Max Essex is the Lasker Professor of Health Sciences at Harvard University and the Chair of the Harvard AIDS Initiative and the Botswana Harvard Partnership. He talked with Martha Henry, HAI’s Director of Communications, about mentoring students and young scientists.

You’re primarily a research scientist. How important is your role as a mentor?

Extremely important. I think mentoring students to learn how to do research is one of the most important things I do.

Raabya Rossenkhan
The Will to Make It Work

Raabya Rossenkhan was always interested in science, so majoring in biology at the University of Botswana (UB) was an obvious choice. When she was offered a scholarship to continue her education, she saw the need to study HIV/AIDS. The year was 2003. In Botswana, the HIV prevalence among pregnant women was almost 40%.

“A lot of people were dying at the time. I had friends whose parents were dying. There was a lot of stigma associated with HIV. You would hear stories, but nobody ever directly spoke about it,” said Raabya. She wanted to help end the crisis that was devastating her country.

There was just one problem. When Raabya indicated that she wanted to conduct HIV/AIDS research, the UB Biological Sciences Department said it would be difficult. For the Master’s programs, there was either a food

Kathleen Wirth
In Search of the Purposeful

Growing up, Kathleen Wirth knew she wanted to see the world outside of her small hometown of Irmo, South Carolina. She felt she didn’t quite fit in. Her mother’s family had fled from Cuba in 1960. Her grandfather, who’d been a respected doctor in Havana, worked as a hospital janitor until he could qualify to practice medicine in America. Though she got into minor trouble, it wasn’t enough to keep Kathleen from becoming her high school valedictorian. A scholarship to attend the University of North Carolina (UNC) at Chapel Hill was her ticket out of Irmo.

Maybe that wasn’t far enough away. Once in college, despite the fact that she maintained a perfect grade point average, “it just all felt pointless,” remembers Kathleen. The summer after her freshman year, she worked for Budget car rental, figured out their computer system, and within a few weeks was a star employee. She saved enough money to drive with friends to British Columbia. They worked odd jobs and snowboarded at Whistler Mountain, which was open all year.
At the end of the summer, her friends were ready to return to UNC. Kathleen wasn’t.

She asked to be dropped off in Seattle. There she found work tutoring at a school for kids who’d been expelled from other schools for truancy, violence, or drugs. “Essentially no school would take them,” said Kathleen. “This was their last stop.” Most of the kids were from poor, immigrant families. Many of them lived in single- or no-parent households.

The job, while difficult and exhausting, gave Kathleen the sense of purpose she’d been lacking. “It taught me what it means to not have a security blanket,” said Kathleen. “For the first time in my life, I felt grateful for my circumstances.” With newfound perspective, she returned to UNC and earned a degree in economics, graduating with highest honors.

After graduation, she worked on public health economics at the consulting firm RTI International. “It was math, but math for a good cause,” said Kathleen. She assisted with a cost-effectiveness analysis for a Hepatitis A vaccination. The analysis helped the Centers for Disease Control and Prevention (CDC) make decisions.

Kathleen became interested in the question of how knowledge is put to use. “How do we go from what we know to making actual public health impact?” The question led her to the Harvard School of Public Health (HSPH), where she earned a doctorate in epidemiology. In her research on sex workers in India, she published one of the first rigorous studies on HIV and human trafficking.

“Kathleen has a great analytic mind, paired with a deep-rooted commitment to and passion for public health,” said Dr. Eric Tchetgen Tchetgen, a Professor of Biostatistics and Epidemiologic Methods at Harvard and Kathleen’s mentor. “She can both do high impact science and be an advocate for public health change and justice, which is not a common combination of qualities found in researchers.”

After graduation, she moved to Botswana with her husband Matt, a physician whom she met in class (Epi 202) at HSPH. Kathleen researched what factors influence the acceptance of male circumcision. Clinical trials, many done in sub-Saharan Africa, have demonstrated that circumcision reduces HIV infection risk by 50 percent to 60 percent. The couple stayed in Africa for two years.

Kathleen recently became the senior epidemiologist for the Botswana Combination Prevention Project (BCPP), a large HIV/AIDS trial that aims to dramatically reduce the rate of new HIV infections at a community level. Max Essex, Chair of the Harvard AIDS Initiative, is a Principal Investigator of the trial. “It’s a challenge to work on a study of this magnitude,” said Kathleen, referring to the over 100,000 people involved in the BCPP.

“Kathleen’s previous experience in Botswana adds insight about and understanding of conditions on the ground for BCPP, which make her a very effective lead epidemiologist for the study,” said Tchetgen Tchetgen.

“There are a series of evidence-based interventions that we know work,” she said. “The idea is that if you can put them together, you get something that’s greater than the sum of the parts—what we in epidemiology call synergistic effects. The hope is that this combination of efforts will disrupt transmission and reverse the epidemic.”

“It’s the ultimate implementation study,” continued Kathleen. “Although it’s a randomized trial, it’s very much in the real world. We’re going into communities and talking to people who don’t normally participate in research. We’re trying to marry the rigor of randomized trials with the reality of implementing interventions in the field.”

She didn’t. Stubborn and resourceful, she thought about studying HIV in breast milk, which could be classified as food. “But where on earth am I going to find breast milk to do this project?” she wondered.

Cue Dr. Thumbi Ndung’u, who at the time was head of the lab at the Botswana Harvard AIDS Institute Partnership. He visited the UB campus to teach a small class on how to do an HIV PCR. PCR is short for Polymerase Chain Reaction, a tool in molecular biology used to amplify a single copy of a piece of DNA to generate millions of copies of a particular sequence. Of the few students in the class, only Raabya’s first PCR worked that day. This gave her the confidence to ask Ndung’u for advice on getting samples.

He laughed and said, “You won’t believe this, but we have hundreds of breast milk samples stored in our freezers. The only catch is that you’ll have to convince Max, a professor from Harvard, that you’re good enough to use them.” He was referring to Dr. Max Essex, Chair of the Harvard AIDS Initiative, as well as the Botswana Harvard Partnership (BHP). Ndung’u suggested that she come up with a proposal and present it to Essex, who would be there in two weeks.

Kathleen Wirth (left) with colleagues at the Bontleng Adult Circumcision Clinic in Botswana

Raabya Rossenkhan (continued from page 1)
isolate the effect of formal education on the risk of becoming infected with HIV, the study used a school policy reform implemented in 1996 as a “natural experiment” to determine the impact of increased years of secondary schooling on infection risk. The reform provided free grade ten education as part of junior—rather than senior—secondary school.

The policy change presented a unique opportunity to estimate the causal effect of length of schooling on risk of HIV infection by comparing birth cohorts exposed to the reform versus those unexposed. The researchers used statistical techniques commonly used in economics and political science to analyze natural experiments. The authors investigated the causal effect of an additional year of schooling on HIV status in 7018 men and women.

Continuing Secondary Schooling for Girls Reduces Risk of HIV Infection

Educating young women has many health and economic benefits, but does continued schooling reduce a young woman’s risk of HIV infection? A study conducted in Botswana suggests that it does. The results, published in The Lancet Global Health, showed that secondary-school students who stayed in school for an extra year had an eight percent lower risk of HIV infection a decade later, from 25% to about 17% infected. The effects were especially strong among young women, with an additional year of secondary schooling reducing infection risk by 12 percent.

Botswana has one of the highest rates of HIV prevalence in the world with over 20% of adults aged 15–49 infected. Though it’s difficult to isolate the effect of formal education on the risk of becoming infected with HIV, the study used a school policy reform implemented in 1996 as a “natural experiment” to determine the impact of increased years of secondary schooling on infection risk. The reform provided free grade ten education as part of junior—rather than senior—secondary school.

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"Information about prevention methods and reasoning skills gained in school may play a preventative role against HIV, enabling people with education to adopt healthy strategies to avoid infection," said Dr. Jan-Walter De Neve, first author on the study and a doctoral student at the Harvard T.H. Chan School of Public Health. “Secondary schooling may be particularly effective in reducing HIV risk by targeting a critical period of growth in adolescence.”
When a student or young researcher asks to work with you, what are you looking for?

Intelligence, energy, and a willingness to ask questions that require complex thought to get the answers. You have to look for some spark in people for thinking more deeply as opposed to just compartmentalizing information.

Scientific research involves a lot of dead ends and failed experiments. As a mentor, how do you help your trainees deal with discouragement?

I’ve seen very few instances where you didn’t learn from so-called failed experiments. You can have a couple of reasons for failed experiments. One is that you didn’t follow the mechanics of the protocol and the cells died and you got no results—you can’t do much with that.

But if your results are that your experimental arm wasn’t different from the control or you know for a fact that the virus infected the cells, but didn’t induce the expected effect of change in those cells that you thought it would—in those kinds of instances, you learn. It may not be something that’s easy to package and publish, but you learn. And you certainly use that information in subsequent designs.

It’s often said that in scientific research, if you’re doing good experiments and asking the right questions, your answers very often lead to more hypotheses as opposed to just packageable results that are immediately reduced to practice. What some people might call failed experiments often lead to even better hypotheses.

Did you have a mentor?

I had several, but the most memorable one by far was a guy named George Klein, a brilliant thinker. He was a physician/PhD Hungarian refugee who was a professor of tumor biology at the Karolinska Institutet in Sweden.

He asked questions about everything all the time. He had a deep interest in many different disciplines: immunology, virology, cell biology, genetics, ecology, biochemistry, and radiation biology—a whole range of disciplines. Having an interest in all of these was key to his ability to think through large problems.

What role did your mentor play in your career?

An important role. He took interest in me and his other students and postdoctoral students from all over the world, introducing us to other scientists and mixing us into conversations with different generations. He’d have Nobel laureates and undergraduate medical students and postdocs and technicians and everybody else to dinner to talk together about research questions. It was not at all hierarchical, so it was very effective.

You've made a strong commitment to training African researchers in hopes that they’ll return to Africa. Why is that important to you?

It’s important because there’s great need to empower the medical and scientific establishment within sub-Saharan Africa so that the people who best understand the local situation in a political sense, in a socio-economic sense, in a behavioral—all of these can make sure that the questions that are most important for those populations are being raised. We must be sure that the way in which those questions are being answered helps local populations in the best and fastest way possible.

I think you can never do that well unless the people who are most familiar with the value systems and the culture are deeply immersed in the research and, in many cases, leading it. With the developing situation in Africa, we’re only now getting to the state where that can be done in very many African countries. It should be done in a lot more.

HAI is dedicated to research and education to end the AIDS epidemic in Africa and developing countries. Since 1988, HAI has been at the forefront of HIV/AIDS laboratory research, clinical trials, education, and leadership.

www.aids.harvard.edu
Elliot Eton
The Precocious Researcher

First he had to convince Max Essex.

Elliot Eton had just graduated from high school when he ended up in Essex’s office. After receiving his acceptance letter to Harvard, Elliot assumed he’d begin college in the fall with the other freshmen. Then he read a letter from the Dean of Admissions, encouraging students to consider a gap year. The idea of pursuing his own interests, “unencumbered by academics,” appealed to Elliot. His parents, both doctors, were initially skeptical, but soon agreed. Elliot learned about Essex’s research when he read an article about an AIDS prevention trial in Botswana. He emailed Essex, who responded almost immediately with an invitation to talk.

What impressed Essex was that Elliot, though still a teenager, already had significant research experience. The summer he was 15, Elliot attended the Advanced Biotechnology Institute at The Roxbury Latin School in Boston. At 16, he attended Harvard Summer School, taking courses in neuroscience and writing. (He got As in both.) At 17, he worked in an MIT lab that studies learning and memory.

“He was quite mature in his thinking and in his willingness to deviate from standard paths and not just take the year off to travel around Europe,” said Essex, who invited Elliot to work at the Harvard AIDS Initiative.

Elliot arrived at the Harvard T.H. Chan School in the fall of 2014. He quickly completed lab safety courses, but because he was neither a student nor an employee, state labor laws did not permit him to work in the Boston lab. He took the setback well. With Essex’s encouragement, Elliot made plans to travel to Botswana in January to conduct research at the Botswana Harvard Partnership, where regulations would allow him to work. In the meantime, he learned computational methods for genomic analysis, reviewed the scientific literature about immune system-driven HIV adaptation, and attended lectures—sometimes several a day—at both the School of Public Health and the Medical School.

“He is adept at handling a lot of situations and participating in scientific conversations with much more experienced students,” said Essex.

Elliot left for Botswana in late January to spend several months working at the Botswana–Harvard HIV Reference Laboratory on the grounds of Princess Marina Hospital in Gaborone. Back in Boston this summer, Elliot presented his research at an Essex Lab meeting. He showed his data and discussed how HIV responds and adapts to various human immune system pressures.

The fall semester starts soon. Elliot has his roommate assignment. Soon he’ll be hiking in the White Mountains on a weeklong orientation trip with other Harvard freshmen. He’s working on narrowing down his course selection. “This year I developed skills in molecular biology, but I realized, even in my own project, that research requires integrating knowledge from different disciplines. I’d like to build a stronger foundation in physics, chemistry, engineering, statistics, programming, and ethics.”

Eventually Elliot would like to become a clinician/scientist and hopes his work will help influence public policy. “I’m interested in medicine and understanding the path from the bench to the bedside to the community and back,” he said. “In research, being able to figure out why something isn’t the way you thought it would be is a good skill to have.” Keep an eye on him. Elliot Eton is likely to make important contributions to biomedical research.

On the Way to Market

We wanted to update you on Dr. Iain MacLeod, another young HAI researcher, who is building a biotech start-up around a rapid HIV drug-resistance test that he and Dr. Christopher Rowley developed in the Essex Lab. MacLeod and another Harvard colleague founded Aldatu Biosciences after winning the 2014 Deans’ Health & Life Sciences Challenge hosted by the Harvard Innovation Lab (i-lab).

This March, the Aldatu team won a $1.5 million Direct to Phase II Small Business Innovation Research award from the National Institutes of Health (NIH). The new funding made it possible for Aldatu to move into laboratory space at LabCentral, a Kendall Square incubator that provides lab space and resources to support small biotech startups. The team is currently working with manufacturers to create a kit-based test to detect HIV drug resistance in patients. The test is specifically designed for resource-limited countries.
Roger Shapiro Appointed Associate Professor

Congratulations to Dr. Roger Shapiro, a key member of the Harvard AIDS Initiative team, for his recent appointment as Associate Professor of Immunology and Infectious Diseases at the Harvard T.H. Chan School of Public Health.

Shapiro’s research focuses on the prevention of mother-to-child transmission (PMTCT) of HIV and improving childhood survival in the developing world. His groundbreaking research in the area of PMTCT via breastfeeding was used to update World Health Organization (WHO) guidelines.

Shapiro conducted the largest study to date evaluating the impact of maternal antiretroviral use in pregnancy on adverse birth outcomes. He has led several trials aimed at improving survival among HIV-exposed uninfected children in Botswana. He recently initiated a trial of early diagnosis and treatment for HIV-infected infants to improve long-term treatment outcomes in these children.

The Young Investigators Issue

Though the Harvard AIDS Initiative has been conducting innovative research since 1988, the sustained level of excellence wouldn’t be possible without a constant influx of smart, dedicated, young men and women. In this issue, we highlight some of those creative minds, including both their stories and their accomplishments (thus far).