

to be drug resistance.” They began going house to house, patting residents on the back and getting them to cough into a cup. Back in the United States, lab analysis of the sputum confirmed their suspicions. This was resistant disease, and clearly, as the death of

“We started finding people dying of TB—in the middle of what was supposed to be the best TB-control program in all of the developing world.”

their friend proved, it was being transmitted. “The DOTS protocol without question is one of the great public-health achievements of all time,” Kim says. “It took countries from random, chaotic treatment to an organized approach that had much better results. It detected and cured many, many more patients.” But when initial treatments with first-line drugs failed, DOTS called for adding a single additional antibiotic. “The one thing you never do in TB treatment,” says Kim, “is to add a single drug to a failing regimen—never. If you do, the great risk is that you are going to develop resistance to that drug as well.”

At the time, drug-resistant tuberculosis was considered too difficult and too expensive to cure in resource-limited settings. Kim and Farmer’s answer was to increase the pool of resources by making sure the whole world knew what was happening in

Peru. They also developed lower-cost treatment protocols, using mostly community-health workers and nurses, and in their first cohort of 45 patients, achieved a cure rate of more than 80 percent. When they presented their results at the American Academy of Arts and Sciences in 1998, WHO leaders were astounded, and soon adopted a new policy dubbed “DOTS plus” that allowed for treatment of MDR TB.

Still, the cost of the necessary drugs was high, as critics of their “healthcare for all” approach frequently pointed out. In 1999 Kim went a step further, and worked to get TB drugs, all but one of which were off-patent, manufactured inexpensively in China and India. Eli Lilly and Company, which makes two of the most important drugs for MDR TB, made large donations of these drugs, transferred the technology to China, Russia, and Africa, and trained people in those countries to make the drugs, spending \$200 million on the effort—“pure philanthropy,” Kim says. In a single year, the cost of treatment dropped 95 percent, from \$25,000 to as low as \$1,500 per patient. Says Eric Rubin, “Jim, as much as anyone, is responsi-



TACKLING TB IN THE FIELD

LESOTHO IS A COUNTRY of breathtaking beauty and heart-breaking poverty. The twin epidemics of HIV and drug-resistant tuberculosis may also make it the site of the most devastating pandemic of the twenty-first century.

I am in the capital, Maseru, wearing a face ventilator and standing with Partners in Health (PIH) director Jim Yong Kim—professor of social medicine at Harvard Medical School and François-Xavier Bagnoud professor of health and human rights at the Harvard School of Public Health—outside a new 24-bed hospital devoted to the most serious and infectious of Lesotho’s extensively (XDR) and multidrug-resistant (MDR) TB patients. It is Kim’s first visit in more than a year, and the PIH hospital, four months old and the first in the country with state-of-the-art infection control, bears witness to the devastation of the disease.

Take Molahlehi (not his real name), a patient on the wards who used to work in the South African mines. HIV-positive and now, after intermittent and incompetent treatment for tuberculosis, resistant to all of the most important drugs, he is a classic XDR TB case. The stigma associated with his condition is such that his village won’t have him back, nor would his children when he tried to return home over Christmas. He called PIH to pick him up again when he realized the extent of his isolation. While PIH is caring for his family members (his wife left him) and educating his village about his condition, PIH’s MDR-TB program director, physician Hinda Satti, is praying that he will respond to treatment. The outlook is grim; a cure rate of 50 percent is deemed the highest success.

“These are, hands down, the most complicated patients I’ve

treated in my life,” says Jen Furin, PIH’s country director in Lesotho and a physician at Harvard-affiliated Brigham and Women’s Hospital in Boston. Furin has worked on MDR cases at PIH sites from Haiti to Peru. But in Lesotho, where the incidence of HIV and TB coinfection is among the highest on earth, the patients are far sicker—and far more likely to stay that way.

The challenges extend far beyond clinical treatment of the condition. As patients move from the hospital wards to PIH-run halfway homes, and, finally, back to their villages, community health workers trained and employed by PIH help them navigate their twice-daily drug cocktails—more than 20 pills a day for many, for a minimum of two years—and educate community and family members.

The success thus far has been astonishing. Of the 94 patients who have made their way through the wards since November, Satti says, not one has defaulted on therapy. The hospital is already attracting international attention: a contingent of doctors from the South African province of KwaZulu Natal—doctors who, given their own country’s wealth, medical infrastructure, and history with XDR TB, should be training Basotho (as citizens of Lesotho are called)—were learning from the hospital staff the day I arrived. And Kim, after visiting the newly reno-



ble for driving down the prices of drugs that are required to treat MDR TB—personally responsible—even though he wouldn't take credit for it."

In 2000, with a \$45-million grant from the Bill and Melinda Gates Foundation, Kim and Farmer scaled up PIH's program. Today, the Peruvian government has taken it over and everybody has access to care. "Half the people who have been treated for drug-resistant TB in the developing world have been treated in Peru," says Kim. "That is the one place where we really achieved universal access to MDR TB treatment. It doesn't yet exist in other places."

Yet even as their efforts in Peru were rewarded, a new disaster loomed. In a 2000 report funded by the Soros Foundation, PIH predicted that the problem of drug-resistant tuberculosis was going to explode in two places: "South Africa, where TB and HIV were coming together," Kim recalls, and in the former Soviet Union, "where there were huge prison populations, the health systems had been destroyed, and there was a long history of using single drugs" for treatment. Still, there were some who argued that DR strains would never become a big problem.

Eight years later, the development of clusters of new cases indi-

cating active transmission of rampant drug-resistant disease in both places has essentially settled the matter, and genetic work has confirmed that they do maintain fitness: after a mutation confers drug resistance, some of the resulting strains remain fully capable of reproducing and infecting new patients, while others are enfeebled. The fit strains survive and soon grow to become a significant proportion of cases in a population. At the molecular level, the bugs that acquire mutations conferring drug-resistance *are* weakened at first. They languish and fail to divide and reproduce as well as normal strains. But these sacrifices in function don't appear to last long. Within a few bacterial generations, compensatory mutations at other locations in the genome rescue the bug and restore its vigor. Megan Murray, with the support of HMS professor of systems biology Eric Lander, director of the Broad Institute, and a team of Broad scientists, has been sequencing some of these drug-resistant strains to ascertain what makes them hard to kill.

"Two years ago," Lander says, "the greatest barriers to progress were technology and the lack of communities of young scientists who were committed to these problems. Both of those things are changing, so now it is a question of all of us putting our support behind this generation of visionary scientists." He predicts that "in the next five to 10 years we will understand the processes that TB uses both to infect us and to avoid our immune system and our drugs. That doesn't mean we are going to cure TB, but it is an amazing foundation."



In Lesotho, Partners in Health (PIH) has set up a modern laboratory and treatment center for the care of patients with drug-resistant TB. Many are also infected with HIV. Clockwise from left: At a rural clinic, PIH's Jen Furin admits a patient with AIDS, TB, and meningitis; a recovering TB patient lives in a home near the hospital where doctors monitor her care; PIH leader Jim Kim (right), with Furin (center), meets Moses Phakis, a local clinic administrator, in Bobete; Kim in the new PIH-affiliated hospital pharmacy in the capital, Maseru.

vated TB and microbiology lab (which eliminates sending specimens to South Africa for testing), was as excited by its capacity to help Lesotho as by the precedent set for other countries: "I was talking to the director of the TB department at the World Health Organization about your work here," he raved to lab head Mathabo Mareka, "and he is so excited about it."

As important as these TB projects are to PIH's healthcare-de-

livery and capacity-building efforts in Lesotho, they are far from the whole story. Unlike organizations that pursue narrower aims or are restricted in their use of funds, PIH owes some of its success to its commitment to comprehensive care: not just to the most serious XDR cases, but to any patient in need.

I encounter a vivid example on a visit to a patient with Furin. We are idling in our car along a rain-washed road, lost in the sea of shacks and shanties outside Maseru, looking for a six-year-old boy, Molise, whom we saw earlier in the week. HIV-positive and rail-thin, he hasn't been able to walk since dislocating his knee last year. His hands are swollen and elongated from shuffling around, crab-like, on the ground; his leg, permanently skewed to the side, is unusable. If PIH had a mandate, that leg would likely fall outside it. But Furin has a plan to fix not just the leg, but the leg and everything else.

An hour passes before Molise, wearing shorts and a shirt provided on our last visit, crawls excitedly toward us. As Furin examines the boy on her knee, for a moment the hospital wards, the dying Basotho isolated in the mountains, the pandemic quietly sweeping southern Africa—all fade into the humanity of the child's grin. "This [leg]," she says, the lines of exhaustion on her face fading briefly into a smile, "this is actually something, something that's savable." ~SAMUEL BJORK

Ledecky Undergraduate Fellow Samuel Bjork '09 filed this report from Africa, where he worked in a Botswana AIDS clinic from August 2007 until March 2008.