The Botswana Combination Prevention Project

BEHIND THE SCENES OF A COMPLEX HIV/AIDS TRIAL
# ACRONYMS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ART</td>
<td>Antiretroviral Treatment (or therapy)</td>
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<td>ARV</td>
<td>Antiretroviral (drug)</td>
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<tr>
<td>BCPP</td>
<td>Botswana Combination Prevention Project</td>
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<td>BHP</td>
<td>Botswana Harvard AIDS Institute Partnership</td>
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<td>BHS</td>
<td>Baseline Household Survey</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<td>CEWG</td>
<td>Community Engagement Working Group</td>
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<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>HAI</td>
<td>Harvard T.H. Chan School of Public Health AIDS Initiative</td>
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<td>MoH</td>
<td>Ministry of Health</td>
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<td>PMTCT</td>
<td>Prevention of Mother-to-Child (HIV) Transmission</td>
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<td>WHO</td>
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The Harvard T.H. Chan School of Public Health AIDS Initiative is dedicated to research and education to end the AIDS epidemic in Africa and developing countries.

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The Botswana Combination Prevention Project

BEHIND THE SCENES OF A COMPLEX HIV/AIDS TRIAL

spotlight special issue
WINTER 2016
BCPP field team members and villagers in Shakawe
Much of science happens in messy offices. Ideas are batted about amongst colleagues. Some are discarded; others improved upon. The opportunity to test an idea depends largely on funding cycles. An inordinate amount of time is spent writing grants. One is funded. Budgets are revised, staff hired. Hours are spent on conference calls. Finally, the first person is enrolled in the clinical trial. After so much work, the work begins.

THE BOTSWANA COMBINATION PREVENTION PROJECT
A Way to End the Epidemic?

The end of AIDS as a public health threat may not come from an effective vaccine, as many had hoped for decades, but from a collaborative effort across nations to prevent new HIV infections. The epidemic that spread mainly through sexual connections may be subdued not from a single breakthrough, but through long-term transnational collaborations.

According to the World Health Organization (WHO), since the beginning of the epidemic, 78 million people have been infected with HIV. About 39 million of those have died from AIDS-related causes. Today, 36 million people are living with HIV. Sub-Saharan Africa remains the area most severely affected, accounting for over 70% of people living with HIV worldwide.

In 1981, what would later be named AIDS was first mentioned in the medical literature as a strange illness killing gay men in Los Angeles. By the late 1990s, the epidemic was devastating Africa. “We are threatened with extinction,” said President Festus Mogae of Botswana at an AIDS conference in Durban in 2000. “People are dying in chillingly high numbers.” That year, Botswana had the highest rate of HIV in the world—a staggering 35% of adults were infected.

A lot has changed since then. We now know how to treat HIV effectively with antiretroviral treatment (ART). Drug costs have dropped dramatically. Botswana established a national ART program in 2001. “The Botswana MASA program is the best in sub-Saharan Africa from the standpoint that it gets the largest fraction of individuals who need ART on ART, keeping them on treatment and virally suppressed,” said Dr. Max Essex, Chair of the Harvard AIDS Initiative (HAI) and the Botswana Harvard AIDS Institute Partnership (BHP). Essex has worked in Botswana since 1996.

Though great strides have been made in HIV treatment, the rate of new infections remains high. About two million people worldwide became infected last year, including an estimated 15,000 in Botswana.

BCPP: What it is and why it might work

The Botswana Combination Prevention Project (BCPP) is designed to evaluate whether a combination of proven HIV-prevention measures introduced into a community can significantly reduce HIV incidence—the number of new infections over time. In other words, by rapidly implementing what’s been scientifically shown to work, the BCPP hopes to dramatically decrease new HIV infections throughout a village. If the BCPP strategy works and is implemented on a large scale, the AIDS epidemic, with fewer and fewer new infections to fuel it, will burn itself out over time.

Modeling studies have suggested that a rapid scale-up of several evidence-based HIV prevention interventions may significantly reduce population-level HIV incidence. But models are not the real world.

“The BCPP is a way to determine whether treatment as prevention can work at the
population level in southern Africa," said Essex. The best-case scenario is “that we demonstrate that transmission can be effectively stopped, and thus that the epidemic will no longer be an epidemic in 20 years.”

“We strongly believe that with this project we have the chance to make history in the fight against AIDS,” said Michelle Gavin, the U.S. Ambassador to Botswana at the time of the November 2013 launch of the project in Gaborone, the capital of Botswana. “If this combination prevention strategy is shown to be effective and affordable, Botswana will be a global leader in providing scientific evidence needed to turn the tide on this epidemic.”

Study Design

Ambitious in scope, the BCPP will track the number of new HIV infections in 16–64 year olds in 30 villages in Botswana over a three-year period.

The study format is a pair-matched community randomized trial, meaning that the 30 study communities are matched, based on similarities, into 15 pairs. In each pair, one village is randomly assigned to receive the combination prevention package and the other village receives the standard of care, as well as enhancements to its clinics, labs, and data management systems.

A Baseline Household Survey (BHS) of approximately 20% of randomly selected households is conducted in all 30 villages. From those households, an HIV incidence cohort of HIV-negative individuals is established. After the baseline survey is completed, the package of combination prevention interventions is rolled out in one of the villages in each pair. The villages that don’t receive the combination prevention interventions act as a control, but receive extra support in the way of HIV testing and referral for the survey participants. Residents of non-intervention communities can access free ART in the government treatment program.

The combination-prevention package includes:

- Rapid scale-up of HIV testing and counseling services
- Rapid scale-up of ART for adults eligible under government guidelines
- Rapid scale-up of ART for adults with high viral load who otherwise don’t qualify for treatment under government guidelines
- Beginning in 2016, rapid scale-up of ART for all HIV-infected individuals
- Rapid scale-up of Voluntary Male Circumcision
- Rapid scale-up of Prevention of Mother-to-Child-Transmission services

The people in the HIV incidence cohort will be retested annually. At the end of the study, researchers will compare the number of new HIV infections in villages that received the combination prevention package with the villages that did not. The hypothesis is that new HIV infections will be significantly lower in the villages that received the package of interventions.

Who's Doing What?

The BCPP is a joint effort of the Botswana Ministry of Health, the Harvard T.H. Chan School of Public Health AIDS Initiative (HAI), the Botswana Harvard AIDS Institute Partnership (BHP), and the U.S. Centers for Disease Control and Prevention (CDC).

The Ministry of Health and the CDC lead the Intervention Protocol, rapidly rolling out the combination prevention package. The Harvard team leads the Evaluation Protocol, conducting a baseline survey before the interventions are rolled out, then returning at 12, 24, and 36 months to evaluate the impact of the interventions in the participating communities. Funding for the BCPP is provided by the U.S. State Department’s Office of the Global AIDS Coordinator (OGAC) through the CDC. Results from the BCPP are expected in 2018.

WHAT WE KNOW WORKS

- HIV testing influences behavior change positively.
- Male circumcision reduces risk of HIV infection by up to 60% in heterosexual men.
- Prevention of Mother-to-Child Transmission (PMTCT) can reduce infant infections to around 1%.
- Antiretroviral treatment (ART) for those infected with HIV significantly reduces the risk of infecting a partner.
MAX ESSEX
The Persistent Investigator

It’s unlikely that you’ll ever meet anyone more focused than Max Essex.

A 1986 *New York Times* profile described him as “mild mannered” with “a thatch of thick hair” and “among those in the forefront of the worldwide effort to find a cure for acquired immune deficiency syndrome.” Today, though his hair is white, that description still fits. Essex, now in his 70s, still arrives at the office by six o’clock most mornings and spends long days planning and improving research projects around the world. He remains, as the *Times* reporter described, “deeply exercised about the fate of AIDS patients.”

Early Career

As a young microbiologist, Essex started out studying the relationship between viruses and cancer. He arrived at the Harvard School of Public Health in 1972 as a junior faculty member. He worked to understand how viruses cause leukemia and lymphoma in cats and whether or not similar viruses might cause similar forms of cancer in people.

In 1974, Essex showed that a retrovirus caused immune suppression in cats. A few years later, Dr. Robert Gallo discovered the first retrovirus in humans. As soon as Essex knew that human retroviruses existed, he wanted to know if they could also cause immunosuppression, significantly damaging the body’s ability to fight disease.

The Epidemic Begins

In 1981, Essex read a short report published by the Centers for Disease Control (CDC) that began, “In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed Pneumocystis carinii pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died.” This was the first mention in the medical literature of what would later be termed AIDS. Pneumocystis pneumonia is usually found in severely immunosuppressed patients.

As the disease spread, Essex hypothesized that a retrovirus might be the cause of AIDS. He was right. The CDC called to enlist his help. Samples of the virus were sent to his lab. At the same time, AIDS patients began showing up in Boston hospitals. Essex collaborated closely with Dr. Martin Hirsch, an infectious disease researcher and clinician at Massachusetts General Hospital. "In the 1980s, AIDS was a devastating diagnosis to receive,” said Hirsch. “Our hospital was loaded with people dying from this infection.”

People were dying fast from a disease no one understood. Panic and stigma were widespread. Researchers at Harvard and around the world worked impossibly long hours to answer basic questions about the virus.

Essex and his team provided many of the early answers. They determined that HIV could be transmitted through blood to hemophiliacs and transfusion recipients. They identified the specific protein (gp120) that’s used worldwide for AIDS tests and blood safety screening. They provided the first evidence that AIDS could be transmitted by heterosexual intercourse. With collaborators, they discovered the first evidence of simian immunodeficiency virus (SIV), the counterpart of HIV in primates. With Senegalese collaborators, they discovered that a second type of HIV, HIV-2 existed in western Africa and that it was less virulent than HIV-1, the virus found predominantly in the U.S. and Europe.

Dr. Richard Marlink, at the time a research fellow in the Essex Lab, remembers, “It was a
time when discoveries were happening almost monthly—major discoveries—with Tun-Hou Lee and Phyllis Kanki and others. They were deciphering and figuring out where this virus came from and how it worked and then how we could detect and, ultimately, how we could treat it."

**HAI Created**

Essex and other Harvard researchers made many of the early discoveries about HIV/AIDS. In the late 1980s, Dr. Harvey Fineberg, Dean of the Harvard School of Public Health, proposed creating the Harvard AIDS Institute (HAI) to coordinate and strengthen efforts across the university. "Max Essex was the obvious choice to lead the enterprise," said Fineberg. "He had the personal connections with the investigators throughout the university and beyond. And by personality, he was a great leader and one that we knew we could count on to make this the enterprise we wanted."

**Crisis in Africa**

The introduction of triple-cocktail antiretroviral therapy (ART) in 1996 changed the fate of AIDS patients. People who were expecting to die got better. After years of agonizing deaths, there was suddenly hope, at least for people in wealthy Western nations. The cost of ART was well over $10,000 a year per patient.

It was also becoming increasingly clear that AIDS was devastating Africa. In the 1980s, Essex and Senegalese colleagues had established a study of commercial sex workers in Dakar to investigate the dynamics of transmission and methods to prevent the spread of HIV. New infections in Senegal had been controlled. Something completely different was happening in southern Africa. Essex wanted to know why.

Maurice Tempelsman, a U.S. businessman working in Africa, had been instrumental in helping Essex establish collaborations in Senegal. Essex turned to him again for advice. When Ketumile Masire, the President of Botswana, was visiting Washington, Tempelsman arranged for Essex to meet him. Masire invited the Harvard professor to visit Botswana and welcomed his guidance.

Essex was soon on a plane. He knew that to make the biggest difference, he had to work in the area most affected. Botswana had one of the highest rates of HIV in the world, with over 20% of adults and 37% of pregnant women infected. The purpose of his trip was to explore the possibility of collaborating with Botswana’s Ministry of Health and collect blood samples to analyze in his Boston lab.

"I think he was overwhelmed by what he saw. I can remember how quiet he was as he absorbed the pain and suffering by patients when we walked him through the medical ward," said Dr. Joseph Makhema, then an internist treating AIDS patients at Princess Marina Hospital in Gaborone, Botswana’s capital. "Bed occupancy was greater than 120% and floor beds were the..."
order of the day. Mortality was high and staff morale was low. It was common to have five to ten deaths per day.”

Essex helped Makhema collect blood samples. At the time, Botswana had no access to antiretroviral drugs. Doctors could only treat their patients’ opportunistic infections and keep them as comfortable as possible.

Essex returned to Boston. Flying to and from Botswana would soon become commonplace for him. That same year, 1996, the Botswana Harvard AIDS Institute Partnership (BHP) was established. Essex was given space in a trailer on the grounds of Princess Marina Hospital. A small lab was created in a nearby storage shed.

The best model for collaborations, Essex had learned, was to have the host country determine priorities and set the research agenda. Meetings took place with the Ministry of Health and others.

In 2001, the Botswana–Harvard HIV Reference Laboratory opened. The 25,000-square-foot research center has become one of Africa’s leading scientific institutions and also serves as headquarters for the BHP.

As a leading AIDS researcher, Essex was able to win competitive grants from the U.S. National Institutes of Health. The first big clinical trial in Botswana was on the prevention of mother-to-infant transmission of HIV. Other important studies have followed, in areas including HIV treatment, acute infection, AIDS pathogenesis, cost-effectiveness of ART, genetics of susceptibility to HIV, AIDS in children, and cancer and HIV.

With guidance from the BHP, the Government of Botswana established a national ARV program in 2002 to provide free treatment to any citizen in need. For the first years of the program, drugs were donated by the Bill & Melinda Gates Foundation and the Merck Foundation.

In 2015, the BHP employed over 300 people, mostly Africans. Makhema, the doctor who worked with Essex in 1996, is now the C.E.O.

The Next Generation

Makhema credits Essex’s “ability to attract quality loyal and dedicated staff” as one reason for the BHP’s success. Essex considers teaching and mentoring to be high priorities, especially training young Africans in hopes that they will return to Africa. A two-way flow of trainees between Harvard and the BHP helps bolster projects at both places.

Dr. Pride Chigwedere was a young doctor treating AIDS patients in Zimbabwe when he met Essex. “Max was doing work on AIDS in southern Africa, my interest area,” said Chigwedere. “I had no dreams of coming to Harvard. Max reached out and sponsored me.”

Chigwedere earned his doctorate at Harvard. He currently works as a Senior Advisor to the UNAIDS Office to the African Union. “Max remains my mentor. I keep asking for his guidance and support,” said Chigwedere.

Preventing New Infections

In the past decade, preventing new HIV infections has been a major focus for Essex. He and his team have had success in determining how best to prevent pregnant HIV-positive women from transmitting the virus to their children. Transmission rates in Botswana, once as high as 30%, have been reduced to 1% in clinical trials.

Preventing adult HIV infections is a more difficult challenge. As a Senior Principal Investigator for the Botswana Combination Prevention Project (BCPP), Essex currently spends much of his time troubleshooting problems. The ambitious clinical trial he and his team designed is now entering its second year in 30 villages.

As hope for an AIDS vaccine dims, Essex sees the use of antiretroviral therapy, which has
Dr. Max Essex greets the staff at a clinic in Botswana.
been shown to nearly eliminate transmission in trials conducted in discordant adult couples, as the best strategy to prevent new infections and eventually end the epidemic.

“I don’t believe for a minute that AIDS is going to disappear as a disease in the next 50 years,” said Essex. “I think it’s impossible that will happen, or near impossible. I think, on the other hand, that it could be reduced to a very rare disease when transmissions would be thought of as very unusual.”

Making AIDS “very unusual” is what still motivates Max Essex.

“He continues to work extraordinarily hard,” said his old friend Marty Hirsch. “The current studies that he’s doing on trying to prevent spread at a local level are extremely important. Exactly what the results of these trials are going to be, of course I don’t know, but one way or another, they are going to significantly influence our efforts to control infections in areas like Botswana.”

Joe Makhema says the same thing in a slightly different way: “Max is a stellar scientist and human being driven by commitment and passion to end human suffering from the HIV/AIDS epidemic.”

**ESSEX TEAM MAJOR ACCOMPLISHMENTS ON HIV/AIDS**

- **1974** Showed that retroviruses cause immune suppression in cats.
- **1982** Hypothesized that a retrovirus is the cause of AIDS.
- **1984** Identified the envelope proteins of HIV, which would be used for HIV tests and blood screening.
- **1985** Identified Simian Immunodeficiency Virus (SIV) in monkeys.
- **1985** Identified HIV-2 in people in West Africa.
- **1988** Identified HIV antibodies in saliva, paving the way for a blood-free diagnostic test.
- **1994** Demonstrated that HIV-2 is transmitted much less efficiently than HIV-1 and causes AIDS less often.
- **1995** Demonstrated that HIV-2 can partially protect against HIV-1 infection.
- **2000, 2006** Demonstrated uses of drugs to reduce rates of mother-to-child transmission.
- **2007, 2009** Showed different patterns of drug resistance for HIV-1C, the virus of the largest epidemic in Africa.
- **2010** Demonstrated that women taking antiretroviral drug combinations can breastfeed with minimal risk of transmission of HIV/AIDS to their infants.
COUNTING TO 73,700
A Guide to Randomization

From: Scott Dryden-Peterson
Sent: Friday, June 19, 2015
Subject: BCPP milestone

Today we completed mapping of the last study community. In one of the many remarkable behind-the-scenes contributions that has made a project of this scale possible, during nights and weekends over the past 18 months, Oaitse (cc’d here) single-handedly identified and labeled ~73,700 households from Ranaka to Shakawe. We are indebted to you, Oaitse.

Thanks,
Scott

Why Randomize?

Randomization is a key element in the best clinical trials. It insures that researchers don’t inadvertently introduce their own preferences or biases into the hard work of trials. It helps safeguard the integrity of the data.

In the Botswana Combination Prevention Project (BCPP), randomization occurs at several levels. In each of the 15 pairs of villages in the trial, one village gets the combination prevention interventions and the other village acts as a control. In each pair, a lottery system was used to decide which village received the combination interventions. Village names were placed inside plastic, egg-like containers and randomly selected in the presence of Ministry of Health officials and independent observers.

But randomization doesn’t end there.

Researchers hope the BCPP will show how to reduce new HIV infections at a community level. Testing for incidence (the number of new infections in a year) has always been a challenge in AIDS research. To do it accurately involves labor-intensive testing of a large number of people year after year to determine how many are newly infected.

The total population of all 30 BCPP villages is about 180,800. Of those people, about 105,000 are age-eligible (16–64) for the trial. Rather than testing all 105,000 people, the BCPP team is testing 20% of them. But for that 20% to act as a proxy for the entire population, the people must be randomly selected. That crucial process involves a number of steps.

The Best Woman for the Job

One of the first steps was using Google Earth to number the households in all 30 villages. Households in Botswana usually include a
A Research Assistant looks for a specific household.

In a traditional Botswana household, several buildings are often enclosed by a fence to define the compound. The fence helps with security, reinforces land boundaries, and keeps animals from trampling plants in yard. But not all households have fences and sometimes two or more households are contained within a fenced area.

Multigenerational living is also the norm in Botswana villages. Oaitse, for example, lives in her grandmother’s house in Ramotswa, a town near the South African border. Her uncles, sisters, and nephew live in the same compound, but different houses. If new houses are built, old houses are often left standing.

All these factors made the task of numbering households, or “plots” as they are called in the study, anything but simple.

Working on a MacBook Air, Oaitse numbered plots during her lunch breaks. At the end of a workday, she’d often stay in the office and number for a few hours, go home, take a shower, get something to eat, and number more plots before bedtime.

She mapped on the weekends. Her sisters complained that she was always working. “It was a little bit addictive,” Oaitse admitted, like the video games she played on her phone. She got frustrated when the Internet was slow or not working at all. When Scott opened Google Earth to review her work, he could see the late hours she was keeping.
Oaitse had to keep ahead of the BCPP rollout. As the field team completed their work in one pair of villages, plots in the next pair had to be randomly selected before the team could begin work. The random selection depended on Oaitse’s numbering. She kept pace.

After she finished numbering all the plots in a village, the file was sent to Scott for review, then on to the IT department at the BHP, where the data was entered into the EDC (Electronic Data Collection) system, which renumbered each household with a unique study ID. The file was then forwarded to a senior epidemiologist who ran an automated script to randomly select 20% of the numbered households for the field team to visit, plus another 5% to replace any households in the 20% that were uninhabited or whose members chose not to participate.

When the field team arrived in a village to conduct the Baseline Household Survey, the coordinates for each plot were loaded onto GPS receivers. With GPS in hand, Research Assistants were assigned to find specific households. If things went according to plan, at about five meters away from the front door—the point where Oaitse placed her virtual flag—the GPS screen flashed the message, “Arriving at destination.”

Needless to say, things didn’t always go as planned. When you’re numbering 73,700 plots, there are bound to be discrepancies between the map on a computer screen and reality on the ground. Some households turned out to be churches or businesses. Some plots were deserted. But the system, created from scratch, worked surprisingly well.

“It was exciting to do the mapping,” said Oaitse. She sometimes runs into members of the field team at BHP headquarters in Gaborone. “Some of the research assistants would talk about which village they were working in and I’d be like, ‘I know that village. I’m the one who mapped it.'”

The mapping also gave her a wider sense of the world. “I felt like it would be great for me to go and physically see these places, to go around and see my country and how people are living. I need to create some time and save some money and travel around and see.”

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**BCPP BY THE NUMBERS**

- **30** Communities
- **15** Matched pairs
- **6,000** Average community size
- **180,000** Total study population
- **105,000** Eligible adults
- **9,000** HIV Incidence Cohort
IT TAKES 30 VILLAGES
Building Trust in a Clinical Trial

Because of his own history, Dr. Mompati Mmalane had ideas about how best to introduce a complex clinical trial to communities like Shakawe, a remote village in northwestern Botswana.

HIV is no stranger to rural villages. Although the national adult prevalence is 24%, the rate is much higher in some villages. Older adults remember the days before antiretroviral treatment (ART), when Saturdays were crowded with funerals for friends, relatives, and neighbors who had died of AIDS.

The Botswana Combination Prevention Project (BCPP), a trial designed to reduce HIV incidence at a community level, takes place in 30 villages across the country. In theory, people should welcome improved HIV testing and treatment efforts as well as improvements to local clinics. Rural villages like Shakawe often lag behind urban areas in access to medical care.

In reality, services will only be utilized if a sense of trust is established between residents and the BCPP team. For the study to succeed, researchers had to first gain the community’s confidence. Without it, their clinical trial would fail.

As Co-Chair of the BCPP Community Engagement Working Group (CEWG), Mmalane was charged with explaining the study and encouraging people to participate. “When you want to do something with a community, you need to understand their culture,” he said. “Batswana are a consultative people. We like consulting. Some people say there’s too much consulting, but we like to consult.”

“My team’s role is to get them to take part in the study,” he said. “That’s the main objective.” Participation in the trial is voluntary, he emphasized. Individuals are enrolled in the trial only after a strict informed-consent process is followed. Once a participant agrees to enroll, he or she may withdraw at any time.

The Unusual Life of Dr. Mmalane

Mompati Mmalane was born to a single mother in Semolale, a small village in eastern Botswana. “There was no doctor, no clinic, nothing,” was how he described it. His grandfather named him Mompati, meaning my partner, and taught him how to farm and tend cattle.

When riding on the back of his uncle’s bicycle, the young Mmalane’s foot got stuck in the spokes of the back wheel. The wound became infected. His grandfather took him by bicycle to the big village of Bobonong, about 30 miles away. There weren’t any roads, just tracks over the hills, so the trip took a whole day. At the clinic, the health worker applied ointment to Mmalane’s wound and gave him antibiotics. His grandfather pedaled him home the following day.

When his grandfather died a few years later, Mmalane stayed in school. It wasn’t the obvious choice for a boy who was now the man of the family. Many of his classmates left after fourth grade to work on potato or cotton farms. “At that time, most Semolale parents felt that if you could read and write your name, you were educated,” remembered Mmalane. His mother had little schooling herself and by then had five children, but she encouraged her oldest son to continue in school.

He excelled and earned a scholarship to university. He hoped to become a doctor. After two years at a local university, he would be sent
Dr. Mompati Mmalane

Young Mompati Mmalane (dark jacket) says goodbye to friends at Gaborone Airport.

Dr. Mompati Mmalane

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to a foreign medical school, ideally in Canada, Britain, or New Zealand. But when a sponsored spot opened up in Germany, he took it, though he didn’t speak a word of German. He boarded a plane for the first time and left Botswana.

The expectation was that Mmalane would study German for a year to pass the medical school entrance exams. After just six months, he felt ready. He took the exams, passed, and was accepted at the University of Tübingen. He was the only African in his class.

“Initially, life was a bit of a challenge,” he said. Someone gave him an old bicycle. One day he rode it on the Autobahn. Cars passed him honking loudly. He thought, “Oh, well, they must be racist.” When he mentioned the incident at school, a teacher said, “You never go on the Autobahn with a bicycle! Not even a moped!” Mmalane smiled when recounting the incident.

He thrived, made friends, studied hard, and graduated with his MD in 1986. He describes his years in Germany as the best experience of his life. “Being accommodating of other people’s culture was very important.”

He returned to Botswana to work at Princess Marina Hospital, where he stayed for nearly two decades, leaving once to train in surgery at the Royal College of Surgeons in Edinburgh and later to train in orthopedics at University College London. He married a nurse. Together they had four children.

In 2005, Mmalane was asked by the Ministry of Health to become Botswana’s first Director of Clinical Services. He stayed until 2008. In 2009, he joined the Botswana Harvard Partnership (BHP).

Lasting Relationships

The CEWG returns to a village about a month before the BCPP field team arrives. The
THE MEANING OF YA TSIE

In the Setswana language, the name of the study is Ya Tsie, a term Dr. Mompati Mmalane came up with. The name comes from a proverb that roughly translates as “Teamwork bears more fruit than individual effort.”

Mmalane explains: “In the past, we used to gather locusts to eat. If you put locusts in a bag, they will fly out. To keep them in, somebody has to help you hold the bag as you gather them. There has to be somebody to help you. With this study we are saying, the fight against HIV is complicated—we need people to help us. And now these three partners, Harvard, CDC, and the government of Botswana, have come together to try to prevent HIV and keep it from spreading. The more hands you have to the problem, the better.”

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purpose of the visit is to bring the leadership up to date about the study and inform the community about what to expect in the coming weeks. Because Botswana has a number of different ethnicities, each with its own customs and code of conduct, every meeting is different. In these situations, Mmalane, a villager himself with knowledge about how to negotiate different cultures, works hard to unite local concerns with the requirements of a rigorous clinical trial.

Meetings are held with the village leaders first. Especially important is the meeting with the Kgosi—the chief. Others consulted are the Village Development Committee (VDC), political and church leaders, community-based organizations, and traditional healers. “You really need to work with these guys right from the get-go so they’ll assist you in answering questions from the community,” said Mmalane. “The community should see that the leaders are already on board.”

After speaking with the leadership, Mmalane requests permission to address the Kgotla, the public village meeting (much like a town hall forum) where community decisions are arrived at by consensus.

At the Kgotla, Mmalane talks to the people, explaining how the study, called Ya Tsie in Setswana, will help determine the best methods to prevent new HIV infections. He explains that the field team will begin door-to-door HIV testing and the steps that will follow. He asks villagers to consider providing accommodation for the 30 members of the team. “If we segregate ourselves, we will always be looked at as those people from Gaborone. It helps us recruit if people feel that we are part and parcel of them,” he said.

Questions from the community are encouraged. If the CEWG has done its job well, the Kgosi and village leaders provide many of the answers. Mmalane stays as long as necessary, patiently talking with anyone who has a concern. “He’s got a medical background, so people ask him all sorts of things related to their health,” said Ernest Moseki, a member of the CEWG. “At the end of the meeting, they feel like this man has responded to their questions over and above the fact that he came there to sell them the study.”

“Dr. Mmalane is a humble man,” said Kutlo Manyake, a BCPP field team supervisor. “He takes time to get to understand what people want. He always brings their interest before his own. In the Setswana culture, a humble man is a respected man.”

At the end of the campaign in each village, there’s a farewell meeting that Mmalane often attends. Team members thank the villagers for accepting them, for providing accommodation, and for giving them their time and trust. The villagers discuss how they view the clinical trial and the team’s conduct. There are heartfelt remarks, some criticism, and often laughter between the team and the people who have hosted them.

Leaving on good terms is important. The relationships must be honest enough to last. The team will be back again next year, and the year after, and the year after that for the final visit.
Keotshepile Molokwane (right) interviews a woman in her yard in Shakawe.
A MONTH IN SHAKAWE
The Field Team at Work

Tourists who visit Botswana’s scenic Okavango Delta rarely visit Shakawe, the most remote village participating in the Botswana Combination Prevention Project (BCPP), a large HIV-prevention trial of over 100,000 people.

The results of the trial will likely end up as an orderly table published in a prestigious medical journal. Though the numbers in that table may provide much-needed evidence on how best to operate HIV/AIDS programs across the globe, they won’t show the hard work, mistakes, corrections, and triumphs of the field team. The data won’t reveal the thousands of daily interactions between the Research Assistants (RAs) and the villagers—the stories condensed into each data point.

The Visit

In September 2015, the field team was finishing up the Baseline Household Survey in Shakawe. They had been in the village for a month. Keotshepile Molokwane, a 27-year-old RA who everyone calls Keo, had one last visit to complete.

The BCPP driver maneuvered the SUV through the sand. When the road ended, he helped Keo get his gear from the back of the vehicle. By the time he was loaded up, Keo was carrying a MacBook Air, a phone, a GPS, a bag of phlebotomy supplies and HIV tests, a cooler bag with an ice pack, a CD4 test kit the size and weight of a six-pack, and a small folding table.

“We are trying to make testing to be easy, to be more friendly, more accepted,” said Keo, who wore a white coat over his polo shirt. “We’re bringing the clinic to them.”

Laden with equipment, he trudged through the hot sand, passing several rondavels—round earthen houses with thatched roofs. GPS in hand, he located the right one in a compound that contained several houses, a faucet in the yard, and an outhouse, all bordered by a chicken-wire fence.

The woman he was looking for was at home. She wore a print blouse, black skirt, and black canvas shoes. She was maybe a little older than Keo and had a warm smile. To ensure privacy, RAs arrange for discussions and testing to take place out of earshot of other family members, unless a participant wants them to be there. The woman said she’d prefer to talk outside, so Keo unfolded his table and set up his makeshift office in the sand. The woman brought out two chairs—a plastic chair and a metal chair missing its seat. The RAs had been instructed to always take the least comfortable chair, so Keo took the seatless chair and sat forward on the edge.

He spoke to the woman in Setswana. The team had anticipated a language problem in Shakawe where a large number of people are ethnic Bambukushu, but almost everyone, it turned out, spoke Setswana. Keo had been to the household several times before to enroll other family members.

Without rushing, he went through the consent form that the woman had to sign to participate in the trial. He explained what the trial was about, what participating involved, and how, if she did agree to enroll, she could withdraw at any time. The woman asked a few questions.
After Keo answered, she signed the form. A skinny chicken wandered around the yard. Two young boys ate fruit and ran around in circles.

With the consent form signed, Keo proceeded with the detailed questionnaire that’s part of the Baseline Household Survey. The questions cover socio-economic information, residency status, and sexual activity. He went through the questions unhurriedly, listening closely when the woman spoke and recording her answers on his MacBook Air. There was a nice rapport between them.

When the questionnaire was complete, Keo moved his laptop to the side, opened a bag, and took out supplies for the HIV test. He pulled on latex gloves. The woman giggled nervously when she gave him her hand to draw blood. He pricked her finger, collected the samples, then labeled each tube with a black marker. By now the table was crowded with alcohol wipes, a yellow cup for sharps, and a red biohazard bag. Keo prepared the HIV test and set a timer for 20 minutes. If the result was positive, he would do a CD4 test immediately after to measure the health of the woman’s immune system.

They talked as they waited. Keo used the time to answer additional questions. Afternoon clouds rolled across the sky, making the hot day a little bit cooler. The woman kicked off her shoes. When her cell phone rang, she took the call at the table. On the other side of the chicken-wire fence, children dressed in white shirts and gray pants or skirts walked home from school.

Minutes later the timer went beep-beep-beep. Keo pushed the button to quiet it. He checked the HIV test results. He and the woman spoke
calmly for a few more minutes, then the interview ended. Keo packed his equipment, folding up the small table last. He and the woman shook hands. Then, giggling, the young boys who’d been playing in the yard ran up to Keo and he shook their hands as well.

Two trailers parked outside the Shakawe clinic served as the field team’s base of operations in the village. One trailer houses a mobile laboratory with storage space for the RAs’ equipment. The other serves as working space for the IT team and a charging station for laptops.

When Keo neared the IT trailer, his laptop automatically connected to the secure Wi-Fi network created for the team. Without his having to do anything, the encrypted information on his MacBook Air synchronized onto the central server.

After returning his laptop to the charging station, Keo handed his blood samples to the technician in the mobile lab. The samples are temperature sensitive and must be quickly processed. Once processed, they’re packed in dry ice and kept at an ultra low temperature. The next day, a courier would pick up samples and drive them 700 miles to the Botswana Harvard Partnership Lab in Gaborone.

With his work done for the day, Keo joined the other RAs sitting in plastic chairs outside the trailers—their equivalent of an employee lounge. The temperature was still in the 90s, with little shade. The team was in good spirits after their month in Shakawe. In a few days, they would have to move to a village hundreds of miles away, find new places to live, and begin
knocking on doors again.

But for now the team was enjoying their accomplishments in Shakawe. When planning the study, Shakawe and Gumare, its paired village 80 miles away, were expected to be the most challenging because of their remoteness and ethnic diversity. Counter to expectations, the team had done well here, finishing early and over quota. They had now completed 13 of the 15 pairs of villages in the Baseline Household Survey.

Though work at the start of the study had been harder than anticipated as procedures were being worked out and systems refined, the team could now appreciate how much they had adapted and how well they worked together. That evening, Keo and the Shakawe team would join their Gumare colleagues for a goat roast and celebration.

Research Nomads

Each of the two field teams consists of 16 RAs, seven drivers, two supervisors, two lab assistants, and two IT assistants. Team members come from across Botswana. In addition to Setswana, many of the RAs speak other local languages. They range in age from early 20s to late 30s. Many of them worked as HIV counselors before joining the team.

When the team arrives in a new village, each member must find his or her own meals and lodging. Though there’s help from the advance team, basically it’s a scramble to quickly get settled and begin work. Most team members rent a room or rondavel in the village.

Conditions can be difficult in rural villages, with no showers and water only from a shared tap. The constant uprooting can be stressful. Crime can be a problem. Often there is poor cell phone reception so keeping in touch with friends and family is hard. The team will be on the road for the better part of three years. Several RAs have recently married. Many have partners and children they rarely get to see.

In Gumare, one of the RAs, Neo Kelapile, was bitten by a dog when she entered a house. The local clinic was out of rabies vaccine, as were the surrounding villages. The BCPP staff called Maun, the tourist center 150 miles away. Surprisingly, no vaccine was available there either. To work effectively, the rabies vaccine must be given soon after a bite. Neo and a driver ended up making a 10-hour drive to Francistown to get a dose at a private clinic. They brought the remaining two doses back to Gumare in a cooler. At the time, Neo was eight months pregnant. (She delivered a healthy baby girl a month later. She and her daughter are doing fine.)

“They’re living in an environment that is very challenging,” said Dr. Mompati Mmalane, Co-
chair of the BCPP Community Engagement Working Group.

Along with challenges, there are rewards. The RAs have a strong sense of the contribution they’re making to end the HIV/AIDS epidemic in Botswana. They’re also getting to know their country in a way that few others experience.

When senior BCPP leaders from Gaborone or Harvard make a field visit and witness the RAs’ sense of purpose and camaraderie, the leaders often leave with a renewed sense of their own mission.

At the goat roast that evening to celebrate the team’s accomplishments in the furthest village in the study, Molly Pretorius-Holme, a BCPP leader visiting from Boston, addressed the group. “I’ve been involved with this project from the beginning. We’re all looking forward to the data at the end and the science that’s going to come out of it, but the real action is here now with the care and the dedication you have for the jobs that you do.”
A BCPP truck with loudspeaker broadcasts in Shakawe.
GREETINGS TO YOU ALL!

When the field team arrives in a village, loudspeakers announce the start of the study.

Our people! Greetings to you all!

We are members of the Ya Tsie study which you might have heard about already at a recent Kgotla meeting or have read about it in the flyers posted in different places in your village. This is to let you know that we have arrived in this village and this is the beginning of the study. We are here to invite and encourage you to, first, spread the message about the study. Secondly we encourage you to take part in this study whose purpose is to come up with measures which can stop the spread of HIV in the society. Your village is amongst the 30 villages in Botswana which have been selected to take part in the study we are here for.

Good people! We all know that HIV is ravaging this country. We are perishing. Funding for treatment is not like an ever-flowing spring! If we are not doing anything, time will come when the money will not be enough or gets totally finished. That is why the three parties, the Ministry of Health Botswana, Centers for Disease Control from the United States of America and the Harvard University also from United States of America, came together to come up with ideas of the study we are talking about called Ya Tsie.

You are therefore informed that the study team will start visiting you in your households and we kindly request your participation. The testing is voluntary and it will be done in your homes. The testing is done in private. I would like to emphasize: You will be tested in private.

We kindly request your positive reception!
THE TROUBLE OF FINDING PEOPLE AT HOME
Adapting to a Mobile Society

The Botswana equivalent of knock knock is ko ko. For the Botswana Combination Prevention Project field team, trying to contact family members of the 20% of randomly selected households in each village is their biggest challenge.

Adults of selected households are invited to participate in the Baseline Household Survey (BHS). Those who are HIV-negative are then invited to become part of the HIV Incidence Cohort that will establish the number of new infections that occur over the course of the study.

By randomly selecting which households will be visited, researchers control for the bias that easily finding people at home would have. It’s possible that people who are often absent from home are different in some ways relevant to the study from people who are usually present, making it even more important to reach and enroll people who are initially absent.

Working Hours

A number of factors influence when people are at home. The typical workweek in Botswana runs from 7:30 to 4:30, Monday through Friday. The team quickly realized that their hours would look nothing like that. Their task was to
enroll 16- to 64-year-olds. Many of the people they found at home during working hours were young children or the elderly. The optimal time to reach adults was early evening or weekends. The team adapted accordingly, working mostly in the early evening and on weekends.

By protocol, a Research Assistant (RA) will make three attempts to reach each adult in a household. Depending on the size of the household, that could mean returning a dozen times, interviewing and testing one or more people, then returning again to reach other family members. RAs use cell phones, notes, and word of mouth to reach those who are missing.

**Seasonal Migrations**

In Botswana, people move with the seasons. To reach villagers in this highly mobile society, the team must time their campaigns for when most of a community will be in residence. If they arrive during certain seasons, they’ll miss important segments of the population.

“Each part of Botswana has different cultures, different ways of doing things for economic survival,” said Kutlwano Mukokomani, Operations and Project Manager for the BCPP. “Normally, we have three settlements, maybe four.” For example, he said, “I have where I stay, my home village. Then I have the lands where I plow; I’ll relocate and stay there through the plowing season. And then I have where I raise cattle—my cattle post. I also can go there sometimes.”

The village of Shakawe, located on the Okavango River, has a fishing season, a season for harvesting grass for thatch roofs, and the tourist season, during which many villagers leave to work at tourist lodges.

Knowledge of and respect for local cultures are essential to the study’s success. The team’s schedule relies heavily on guidance from in-country leadership. Despite the challenges of enrolling adults for the study, in late 2015 the team met their targets for the Baseline Household Survey (BHS).
Team meeting at the BHP with (left to right) One Pharatthathe, Kutlwano Mukokomani, and Dr. Tendani Gaolathe
THE INNER LIFE OF A COMPLEX CLINICAL TRIAL
Real-Time Challenges in the Real World

Sent: October 30, 2013
Subject: YA TSIE-In the Field

Hi,

This is to confirm that the “YA TSIE Study - The Botswana Combination Prevention Project” is underway and the team deployed today 30th October in the field at both Ranaka and Digawana. While there have been challenges and some initial delay in study initiation, it is with great confidence in the team and their ability to rise up to challenges that I am confident this shall become one of BHP’s blue chip studies. I wish the team success and God’s Speed as they roll out this immensely challenging study.

Joe
Dr. Joseph Makhema
C.E.O. Botswana Harvard AIDS Institute

Evolving Guidelines

It was the first week of June in 2015. The BCPP leadership team was stressed. There were even more conference calls than usual. Two upcoming events could change the course of the trial. The first was a June 11th meeting of the Data Safety Monitoring Board (DSMB) at the National Institutes of Health (NIH) in Bethesda. The second was the July meeting of the International AIDS Society (IAS) in Vancouver.

In May, preliminary results from the Strategic Timing of Antiretroviral Treatment (START) Trial had been announced. START was designed to determine the best time for HIV-infected individuals to begin antiretroviral therapy (ART). The trial was stopped early because the data showed a strong benefit to starting ART in all HIV-infected individuals as soon as they were diagnosed, regardless of their CD4 count. CD4 cells are white blood cells that play a major role in protecting the body from infection.

Before the START results, there had always been a question about the risks versus benefits of long-term ART treatment for people who felt healthy and had a high CD4 count. With decisive evidence from START, there was widespread speculation that the World Health Organization (WHO) would now recommend a policy known as Universal Test and Treat (UTT), in which all people with HIV start ART as soon as possible. UTT would be simpler to implement, require less monitoring, be good for individuals, and also be good for a community—people put on treatment earlier would be less likely to infect their partners.

Because the strong START results could be used as a justification to alter existing HIV trials, there was a possibility that the DSMB would stop the Botswana project, but there were also good reasons why they wouldn’t. The WHO hadn’t yet changed guidelines, and even when they did, many countries wouldn’t have the money or resources to implement a UTT strategy.

In 2013, the WHO had changed guidelines to recommend initiation of ART in all HIV-infected adults with CD4 below 500 (cells in a cubic millimeter of blood), up from their prior recommendation of 350. Botswana national guidelines were still at 350. In April 2016, Botswana’s Ministry of Health was expected to move to 500. Now there was a question
of whether they would skip 500 and move straight to UTT. Before making that decision, the Ministry would have to consider issues of cost, infrastructure, and competing healthcare needs—including trauma, cancer, and heart disease.

The BCPP team had anticipated the change to 500 and already implemented the change in their study protocol. “If we’re testing a strategy that isn’t keeping up with where the standard of care is headed, it will no longer be an ethical, relevant or useful study,” said Dr. Shahin Lockman, a Harvard investigator. But the START Trial being stopped so early was a surprise to the research community. “In HIV the new data and standard of care change more rapidly than we can often keep up with,” said Lockman. “Some of it should be anticipatable, other elements are not. But you’re also paralyzed if you don’t start a study because you’re waiting for more relevant information to come in.”

Every time a change is made to the BCPP, the study protocol must be amended and then reapproved by both the Botswana and the CDC Institutional Review Boards (IRBs). Every change involves a time-consuming, bureaucratic process.

At the June 11th meeting, representatives of all the BCPP partners crowded into an NIH conference room. Lockman and Dr. Max Essex, Principal Investigator of the BCPP and Chair of the Harvard AIDS Initiative (HAI) were there. The DSMB asked the team to look into moving to UTT, but there was no discussion of stopping the trial. The BCPP would help determine whether widespread rapid implementation of treatment was a possibility. Its findings would provide much-needed guidance for expanding large HIV treatment programs. Within a few years, the BCPP researchers hope to provide what Lockman calls “the strongest possible evidence to people who decide how to spend billions of dollars.”

At the Vancouver meeting in July, the WHO announced they would now recommend a policy of UTT.

**Everything Changes**

“You can’t just design a study and make an assumption that a year or two later you’ll be doing the same thing,” said Essex. “You have to allow for the possibility that the study has to be completely redesigned to get information that will be valuable.”

Besides adapting to new research findings, the team must also contend with the different institutional cultures of each of the BCPP partners. Harvard, the CDC, and Botswana’s Ministry of Health must all coordinate...
schedules, data, and communications to serve a common purpose. “This is a large and complicated study with multiple partners working across different continents and time zones on different components of the overall effort, so communication and rapid decision-making are challenging, especially with the levels of oversight and regulatory review that are required,” said Lockman. “Being quick and effective in making changes is a challenge.”

**Prevalence & Power**

A large trial like the BCPP must be flexible, while at the same time maintaining statistical rigor. If reality in the field proves to be markedly different from assumptions made in the original study design, the team must adjust in real time. The BCPP biostatisticians constantly monitor data from the field and make adjustments as necessary.

In some villages, for example, the actual HIV prevalence was found to be much higher than the 28% anticipated when the protocol was written. Rates in a few villages were as high as 40%. This meant that in a high-prevalence village, the field team had to test more people than originally anticipated in order to meet their targets for uninfected adults. The process of interviewing, testing, and counseling one person can take several hours. The additional interviews meant that the team remained in a village longer than expected and began work in the next village later than originally scheduled.

In addition to field conditions differing from models, biostatisticians must also contend with changes in the protocol. Though the BCPP study population is over 100,000, the biostatisticians must make sure that, after changes, their study size is still large enough to show statistical significance.

“The biggest problem with a study like this is that you need a lot of people involved to get the statistical power to see a clear difference for the effect that you’re seeking,” said Essex. “If the study has to be changed so often because of new developments and better ways of treating or different ethical standards, then the challenge becomes even greater.” Results from BCPP should be available in 2018.
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