherwise unaffordable for most people: a kidney, for instance, costs upwards of \$250,000. According to OPTN, some 200 HIV-positive people in the US now receive transplants each year from HIV-negative donors.

Still, HIV-infected individuals who are otherwise eligible donors could contribute between 500 and 600 organs to the pool, according to a study by Dorry Segev, an epidemiologist and transplant surgeon at Johns Hopkins Medical Institute in Baltimore⁵. Encouraged by the figures, Segev decided to push for a change in US law. In 2012, he and his then graduate student Brian Boyarsky, got together with advocacy groups such as the



Infectious Diseases Society of America (IDSA) and LGBT activists and drafted a bill called the HIV Organ Policy Equity (HOPE) Act. For the first time, organ banks would be allowed to collect organs from deceased HIV-positive donors, and surgeons would be allowed to transplant them in a research setting.

Boyarsky, now a medical student at St. George University in Grenada, says the team had little trouble convincing legislators of the bill's value. "It's actually more urgent for them to get organs, so we could make this new source available to get them transplanted much faster."

NIAID director Anthony Fauci emphasizes that because HIV is no longer a death sentence when controlled with medications, there is renewed hope. "We wouldn't be thinking about transplanting people if they were in such dire straits," he says. There is precedent for this conclusion: organs infected with hepatitis C virus (HCV) are frequently transplanted into recipients with HCV, which does not appear to affect the recipients' survival⁶.

"It's one of those things that's a win-win because by increasing the total supply, it increases the chance for everyone," says Daniel Kaul, a transplant surgeon at the University of Michigan Medical Center and co-chair of OPTN's HIV working group. The bill sailed through both houses of Congress, and President Obama signed it into law on 21 November 2013. Even so, it will be years before patients begin to benefit from the new legislation: according to the new statute, HHS has until 2015 to develop a set of policy guidelines for things such as the appropriate controls to prevent HIV-positive organs from entering the general population, the criteria for determining appropriate recipients and determining how to manage a waiting list. Once that is completed, researchers will be permitted to begin carefully controlled clinical trials before the HHS secretary will issue final guidelines and legalization as early as 2017.

The HOPE Act tasks NIAID with developing the clinical guidelines: an unusual activity for the institute, says Nancy Bridges, chief of NIAID's transplantation branch, but a necessary one. There are plenty of questions that will need to be answered to ensure that the process is safe before legalizing it completely, she says. For instance, what happens if the donor had a different strain of HIV than the recipient, who then gets a second dose of the virus? Such 'superinfections' are known to occur when HIV-positive people are re-infected through a new partner, Muller says. The most worrying theoretical risk, however, is transplanting a drug-resistant strain into an individual, which could render their current drug treatment ineffective.

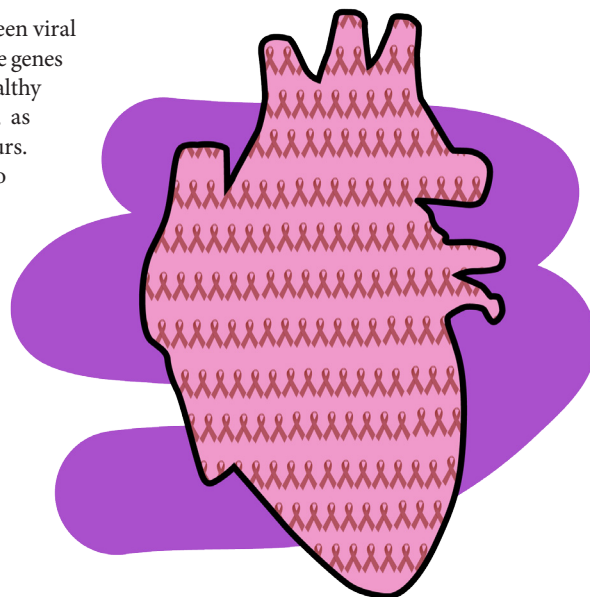
In practice, it will be difficult to screen viral strains for antiretroviral drug resistance genes quickly enough after an otherwise healthy HIV-positive donor dies, says Kaul, as organs are only useful for a few hours. Health workers will mostly have to rely on information from a donor's friends and family and records of what drugs the donor was taking. Other concerns include the possibility of transporting an opportunistic infection or an undetectable cancer along with the organ. "This is going to be research at first, and research means there might be increased risk to the recipient," Kaul says. "But many people die on the waiting list, and there's enormous benefit to getting [an organ] earlier than later."

New links

Stock's research on negative-to-positive transplants is already uncovering surprising links between the immune system's response to HIV and to transplanted organs. Stock is particularly interested in drugs that block the CCR5 receptor on the surface of T cells, which HIV uses as a gateway into the cells. CCR5 is also crucial in mobilizing the immune system to attack an organ in graft-versus-host disease, and an immunosuppressant drug called sirolimus that blocks CCR5 is often used during kidney transplants. In May, Stock and his colleagues published a study of 91 HIV-positive people who received kidney transplants and found that those treated with sirolimus had lower levels of HIV DNA in their blood than patients who had not received the drug, suggesting that it was affecting the virus's ability to persist in the blood⁷. The group now plans to test the effectiveness of sirolimus as a potential new antiretroviral drug.

Stock's team is also currently planning a study to investigate whether an ARV called maraviroc, which also blocks CCR5, could reduce the immune response to organ transplants in 120 HIV-positive patients. "What's fascinating about this is the worlds of transplantation and HIV have always been dissociated," Stock says. "Now we have an antiviral that looks like an immunosuppressant and an immunosuppressant that looks like an antiviral." If it were not for the transplantation work in HIV-positive individuals, Stock says, they probably would not have looked for the second uses for these drugs.

Muller's work and the US legislation have inspired several countries to begin looking at the possibility for themselves. In August 2013, surgeons at Sourasky Medical Center in Tel Aviv,



Israel—a country very hard hit by organ shortages as a result of religious taboos—performed the first transplant from a living HIV-positive donor, transplanting a kidney from a wife into her HIV-positive husband. They had been thinking about the question for some time: a few months earlier, former Israeli chief rabbi Eliyahu Bakshi-Doron, who had supported the use of organs from HIV-positive individuals, controversially declared that such transplants into HIV-negative individuals might be acceptable under Jewish law (although still illegal under Israeli law).

As research progresses, many eyes will be on David and Muller's other transplant patients, whom she monitors annually. Most are thriving: David has returned to work and fathered three children since his transplant in 2008. "I don't have any fear for my future," he says. "Everything is balanced." Transplant surgeons are equally grateful to Muller. "If she didn't have success with this, there's no way this would have gotten passed in the US," Segev says. "She's opened the door and given us a glimpse, but it's for us to walk through."

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