South Africa, KwaZulu-Natal, Durban I McCord Hospital

PHOTOGRAPHY BY PAUL WEINBERG

THE ZULU WORD FOR HOPE

Through a network that extends from Boston to Africa to China, Bruce Walker pairs research with clinical care to counter HIV/AIDS.

BY ROBERT KOENIG

DURBAN, SOUTH AFRICA –

The storm blowing in from the Indian Ocean this blustery morning doesn't quite match the intensity of the whirlwind that forms around HHMI investigator Bruce Walker. Shedding a rain-spattered windbreaker, the lanky Bostonian hurries to join the morning rounds at McCord Hospital, an oasis of health care in this largest city of KwaZulu-Natal province—a region at the epicenter of South Africa's HIV/AIDS epidemic. As chart-wielding doctors and nurses move from patient to patient in a 25-bed men's ward, Walker hears a weak voice call out. He leans over the bed's paint-chipped railing to listen to the patient, a 17-year-old Zulu, describe his symptoms.

The emaciated young man, his immune system weakened by HIV infection, recently battled a case of tuberculosis and now has come down with cryptococcal meningitis; he complains about a burning sensation in his feet. Walker turns to the attending physician and they discuss a change in medications. He holds the youth's right hand, pats his shoulder, and offers encouragement.

The patient doesn't know it, but the man helping him is a leading international authority on HIV/AIDS treatment and research who has collaborated with stakeholders in South Africa, and elsewhere, to develop innovative programs that introduce antiretroviral (ARV) drugs for treating the devastating disease. Walker's high-wattage research, genuine concern for patients, and ability to communicate complex science have impressed and motivated people from Boston to the green hills of South Africa to the ancient imperial capitals of China (see sidebar, page 37). As a result, he has been able to forge international research collaborations and policy relationships and has convinced deep-pocketed donors to help. And he has made a significant difference in the fight against HIV/AIDS—at both the research and the clinical levels.

A MILLION DOLLAR START

One place Walker's efforts are paying off is in KwaZulu-Natal, where *iThemba*—the Zulu word for hope—is gaining a foothold in HIV/AIDS programs. These days, Africans whose future once might have seemed hopeless—an estimated 5.4 million in South Africa alone are infected with HIV—are now learning that the infection can be managed with ARVs.

KwaZulu-Natal has the highest HIV/AIDS prevalence in South Africa; infection rates in high-risk age groups are more than 40 percent, including half the pregnant women in some communities. Here, Walker pursues his campaign to help on several levels: improving treatment; building African research capacity; and conducting research that sheds light on the virus, human susceptibility to it, and the potential to develop a vaccine. These goals apply at his home base in Boston as well as in South Africa, though the daily challenge of HIV infection in this part of the world is much more daunting.

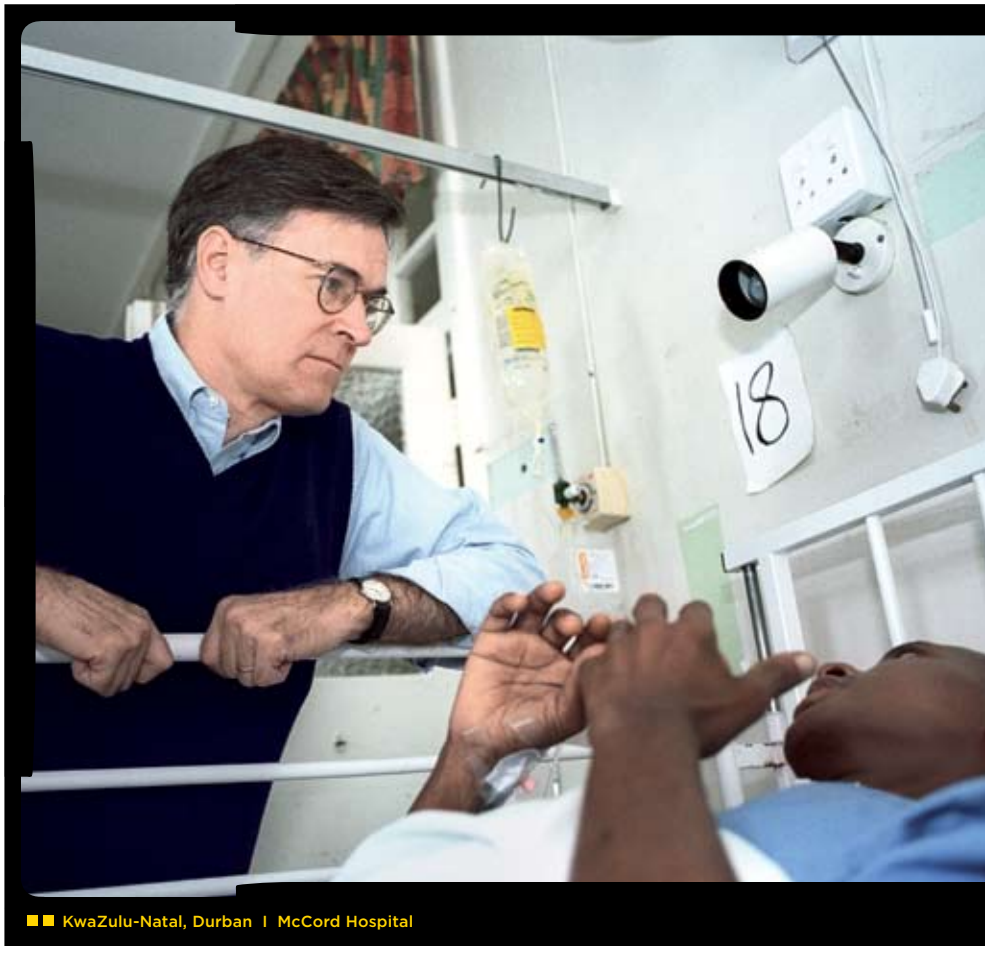
He leans over the bed's paint-chipped railing to listen to the patient, a 17-year-old Zulu, describe his symptoms.

"When I first came to KwaZulu-Natal, in 2002, the magnitude of the problem was almost incomprehensible," says Walker as he moves through the crowded hospital wards. "It was quite a shock to see the conditions in the hospitals at that time—I thought I was prepared, but the sheer numbers of persons filling hospital rooms and lining corridors were overwhelming." The most difficult part, he says, was knowing that HIV

infection had become a treatable chronic disease back home, but in Africa the life-extending AIDS-drug treatments were rarely available.

KwaZulu-Natal was not only ripe for improved access to known treatments, it was also a critical place to study the virus. Nearly all infections there involve subtype C—the major group of HIV variants fueling the global epidemic. "I realized there was plenty of interest in AIDS research, as well as talented and motivated scientists," says Walker, "if we could just provide resources to study the epidemic in the place where it was wreaking the most havoc."

Walker's postdoc at the time, Philip Goulder, now of Oxford University, had the same rationale in shifting his pediatric AIDS research to South Africa in 1998, and he helped convince Walker to start conducting research there as well as in Boston. Walker then turned to philanthropists for help. He first became aware of the potential for significant HIV/AIDS philanthropic funding in the 1990s, when he recognized that some people who had profited from the 1980s financial boom were looking to direct a portion of their substantial resources to the general good. With the help of Massachusetts General Hospital, his group initiated a fundraising program by hosting a simple lunch to let people know of their plans and the opportunities they saw to make a difference. One guest gave $1 million to support the research—the first donation Walker ever received.



KwaZulu-Natal, Durban | McCord Hospital

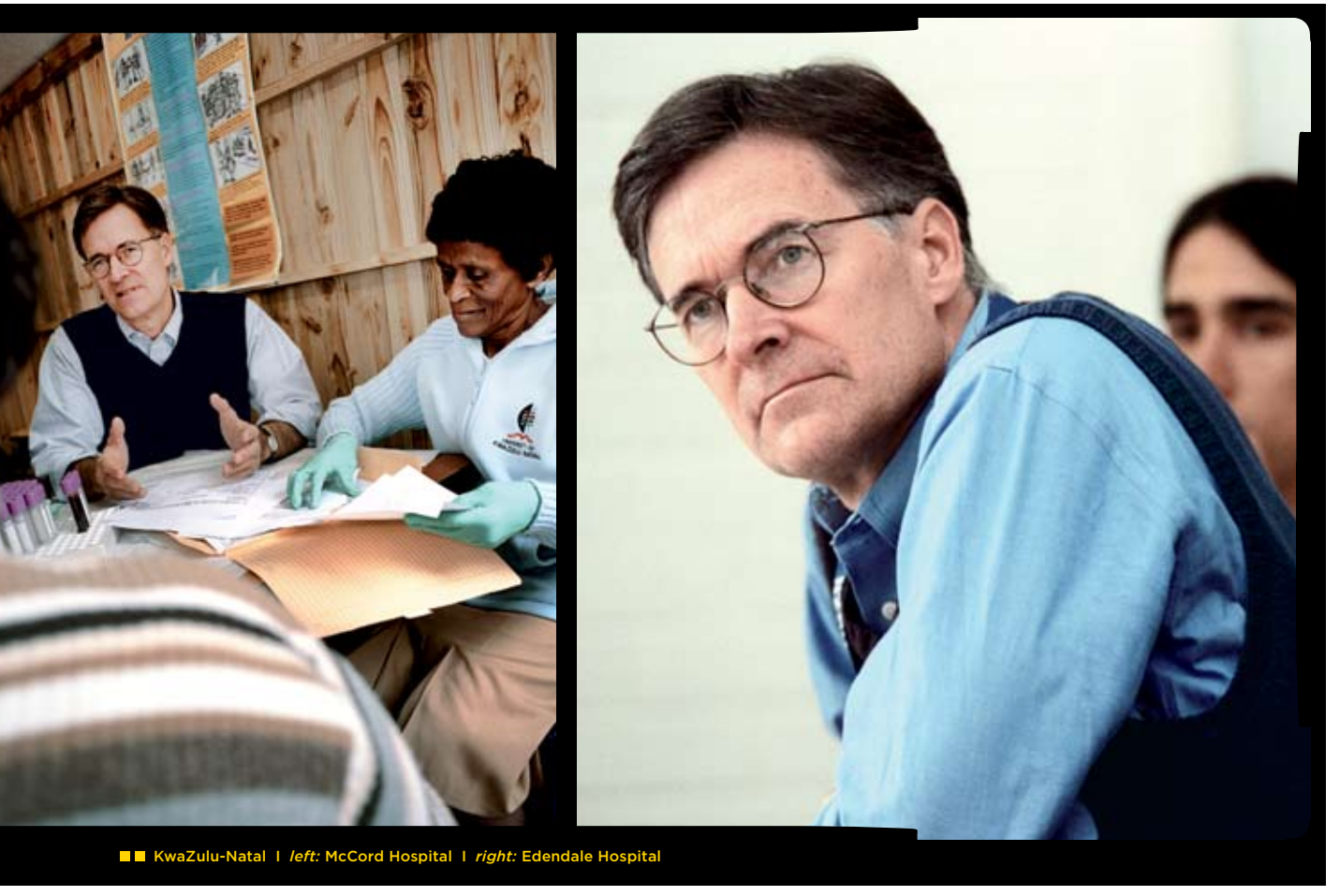
"What an incredible way to start!" says Walker. "For the first time, we were able to think really big. There is no single event that has made more difference to me in my career, and nothing that has more transformed the way I think about science. Rather than thinking about research projects based on what could get funded, we were able to focus on the key issues that really needed solutions and to think outside the box. It is exactly the same kind of scientific freedom that we now get from HHMI."

On this stormy Wednesday, Walker—who had flown to South Africa from Boston two days earlier—sticks to a grueling schedule. After rounds and then meetings at McCord, he heads to the University of KwaZulu-Natal's Nelson R. Mandela School of Medicine to deliver a lecture about trends in HIV/AIDS research. That evening, he trades in his windbreaker for a sport coat and delivers welcoming remarks at a posh reception at the Hilton Hotel to open a conference on HIV/AIDS treatment.

"Bruce is capable of speaking at a conference of the world's best HIV/AIDS scientists, heading straight to an event to raise funds for research and treatment, and then walking into a hospital ward and talking with patients," says Krista Dong, a former infectious-disease fellow at Massachusetts General Hospital, who now directs an HIV/AIDS and tuberculosis program at Edendale Hospital, an hour west of Durban.

ELITE CONTROLLERS

At home in Boston, Walker keeps a similarly demanding schedule as a researcher at Harvard Medical School, a clinician at Massachusetts General Hospital, and director of the Partners AIDS Research



KwaZulu-Natal | *left:* McCord Hospital | *right:* Edendale Hospital

Center. The overarching theme of his research projects around the world is to learn more about how the immune system controls chronic viral infections such as HIV and to use that information to develop appropriate interventions at the bedside.

While still a postdoc, Walker was the first to identify cytotoxic T lymphocyte responses specific to HIV in infected persons, and these responses remain a major focus of his current research efforts. He and his colleagues have shown that early treatment of acute HIV infection leads to increased immunity and the transient ability to control viremia (the presence of virus in the bloodstream) in most infected persons but that the ability of the virus to mutate often allows it to escape immune detection in the first place. From more recent studies of infected patients from Boston to Africa, his group has shown that these mutations occur in a highly predictable fashion, indicating that there are constraints on the virus's evolution—something that Walker believes can be exploited in designing vaccines.

Walker's labs are now working on several projects, including a major new initiative to use genomic analysis to find out why certain individuals—called "elite controllers"—have immune systems that are naturally able to contain HIV and prevent the advent of AIDS. A related group consists of "viremic controllers"—infected persons whose immune systems also control the virus, though at slightly higher, but still barely detectable, levels of infection. Understanding how these controllers keep the virus at bay might offer a key to fighting HIV.

As part of these international efforts, Walker and collaborators are trying to identify 1,000 HIV-positive elite controllers and 1,000 viremic controllers worldwide. Finding and enrolling so many unusual individuals is no easy task; he estimates that among the more than one million HIV-infected persons in the United States, only about 2,000 are elite controllers. So far, the group has found a total of about 300 such persons around the world, but the search continues, with cooperating labs in Africa, Europe, Australia, China, North America, and Latin America.

Making use of the powerful sequencing facilities at the Broad Institute in Cambridge, Massachusetts, Walker and colleagues will compare genetic signatures of elite and viremic controllers with those of HIV-positive people whose bodies are unable to control the virus without the help of ARVs. "Our goal is to discover the molecular basis for these individuals' ability to coexist with the virus," says Walker. "If we can find a way to replicate it in others, we might be able to blunt the impact of the virus and slow or stop the HIV epidemic."

CONFRONTING HIV/AIDS IN CHINA

In the ancient Chinese city of Xi'an, where the Silk Road originated, Bruce Walker is collaborating with a network of local scientists and clinicians. Their intent is to bolster China's HIV/AIDS research capacity, to provide important data for international researchers, and to apply the results to improving treatments.

After years of playing down the threat from HIV/AIDS, China's health officials are now serious about the disease, which was responsible for the deaths of at least 25,000 Chinese in 2005. That same year, an estimated 650,000 people in China were HIV-positive. Scaling up HIV treatment, care, and support will become increasingly important, as some experts predict there may be more than 10 million HIV-infected Chinese by 2010.

Walker's collaboration with Chinese HIV experts is an offshoot of a National Institutes of Health contract to study immune responses and host genetics in different regions of the HIV epidemic. "We started in South Africa and based on our success there were able to expand to China as a newly emerging epidemic came to be recognized," says Walker. Through a scientific colleague in Beijing, Walker met Yongtao Sun—an immunology professor who also heads the Department of Infectious Diseases at Tangdu Hospital in Xi'an—and invited him to visit Boston for several months, in 2002, to learn more about the clinical treatment of HIV and about basic research techniques.

Walker "taught me how to use [antiretroviral therapy] to treat AIDS patients and how to conduct research related to clinical care," recalls Sun. Walker's group also helped train three junior researchers from Sun's department at Tangdu in basic research techniques for characterizing HIV-1-specific T-cell responses. "Now all four of us have returned to China to work at the front lines of fighting against HIV/AIDS," says Sun, who has established an immunology lab in Xi'an, a metropolitan area of more than six million in north-central China. "We apply Bruce's knowledge, experience, and expertise to scale up HIV treatment, care, and support" in impoverished areas around Xi'an, he says.

Yiming Shao, the head of China's National Center for AIDS/STD Control and Prevention, in Beijing, recently invited Walker to speak to the center's scientists. The Boston researcher complied, and he used the occasion to propose further joint research ventures.

"In China, we're trying to build research capacity with collaborations," Walker says, adding that his goal there, as elsewhere, is "to push the interface between research and HIV/AIDS clinical care." — *R.K.*

CLINICAL STUDIES PAY OFF

In South Africa, as with much of his life's work, Walker began with a scientific question—one that could not be addressed in the United States. "Why," he asked, "do children who become HIV-infected from their mothers do so much worse than adults who become infected?" While very few infected children were being born in the United States, large numbers of them were being born in Africa.

As his research programs became established in South Africa, Walker was able to help local collaborators make a major difference in patient outcomes. At St. Mary's Hospital, west of Durban, the iThemba Family Care Centre, established in 2002 by Walker's Partners AIDS Research Center with support from philanthropic sources, provides a high level of care to more than 2,000 people who are HIV positive.

As Walker wades into the crowded wing of St. Mary's that houses iThemba, an HIV-positive woman—she was one of the first patients to receive ARVs there and is now working as an iThemba program counselor—rushes over to hug him. She says that patients are staying with their ARV regimens, even though compliance was anticipated to be a difficult challenge in much of Africa, and that the drugs are helping. "The St. Mary's adherence program became a template for the national ARV rollout in South Africa," says Walker, who worked with the Clinton Foundation in helping the South African government draft that plan.

Later that morning, Walker visits with HIV-infected infants and children enrolled in another program at St. Mary's, the Pediatric HIV Treatment Study. Recently, staffers gathered about 50 of those children with their mothers and siblings for a party to celebrate their progress. "It's inspiring to see a room full of mothers and children who would not be alive if the program did not exist," says Douglas Ross, the hospital's chief executive.

At McCord Hospital, a clinical research program that Walker helped establish at the modernized Hope House clinic sees about 450 outpatients every four months as part of a longitudinal study of HIV-infected persons. "So far, these population-based studies have provided tremendous insights into what the key mutations are that arise in the virus and enable it to escape detection by the immune system," says Walker. "By understanding these pathways, we are trying to devise vaccine strategies to block them." *(continued on page 56)*

CONTINUED FROM PAGE 37
(THE ZULU WORD FOR HOPE)

A Prime Mover

While important data are being collected from those effective clinical programs, Walker's scientific pride and joy in South Africa is the HIV Pathogenesis Program (HPP), housed in a wing of the University of KwaZulu-Natal's Nelson R. Mandela School of Medicine that Walker helped create.

When Goulder, then a postdoc with Walker at Harvard, first visited the medical school in Durban in 1998, he observed that the prospects for research there were promising but that the infrastructure was deficient. Joined by fellow researchers Hoosen Coovadia and Photini Kiepiela, Goulder set up a tiny lab, and later he and Walker worked to interest major philanthropies in modernizing it (see Web Extra). Encouraged by Walker, the Doris Duke Charitable Foundation, together with the university, agreed to fund a whole new research wing.

Since the new building was opened in 2003, Walker has expanded his involvement there. The HPP has become a major center of HIV/AIDS research in Africa, attracting high-quality researchers who are already publishing papers in *Nature* and other top-flight journals and are helping to train a new generation of African scientists. "Within four years, we established an excellent lab," says Kiepiela, who directs HPP and credits Walker for the progress. "Bruce has a heart for Africa and its people. He sees the devastation and wants to help at the human level. He mentors our Ph.D. students and sets high standards for basic science research."

"HPP has grown from strength to strength," says Coovadia, now chairman of HIV/AIDS research at the medical school. He too credits Walker, as well as Goulder, with helping to initiate a sea change in research at the school, which as a non-white institution during the apartheid era had been grossly underfunded.

And Goulder also tips his hat to his mentor, whom he calls "an extremely active and committed person, dedicated not only to his research but also to providing optimal therapy to people with HIV." On top of that, Goulder says, Walker has had success as a teacher and fundraiser because "he does a wonderful job of communicating the excitement of science." ■

WEB EXTRA: To read more about Walker's postdocs and their projects, go to www.hhmi.org/bulletin/feb2007.