Fast, Cheap & Sensitive
Researchers Invent Improved Drug Resistance Test

Over 12 million people are currently taking antiretroviral (ARV) treatment for HIV. That number is expected to rise to 15 million by 2015. An unfortunate consequence of the global scale up of treatment is an increase in drug resistance, which can render a drug regimen ineffective.

About 10% of people fail treatment every year. In areas like southern Africa, where the burden of HIV is greatest, the cost of drug resistance testing is prohibitively high. “There is a need for cost-effective, efficient techniques for the detection of HIV drug resistance,” said Dr. Mark Wainberg, Director of the McGill University AIDS Centre and an expert on HIV drug resistance.

Profile: Dr. Mosepele Mosepele
Coming of Age with the Epidemic

It started in preschool for Mosepele Mosepele. His mother was an Operating Room (OR) nurse in the Mahalapye District Hospital in Botswana. In the morning, she dropped her son off at school on her way to work. If she had an early operation, young Mosepele would sit in an office with a window overlooking the OR. Though only five years old, the boy would watch the surgical team operating. “People were dressed up all in blue with big lights hovering over the patients like in a TV show,” remembers Mosepele, who is now a doctor and researcher with the Harvard AIDS Initiative (HAI). “It didn’t scare me,” he said. “I was fascinated.”

The doctors in Mahalapye were mostly male Europeans, mainly from Scandinavia. “I admired them,” said Mosepele, “but I thought, why aren’t local people doing this? Maybe I could try it.” While still in preschool, he decided to become a doctor.

Mosepele came of age in Botswana at the height of the AIDS epidemic. “In the 1990s, the people of my generation remember our middle school and high school teachers getting sick and dying. Some of my favorite teachers passed away. You would go on school holiday and come back and they would look very different. And before the end of the school term, they were gone.”

At the age of 19, Mosepele spent his year of national service working in the pathology lab at Princess Marina Hospital in Gaborone. Then, because Botswana didn’t have a medical school, he attended the University of Melbourne in Australia to earn a joint undergraduate and medical degree.

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In most resource-strapped areas, drug resistance becomes obvious only after patients show an increase in viral load or get sick because their treatment is failing. Patients are then put on a second line of drugs, which typically costs four times as much as first-line treatment. And if they’re resistant to those drugs, they’re put on a third line of treatment, which can cost up to 15 times as much.

That’s why Dr. Iain MacLeod, a research associate in the lab of Dr. Max Essex, was working with Dr. Christopher Rowley to monitor the development of drug resistance in Botswana. The test they were using was expensive and unwieldy, so one day they invented a better one.

MacLeod recognized that their invention could have commercial potential. It was more sensitive than prevailing tests and significantly cheaper. He teamed up with David Raiser, a PhD student at Harvard Medical School, to form a company they named Aldatu Biosciences. Rowley serves as a consultant.

Their test recently won the top prize in the Deans’ Health and Life Sciences Challenge hosted by the Harvard Innovation Lab (i-lab). The price of the test is $99, about a third of the cost of prevailing tests. The Aldatu team’s mission is to bring their test to countries where the need is greatest. Botswana, where about 22% of adults have HIV, is first on their list. MacLeod and Rowley have both spent significant time conducting HIV/AIDS research there.

Martha Henry, Editor of Spotlight, sat down with MacLeod and Raiser to discuss their recent biotech start-up.

You recently won the grand prize of $40,000 for the Deans’ Health & Life Sciences Challenge hosted by the Harvard Innovation Lab (i-lab). What is your product?

MACLEOD: Our product is a rapid HIV drug-resistance test focusing on six drug-resistance mutations that are most likely to impact antiretroviral therapy in resource-limited areas.

How and why did you develop this technology?

MACLEOD: It came about from a need for better drug-resistance surveillance. I’ve worked with Chris Rowley over the past couple of years on his study looking at drug resistance in Botswana. We had a couple of approaches, but they were all cumbersome. As part of his work, Chris was looking for novel ways to detect drug resistance. It all came together one day when we developed the idea for what we now call PANDAA for “Pan-Degenerate Amplification and Adaptation.” With PANDAA, we’ve taken an existing technology called qPCR and adapted it for HIV drug-resistance testing.

When did you realize that you might have a commercial product on your hands?

MACLEOD: I guess it was a staged realization. We had approached Harvard’s Office of Technology Development in 2012. We were interested in patenting the technology primarily so that when we published our results, no one could just run off with the idea. We just wanted to protect the idea that we’d come up with.

Who could benefit from your drug-resistance test?
MACLEOD: Someone with HIV who is just about to start antiretroviral treatment, or someone with HIV who is failing an antiretroviral regimen.

How big a problem is drug resistance today?

MACLEOD: It’s growing rapidly. There are two different types of resistance. There is acquired drug resistance, so someone who’s on antiretrovirals will develop drug resistance over time. And then there is transmitted drug resistance, where someone gets infected with a strain of HIV that is already drug resistant, so even if they’ve never taken antiretrovirals before, they may be resistant to one or more drugs. One of the unfortunate side effects of the scale-up of ARVs in Africa is a corresponding increase in transmitted drug resistance.

In a place like Botswana, there’s about 5% transmitted drug resistance, but as we’ve seen in other parts of Africa, that will start to increase. In the U.S. and Europe the rate is almost 20% (in some areas) because we’ve had ARVs here for longer.

How is your product better than the existing technology?

RAISER: For resource-limited settings, we anticipate a much lower price point than the currently marketed tests, which should help increase access to testing. In addition to being more affordable, it’s also much faster, with results in a matter of hours as opposed to a matter of days. Our test is also more sensitive and picks up drug resistance earlier than current tests. Being able to detect drug resistance earlier allows for an earlier ARV treatment change, so the virus can be re-suppressed earlier, as opposed to leaving an uncontrolled infection in a patient for a longer period of time.

How did you two join together to form a company?

RAISER: Iain and I found ourselves at the same Innovation Lab workshop on Life Sciences Entrepreneurship. The workshop was a bit overwhelming, so we both ended up leaving early. While we were waiting for the bus, we asked each other why we were there. At the time I was open to the idea of being part of a startup, but the right idea really hadn’t come along. Iain said, “I think I have an idea, but I don’t really know if there’s potential here and how exactly to move it forward.” He took out a piece of paper and drew PANDAA for me. That’s when we decided to really explore the commercial potential.

MACLEOD: That was last summer. Come September, the NIH [U.S. National Institutes of Health] put out a request for a simple, inexpensive, HIV drug-resistance assay focusing on specific resistance you’d find in resource-limited areas. We thought, “That could be written for us.” All of a sudden we found ourselves applying for a grant that had to include business entry and exit and commercialization strategies. We were going to do it, but we were really kick-started by this request from the NIH.

Since winning the i-lab competition, what have you been doing to get your test to market?

RAISER: Right now our two main concerns are funding and building the relationships that will lead to the partnerships that will carry things forward. We’re talking to our scientific advisors about the best way to go about manufacturing the test. Do we do it here? Do we do it in Africa? Do we do it ourselves? Do we outsource it to others? So we’re answering a lot of questions about next steps. When funding does come in, we need to hit the ground running.

Could the PANDAA technology help with other diseases?

RAISER: Yes. We can use the design and optimization that has gone into the HIV drug-resistance test as a model to apply to other diseases that, like HIV, are highly variable.

MACLEOD: Any type of pathogen that’s constantly changing—TB, Lyme disease, influenza, hepatitis, anything where there’s a lot of variability—can prevent you from using qPCR.

RAISER: The value of the technology is being able to overcome that hyper-variability. We’ve begun to look at other infectious diseases where this could have an impact.
How do you define ‘household’ in a culture where extended families split time between town, the farm, and a cattle post? Who else has had trouble enrolling men? What happens if several large, expensive clinical trials deliver completely different results several years from now?

These were some of the important questions asked at the Treatment as Prevention in Africa (T asP Africa) workshop held this May in Gaborone, Botswana.

Worldwide, 35 million people are living with HIV. About 25 million of those people live in sub-Saharan Africa. About 1.5 million people were newly infected with HIV in sub-Saharan Africa last year.

In 2011, the HPTN 052 study found that early antiretroviral therapy could reduce HIV transmission by 96% in serodiscordant couples, that is couples in which one partner has HIV and the other is uninfected. Since then, Treatment as Prevention (TasP) has become a major focus for attention in the global fight against AIDS. In June 2012, the World Health Organization (WHO) wrote a comprehensive guideline to recognize the role of Treatment as Prevention.

Though the concept of Treatment as Prevention has been clearly validated in a controlled trial in discordant couples, it is not known how to use TasP most effectively in populations, especially in sub-Saharan Africa, where the need is greatest.

Several large clinical trials, funded mainly by the Office of the U.S. Global AIDS Coordinator (OGAC), are currently being conducted in Africa. Each trial uses a different approach.

“The use of Treatment as Prevention represents one of the most important advances in HIV control over the past 20 years, but we do not know enough about how to implement this to achieve high coverage or what the impact will be at the population level,” said Dr. Richard Hayes, a Professor of Epidemiology & International Health at the London School of Hygiene & Tropical Medicine, and one of the Principal Investigators (PI) of a large trial taking place in South Africa and Zambia.

The T asP Africa workshop, conceived and chaired by Dr. Max Essex, Chair of the Harvard AIDS Initiative, brought together PIs from the large trials, other noted HIV/AIDS researchers, policy makers, and drug industry representatives to share plans and compare notes.

“Until now, most of the discussion on the use of Treatment as Prevention has been based on populations and cohorts from the U.S. or Europe, with little emphasis on countries that have high prevalence, like those in southern Africa,” said Essex, who is also the PI of a large HIV prevention trial in Botswana.

“This was the first international conference devoted to TasP in Africa to be held in Africa,” he added.

“It was important to bring together the various groups working on these issues in Africa to share information on their methods and findings so that we can move the field forward as quickly as possible,” said Hayes. “Holding the workshop in Africa ensured that there was a strong focus on issues relevant to the implementation and evaluation of TasP in this region and that there was strong representation of African research groups and scientists.”

“The workshop created an atmosphere of trust and collaboration so that, for the first time, investigators could focus on the larger collaborative effort and the potential collective impact of their entire suite of studies,” said Dr. Nancy Padian, a leader in the epidemiology of HIV and a senior technical advisor at OGAC.

“We had open and constructive discussion about common goals and problems,” said Essex. “Those conversations should enable the various projects on Treatment as Prevention in Africa to move ahead more expeditiously.”

“There is much to share regarding lessons learned and logistical issues related to providing early treatment,” said Padian.

T asP Africa was organized by HAI and generously funded by contributions from the MAC AIDS Fund, Johnson & Johnson, Viiv Healthcare, Abbvie, and Mylan.
He returned to Princess Marina Hospital and, a year and a half after finishing medical school, became Head of the Infectious Disease Care Clinic. In his training in Australia, he’d seen only one patient with HIV. Now he was in charge of one of the largest AIDS clinics in Africa, providing treatment to thousands of patients. It was demanding work, but he thrived.

After his clinical experience, Mosepele went to the Hospital of the University of Pennsylvania for his internship and residency in internal medicine. While in Philadelphia, he worked in the Prison Health System, providing HIV care for inmates. Security was tight. Prisoners were brought into the examining room, which had a Plexiglas door so that guards could see in. “It was very challenging,” said Mosepele. “Unfortunately, many of the inmates suffered from mental health issues, or IV drug use, or other risky behavior.” He wore a panic alarm to pull if a situation became threatening, but he never had to use it.

Today, Mosepele combines the hard-driving intelligence of a top researcher with the warmth of a friendly internist. He recently graduated from a fellowship in Infectious Disease at Massachusetts General Hospital and Brigham & Women’s Hospital in Boston. He is currently working towards his Masters in Clinical Epidemiology at the Harvard School of Public Health.

He is also the Principal Investigator of two pilot studies looking at the connection between HIV and heart disease. “My primary interest is to establish whether HIV patients are at an increased risk for heart diseases and strokes,” he said. “And if they are, I’m also looking at underlying mechanisms to explain why, especially the role of persistent residual inflammation, even when HIV is well controlled.”

“Mosepele recognizes the importance of being at the cutting edge of research, like the interaction between AIDS and cardiovascular disease,” said Dr. Max Essex, Chair of the Harvard AIDS Initiative.

Cardiovascular disease (CVD) rates are higher in HIV-infected patients, yet the impact of this condition in sub-Saharan Africa is largely unknown. Addressing CVD risk among the almost 25 million HIV patients living in sub-Saharan Africa requires a detailed understanding of risk factors and actual disease rates. Mosepele’s pilot study will provide much-needed information.

With years of training complete, Mosepele has returned to Botswana to treat patients and conduct research with collaborators at Harvard and elsewhere. He will also teach at Botswana’s brand new medical school.

“Mosepele will be an excellent mentor,” said Essex. “He’ll also be a great example of how young doctors can combine both clinical practice and research that is of particular importance to Botswana.”

Mosepele recognizes the importance of being at the cutting edge of research

– Max Essex

“People respect him and they listen to him,” said Dr. Stephen Gluckman, a Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania and one of Mosepele’s mentors. “He is and will continue to be an excellent role model for young Batswana physicians.”

Mosepele looks forward to his role as a mentor, especially to teaching young doctors how to interact with patients. “You have to acknowledge the person first,” said Mosepele. “That way you can begin to see each other as human beings and work collaboratively to solve your problem. It’s about us working together.”

Strengthening Efforts in Africa

African academics and public health leaders met with Harvard colleagues for two days in June to work out details for a collaborative research and training network. The workshop, “Advancing Collaborative Education and Research in Africa,” was held in Boston and brought together participants from Botswana, Ethiopia, Nigeria, South Africa, Tanzania, and Uganda.

The group discussed developing a collaborative PhD program and increasing opportunities for post-doctoral training. They also considered how to establish more joint research projects and how best to utilize existing demographic information and surveillance systems.

The workshop was convened by the Africa Health Alliance at the Harvard School of Public Health (HSPH), an initiative charged with strengthening public health research efforts between Harvard and institutions within Africa, and the African Academy for Public Health, a Harvard-affiliated organization based in Tanzania with the mission to improve health in Africa through collaborative research, training, and capacity building.

The workshop was generously funded by a grant from the Medtronic Foundation.
On June 10th, Massachusetts General Hospital (MGH) honored BOTSOGO (Botswana Oncology Global Outreach program) as part of the MGH 100 awards. The event, hosted by actor and Cambridge native Matt Damon, recognized 100 individuals and organizations that are leading the fight against cancer.

**The Improvements Issue**

There are few true breakthroughs in science. Most work is made up of slow, steady steps, hopefully in the correct direction. This issue of Spotlight highlights improvements made by HAI researchers. These include a new test for HIV drug resistance, better medical education in Africa, and enhanced communication among large HIV prevention trials.

**BOTSOGO Honored**

HAI is dedicated to research and education to end the AIDS epidemic in Africa and developing countries.

For over 25 years, HAI has been at the forefront of HIV/AIDS laboratory research, clinical trials, education, and leadership.