

Magic Numbers

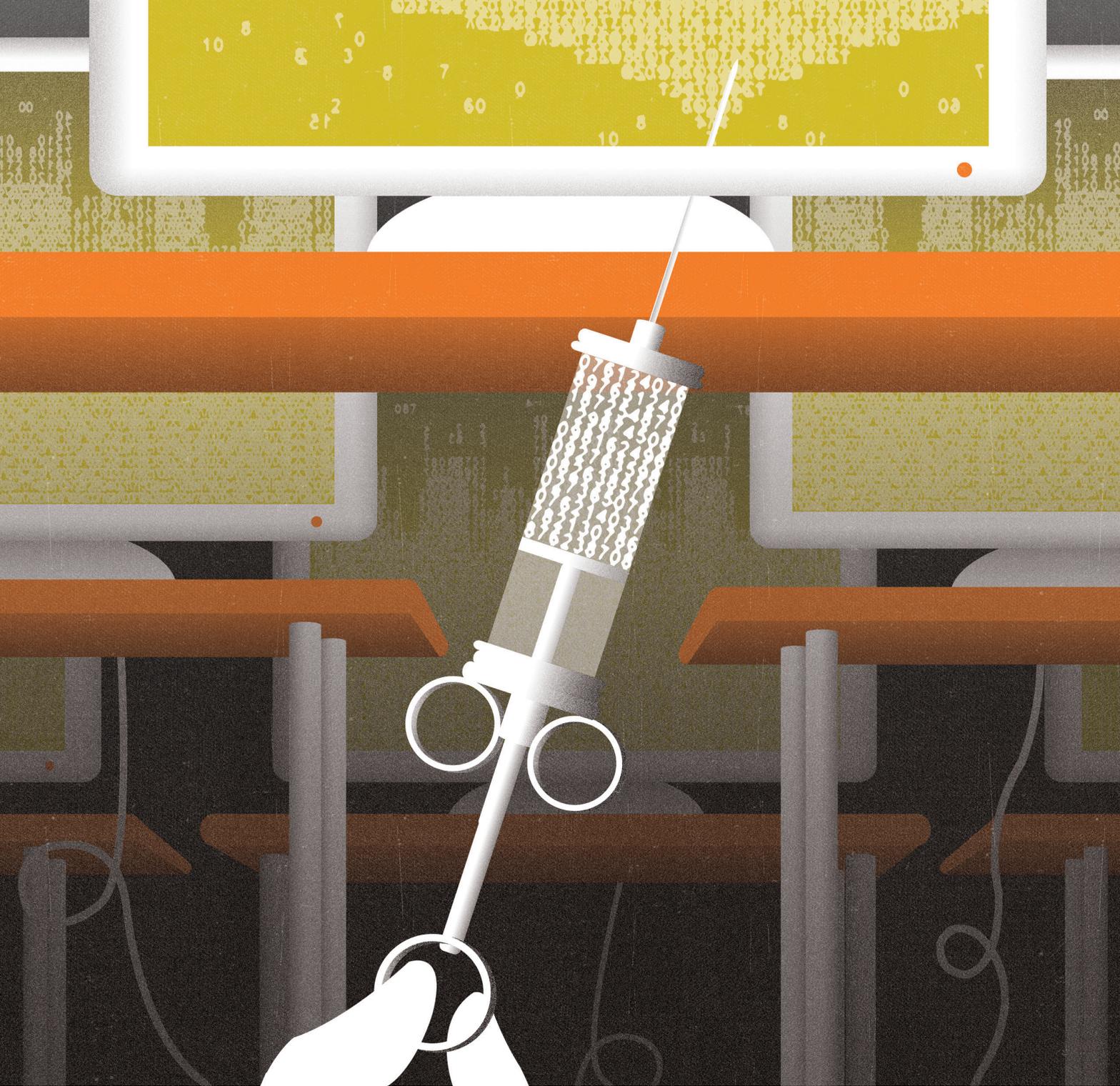
In South
Africa,
researchers
do the
math
behind the
world's
biggest war
on AIDS

*By
Art
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It was the third blow that spun Busisiwe Sithole's aching grief into dread. First, her six-month-old son died while Sithole was carrying him on her back. Then doctors told her that her infant had been infected with HIV. Then Sithole learned of her own test results.

"When I found out I was positive," she says, "it was not an easy thing. I was scared. When I would go to sleep at night, I would see myself dead in my coffin. I would see my older child crying. I was preparing my obituary. Then I talked to a counselor about treatment, and she said, 'You are not going to die.'"

Seven years later, a healthy-looking Sithole works as a data clerk in Johannesburg's Helen



Joseph Hospital, collecting information for the Health Economics and Epidemiology Research Office (HE²RO), a collaboration of Boston University public health experts and researchers from the University of the Witwatersrand. Just downstairs from her office is the Themba Lethu Clinic, where people come for testing, care, and treatment for HIV and the diseases that go with it. There is, it seems, no end to the patients. In South Africa, one in 10 people is infected with HIV, and HIV/AIDS plays a role in 31 percent of deaths. HIV is the country's most pressing health problem, and Themba Lethu is its largest HIV/AIDS clinic. With as many as 20,000 patients expected to

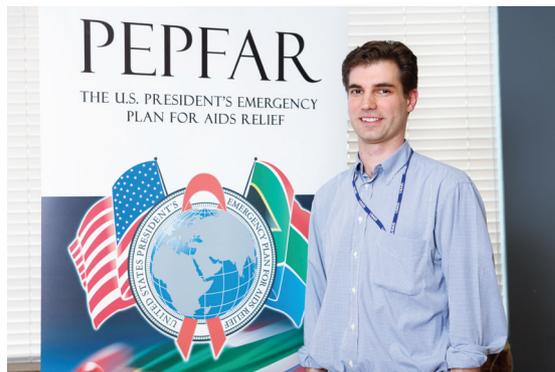
HIV infects roughly one out of every 10 people in South Africa.

"THE BU TEAM TACKLES the HIV problem from three angles: epidemiology, economics, and social science."



Matthew Fox, SPH assistant professor of epidemiology

"HEALTH ECONOMICS drives everything we do: health effectiveness, costing studies, and the new national health policy that South Africa is rolling out."



John Kuehnle, USAID South Africa health officer

Ian Sanne, infectious disease specialist and HE²RO codirector



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pass through the doors in 2012, it may be the biggest clinic of its kind in the world.

Sithole says many people she talks to are surprised to learn that she has been HIV-positive for so long, yet shows no signs of ill health. "Just last week a colleague came to me, because she had a family member who didn't want to take the antiretrovirals because there are stories about them. I told them it's better to get tested. It's better to know. Because you can live with it. You can control it.

Because I know, I also know that AIDS will not kill me. I know that I am going to see my grandchildren."

Ian Sanne, a South African infectious disease specialist and a codirector of HE²RO, witnesses the life-restoring powers of anti-retrovirals every day. "It's like a miracle," he says. "It's really remarkable what can be done with the drugs."

It's also remarkable, Sanne knows, what can be accomplished with data. For the past eight years, he and his colleagues at HE²RO,

including Sydney Rosen, a School of Public Health research associate professor of international health, and Matthew Fox (SPH'02,'07), an SPH assistant professor of epidemiology, both at BU's Center for Global Health & Development (CGHD) and HE²RO codirectors, have been collecting data, running it through algorithms, then delivering it to the National Department of Health. HE²RO's information, empirical evidence of the effectiveness and cost of new and better ways to combat HIV/AIDS, is in

some ways as instrumental among South African health policy makers as the new pharmaceuticals are for AIDS patients like Sithole. Decision makers in both the National Department of Health and the Department of Treasury have used the data to frame an HIV program that treats almost two million people.

“There was a significant debate between the Treasury and the Department of Health about how much money should be made available,” says Sanne. “HE²RO, using real data, was able to solve the debate and create a budget with significantly escalating funding over the next five to six years. We managed to persuade the politicians to increase the amount of funding over time to cover three and a half million people.”

Working in a warren of offices in Helen Joseph Hospital, HE²RO’s researchers have embarked on more than 20 studies, most of which focus on better treatment of HIV and tuberculosis. The group’s work, which has mainly been funded by the U.S. Agency for International Development (USAID), has been influential, not only on the design of national health care policy, but also on the international funders of AIDS treatment programs.

“Health economics really drives everything we do, from health effectiveness to costing studies to the new national health policy that the South African government is rolling out,” says John Kuehnle, a health officer at USAID South Africa and contract manager for HE²RO. “BU and HE²RO have been at the front of this movement to use health economics to drive policy. It’s something that USAID and PEPFAR are very thankful for.” PEPFAR (U.S. President’s Emergency Plan for AIDS Relief) is a government initiative to help save the lives of those with HIV/AIDS worldwide.

“There are a lot of groups that work on research on the HIV epidemic, and typically they

approach the problem from the perspective of epidemiology,” says Fox. “Some come from the perspective of economics, or from social science. We combine all of those. By bringing all of that together, we can look at not just what is the best approach for a patient or for a clinic, but we can model the implications for the country. We can find the best strategies and approaches to use on a national scale.”

Despite the vastness of HIV infection in South Africa, the country’s first meaningful treatment programs got off to a painfully late start. Thabo Mbeki, president from 1999 to 2008, publicly questioned the link between HIV and AIDS, and his denial of medical realities delayed the introduction of antiretroviral drugs. Harvard researchers have blamed Mbeki’s failure to act for the deaths of 35,000 babies, as well as for shortening the lives of 330,000 people.

The years of denial were years of frustration for HIV researchers, including Rosen, who began traveling to South Africa in 1999 to examine the implications of HIV/AIDS among workers in the private sector and who lived in Johannesburg from 2003 to 2007.

That project introduced her to Sanne, who in 2001 founded a not-for-profit called Right to Care. Since 2004, Right to Care has been funded primarily by PEPFAR, which has spent more than \$3.2 billion on programs to prevent and treat AIDS and tuberculosis in South Africa. Right to Care, which has long worked closely with HE²RO, currently provides technical support to 170 treatment sites in five of the nine South African provinces and cofunds treatment for HIV, TB, and cervical cancer for about 150,000 people.

As a base for their joint research on the economics and epidemiology of HIV treatment, Rosen and Sanne founded HE²RO at the University of the Witwatersrand in 2004.

COMING OUT OF HIV DENIALISM

Change in South Africa’s approach to HIV came under Mbeki’s successor, Jacob Zuma, when the National Department of Health considered, in late 2009, adopting treatment guidelines then newly recommended by the World Health Organization (WHO). Those included the sweeping measure of treating HIV-positive people when their CD4 count—a measure of the immune system’s strength—is 350 or below, instead of the 200 count that had been the treatment threshold previously.

“When we came out of HIV denialism, we had a very controlled HIV treatment program,” says Sanne. “We needed to scale it. We also needed a switch in treatment regimens, because we learned that the treatment we had been using was quite toxic and needed a lot of monitoring. We learned that there were better treatment regimens for drug resistance.”

In the new government’s National Department of Health, the deputy director general for strategic programs, Yogan Pillay, had learned the same things. And he was eager to learn more.

“Government officials like myself don’t always know the right questions to ask,” says Pillay, who oversees the department’s programs for HIV, AIDS, and TB. “Often, researchers will lead the process by suggesting which questions need to be answered. Is there, for example, resistance building up in patients? If there is, what drugs do they need to switch to? If clinicians are switching regimens, what is the practice implication, and what are the cost implications? Those things have implications from the individual patient to a systemic level with respect to the ordering of drugs.”

For answers, Pillay was introduced in 2009 to Johannesburg-based HE²RO team member Gesine Meyer-Rath, an SPH research

WEB EXTRA
Watch a video about BU’s work with South African health scientists to help devise new and better ways to combat AIDS at bu.edu/bostonia.

They strike a balance between being academic and rigorous and being part of the real world.

assistant professor at the CGHD. Pillay knew that with Right to Care's health database of 17,000 patients treated at Helen Joseph Hospital, HE²RO had access to one of the biggest treatment cohorts in the country, which meant that it also had the ability to generate authoritative statistics and stable models.

"HE²RO can tell us what's happening to patients who started treatment in 2004," says Pillay. "They can predict what is likely to happen to patients in the long term, and what we need to do to prevent patients from moving from first-line treatment to second-line drugs. We need to keep them on first-line

drugs as long as possible, because the difference in cost between first-line and second-line drugs is five- or sixfold."

Cost data are especially important to the government, because unlike countries that depend more heavily on international donor support, South Africa pays for 85 percent of its national HIV program itself, using domestic tax revenues. Meyer-Rath, a health economist and infectious disease modeler who creates the complex mathematical algorithms at the heart of HE²RO's policy analyses, recalls one of several studies requested by Pillay's department.

"We were asked to look at the cost of introducing new guidelines for HIV treatment," she says. "They wanted to pull in more HIV-infected people, raising eligibility for both adults and children, and there wasn't data out there on what that would mean in terms of the number of eligible patients and the resulting cost. One of the questions we were asked is, what would be the cost implications of starting all children much earlier than was previously the case. There were studies that showed if you wait until children qualify for HIV

treatment under the old WHO guidelines, their immune systems are so run down that you lose half of them. But the cost of pediatric HIV treatment hadn't been analyzed before. So we had to do our own data collection, going into clinics and going through a sample of patient files."

The problem, says Rosen, is that that kind of data collection is much harder than it sounds.

"In many places in Africa—and probably some in the United States—medical records and data systems are not well-developed," she says. "Files get lost, and a patient will show up at a clinic and another file is opened with a new number, and there is no way of knowing that those files are for the same person. There is an endless series of those kinds of challenges. It's very labor-intensive to develop a data set that just says how much something costs."

"We look at every resource that has been used by a patient," says Meyer-Rath. "We count every pill, every visit, and we look at the outcomes. In the end we can say that after X years of treatment, the cost of treating kids is this much, and the outcomes are this. We take all the data and we put it all in a gigantic mathematical model and run it for a couple of years and see what changes. Then we go back, collect more data to fill in the gaps, and start the process anew."

Over the years, the data collected has helped to save many lives, and the job has yielded at least one major revelation: "You can collect all the epidemiological evidence you want," says Meyer-Rath. "You can study the feasibility and all the other things, but if you don't talk about cost and cost-effectiveness, you will not get an intervention off the ground. It's not the first question. The first thing is to prove that it works, but it is almost always the second question."

With the newborn study, the answer to that second question showed that treating infants sooner rather than later would save 80

percent of the costs of inpatient care—an average of 11 days during the first year of life. It turned out to be a good answer, says Meyer-Rath, because it resulted in a price tag that the government was "happy to pay."

LIFE-SPARING PUSH

In another study, HE²RO looked at the feasibility of using nurses to manage treatment for AIDS patients, a task that had traditionally been performed by doctors.

"One of the big challenges in this country is that we don't have enough doctors, but we do have nurses," says Pillay. "But there is a lot of resistance to the idea of using nurses to initiate patients on antiretrovirals, both from doctors and nurses. We needed to know first, is it a good idea from a clinical point of view, can it be done, and third, what are the cost implications? HE²RO helped us in all three areas."

In the last three years the South African government has doubled the budget for HIV treatment. It has tested 12 million people in a single year, is treating 1.7 million, and is budgeting to treat a total of 3.5 million people in the coming years. The life-sparing push started, says Meyer-Rath, with the willingness of the South African government to change its HIV policy and to act based on evidence, including that from HE²RO's calculations.

"The thing about HE²RO," says Pillay, "is they are a group of academics. They're very rigorous and they are independent of us, so the integrity of the results is not questioned. They strike a good balance between being academic and rigorous and being part of the real world."

"South Africa now has the largest antiretroviral program for treating AIDS in the world," says Francois Venter, former president of the Southern African HIV Clinicians Society and an HIV researcher at the University of the Witwatersrand. "For a long time,

we didn't know how to get to that point. HE²RO was instrumental in doing a lot of the costing work, a lot of operational work, and a lot of intellectual work. They were the ones who said, 'These are the choices you have, and this is what it's going to cost.' So for the first time, rather than being a gut-feel program, we have become an evidence-based program. HE²RO can take a lot of credit for that."

For Fox, Rosen, and other CGHD academics who have split their lives between Boston and Johannesburg, the influence of

HE²RO is the fulfillment of an important part of their mission, as well as a validation of the value of multidisciplinary, policy-relevant research. But the biggest fulfillment will come when the tools, team, and skills they have built can deliver the evidence needed for policy decisions even after BU goes home.

"The initial collaboration between Boston University and HE²RO was formative," says Lawrence Long, a South African health economist and a HE²RO division head. "Over time

the role has been to provide expert technical assistance to the local group and to build local capacity. They have done that."

"It's not realistic to assume that we can work here indefinitely," says Rosen. "The funding environment is against that, and countries should have their own capacity to do this work. It's very important to South Africanize our team. We don't want to be an American organization in South Africa. We want to be a South African organization that is thriving in collaboration with Boston University." ■

South Africa's Other Epidemic

A better way to track TB

While South Africa's HIV/AIDS epidemic gets more attention in the international press, tuberculosis, often coinciding with HIV infection, is the single largest killer of South African adults, in part because of the recent explosion of resistant forms of TB that are unaffected by the drugs traditionally used to treat the disease.

In March 2011, South Africa's National Health Laboratory Service was considering replacing the method it uses to diagnose TB from "smear microscopy"—looking for TB bacilli under a microscope, the way it has been done for nearly a century—with a new technology recommended by the World Health Organization. For advice on the costs of such a switch, the service turned to researchers from the Health Economics and Epidemiology Research Office (HE²RO), a collaboration between researchers from BU's Center for Global Health & Development (CGHD) and the University of the Witwatersrand in Johannesburg. The technology, called GeneXpert MTB/RIF, had two advantages over existing methodology: it finds more TB, and it finds it much faster.

The HE²RO researchers found that the new technology would increase the number of TB cases diagnosed per year by at least 30 percent. More important, because GeneXpert also screens for resistance to a commonly used TB drug, the new technology would increase the number of drug-resistant TB cases diagnosed by more than 70 percent, leading to better and more appropriate treatment. It would also diagnose TB much more often during a patient's first visit, rather than requiring the patient to come back for a second or even third visit,

which is typical using smear microscopy. This is an important plus, because many people do not come to the clinic more than once, and continue to spread the disease.

The major downside of GeneXpert, the CGHD scientists found, was that with the new technology, the South African government would pay about 15 percent more than it had been paying to find a case of TB—a lot, but perhaps not too much. The study's projections of both the impact and the cost of GeneXpert helped to persuade the South African National Department of Health and the South African Treasury to support a full-scale nationwide rollout of the new technology.

"GeneXpert drastically reduces the time it takes to get results," says Pappie Majuba, chief medical officer of the not-for-profit Right to Care. "Patients now can get treatment the same day they are diagnosed, so many patients who otherwise might have died will now be saved." AJ

WEB EXTRA
Watch a video about how HE²RO's research changed TB diagnosis in South Africa at bu.edu/bostonia.



Pappie Majuba