Botswana Leads in HIV Treatment

Billions of dollars are spent every year on HIV/AIDS treatment programs. But how well are they working?

In the African country of Botswana, where 25% of adults (aged 16-49) are HIV positive, the answer is extremely well. In a recent paper in The Lancet HIV, researchers showed that Botswana is close to reaching the ambitious UNAIDS 90-90-90 goals.

In 2014, UNAIDS proposed new testing and treatment targets directed towards ending the AIDS epidemic: by the year 2020, 90% of all HIV-infected people would know their HIV status; 90% of those diagnosed with HIV would be on antiretroviral therapy (ART); and 90% of those on ART would have a suppressed viral load (very low levels of HIV in their blood). A growing body of research shows that providing ART to people living with HIV, besides being good for their own health, lessens their chance of transmitting HIV to others.

Researchers Surprised

The data for the paper was taken from the Botswana Combination Prevention Project (BCPP), an on-going clinical trial designed to measure how well a package

The Blood in the Freezer

One tiny vial of blood contains a remarkable amount of genetic information about both the person from whom it was drawn and infectious agents like HIV circulating at the time of the needle prick. Because HIV mutates so quickly, having access to lots of samples to study is a valuable resource. “It’s a diamond for science,” said Sikhulile Moyo, Laboratory Manager at the Botswana Harvard AIDS Institute Partnership (BHP). He was referring to the blood samples banked in the BHP freezers. “Specimens would be a more accurate term,” he corrected, “biological samples freely given to be processed for diagnosis or disease monitoring.”

Over 1.5 million specimens are stored at the BHP headquarters in Gaborone, Botswana. Most are blood samples collected from tens of thousands of patients who have participated in BHP clinical trials over the past 20 years. Besides blood samples, the biorepository also includes specimens of hair, tissue, breast milk, and other bodily secretions.

The samples were collected for one reason: to end the HIV/AIDS epidemic. Botswana has one of the highest rates of HIV in the world with about 25% of adults infected. When the BHP was established in 1996, hospitals were overcrowded with very sick AIDS patients. There was no available treatment. Death, often agonizing, was the expected outcome.
Botswana Leads in HIV Treatment

From left: Lyrilumun Uhaa, UNICEF; Michel Sidibé, UNAIDS; Max Essex, Harvard AIDS Initiative; Pride Chigwedere, UNAIDS, at a meeting for African Leaders in Addis Ababa. Photo by Aida Muluneh

This is significant work as it provides further evidence that UNAIDS 90-90-90 treatment targets are both realistic and achievable.

Michel Sidibé, UNAIDS Executive Director

“Remember that the set-up of the Botswana national health system is that 95% of all people are within five-kilometer access of a healthcare facility,” said Dr. Tendani Gaolathe, BCPP Project Director and first author on The Lancet HIV paper.

“In Botswana, there’s been dedicated governmental action at the highest level to take responsibility for the epidemic. Healthcare, including antiretroviral treatment, is free for all citizens in the country,” said Essex. “The government has also sought international cooperation with us and others to get the latest advice and the best understanding of what can be done.”

Attainable & Meaningful

When the UNAIDS 90-90-90 targets were first announced, many in the international community questioned whether they were achievable, especially by 2020 in resource-strapped countries with a high burden of HIV. The findings from Botswana indicate that the targets are attainable.

“The targets are definitely more than bureaucratic goal posts,” said Essex. “It’s clear that rates of new infections will go down dramatically as a result of reaching these goals.”

Why Botswana?

According to a recent analysis of HIV treatment programs, no country has yet met the overall UNAIDS goals. Very few countries, including the U.S., have come close to Botswana’s coverage.

Why has a middle-income African nation with a high HIV prevalence been able to create a more successful HIV treatment program than richer Western countries?

of HIV prevention measures reduces the rate of new infections. Researchers at the Harvard AIDS Initiative (HAI) and their colleagues at the Botswana Harvard AIDS Institute Partnership (BHP) are responsible for the design and evaluation of the project.

Adults aged 16 to 64 were recruited from a random sample of 20% of households in each of 30 Botswana villages. Participants answered questionnaires and were tested for HIV. The data collected from the BCPP is among the most complete population-level estimates of HIV available for southern Africa, the epicenter of the AIDS epidemic.

Of the 12,610 participants surveyed, 3596 (29%) were infected with HIV. Of those individuals, 2995 (83%) already knew their HIV status. Among those who knew their status, 2617 (87%) were receiving ART. Of the 2609 individuals receiving ART who had a verifiable viral load test, 2517 (96%) had a suppressed HIV viral load.

For a national HIV treatment program to achieve viral suppression in 96% of patients on ARVs is considered exceptional. The high rate was a surprise, even to the researchers.

“I thought it would be very good, by which I would have said 90% or so. I was surprised that it was as high as 96%,” said Max Essex, Senior Principal Investigator of the BCPP and Chair of both HAI and BHP.

This is significant work as it provides further evidence that UNAIDS 90-90-90 treatment targets are both realistic and achievable.

Ibid.

The BCPP is funded by the President’s Emergency Plan for AIDS Relief (PEPFAR), through the Centers for Disease Control and Prevention.
In 2002, Botswana’s Ministry of Health launched a national antiretroviral program to provide free AIDS drugs to eligible citizens. The BHP played an important advisory role in planning, implementing, and monitoring the program. BHP clinical trials evaluated different drug regimens. Samples in the freezers come from those trials and others that followed. Today, with proper treatment, people living with HIV can expect to live a nearly normal life.

“What we have in the freezers is a history of the AIDS epidemic in Botswana,” said Moyo. There are blood samples from across the spectrum of the epidemic: from studies in the 1990s before the national program, to studies of treatment-naïve patients beginning drug regimens in the 2000s, to current studies of sero-converters—people recently infected with HIV.

**Freezers**

Though each sample is small in size, storing over a million samples becomes an issue. The BHP currently houses 70 freezers at headquarters. The majority of samples are kept in big freezers at close to -80°C, but viable cells used for immunological studies are stored in liquid nitrogen tanks at -140°C.

Each big freezer costs about $25,000, weighs 805 pounds, and can hold 24 steel racks of 2000 separate vials for a total of 48,000 samples. Each sample is bar-coded with a unique identifier. Descriptive information such as date and time of collection, study identifier, and specimen type is stored in an electronic inventory system that links to non-confidential demographics such as the age and sex of the participant. Samples are anonymized, meaning personal information such as name and address has been removed.

Because the samples are irreplaceable, efforts are taken to ensure their safety and integrity. The freezers are equipped with a temperature monitoring system connected to the internet, a mobile phone network, and a security company.

Freezers are expected to last ten years or longer, but disasters happen. If a freezer breaks down in the middle of the night, Moyo is awakened by a text and a phone call. If he’s not available, the security company works its way down a list of key staff contacts, with Dr. Joseph Makhema, CEO of the BHP, last on the list. Whoever responds must quickly move samples to a reserve freezer the BHP is required to have available at all times. When the power fails, a back-up generator keeps the freezers cold.

**Shared Access**

The stored samples are useful not only for the BHP, but for the global HIV/AIDS research community. When a study participant signs a consent form allowing the use of his or her sample for a specific research study, the participant has the

BHP lab technicians store cell samples in liquid nitrogen tanks at -140°C. Photo by Dominic Chavez
option to sign a second consent form that allows the unused portion of the sample to be used for future HIV research.

In addition to BHP scientists and students, researchers from other countries can request samples for their HIV studies. If the study doesn’t overlap with work already underway and an ethics review board approves the study, samples will be packed and shipped, as they have been to South Africa, Great Britain, the U.S. and Canada.

“BHP acts as the custodian,” said Moyo. “This resource is open to other scientists as long as their research has been approved.” Though scientists have a reputation for being highly competitive, AIDS researchers have a history of working together. Most large HIV/AIDS studies are collaborative efforts across institutions and countries. “At BHP, we can try to chew the pie,” said Moyo, “but we definitely need others to help us chew the pie.”

“The samples are valuable because they represent a unique population of HIV-infected people at different stages of the epidemic,” said Max Essex, Chair of the Harvard AIDS Initiative and the Botswana Harvard Partnership. “These samples can be used to address a range of research questions, from how much the virus might have evolved over the last 20 years to how the epidemic itself has changed over that time.”

spotlight

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Sikhulile Moyo

A native of Zimbabwe, Sikhulile Moyo moved to Botswana after completing his undergraduate degree at the University of Zimbabwe, Harare in 1996.

He started working at the Botswana Harvard Partnership as a Lab Assistant in 2003 and was promoted to Laboratory Coordinator, then Deputy Lab Manager, then to his current position as Lab Manager.

He holds Master’s degrees in Applied Microbiology and Public Health. In a few months, he’ll complete his PhD in Medical Virology from Stellenbosch University, South Africa. For his thesis, “Evolutionary trends and dynamics of HIV-1C in Botswana,” he used new molecular and serological methods to identify and characterize early founder viruses. And, yes, the samples for his research came from the BHP freezers.

Moyo is happily married and has two sons and a daughter. He and his wife sponsor several children, both relatives and non-relatives, at a school each year. He loves singing, composes gospel songs, and is recording his second album.

“I wake up daily inching towards pursuing my goals with vigor and relentless commitment,” said Moyo. “Working with scientists and mentors at BHP has made me realize that every moment is a great moment for action.”

HAI

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.

visit our website www.aids.harvard.edu
“Data! Data! Data!” he cried impatiently. “I can’t make bricks without clay!”
Sherlock Holmes

Science depends on data. A large clinical trial like the Botswana Combination Prevention Project (BCPP) depends on lots of data. When the multi-year trial in 30 Botswana villages concludes, researchers hope their data will provide a better understanding of how to prevent HIV infections.

To assure that the data is as reliable as possible, every bit of BCPP information is captured electronically. Though your doctor’s office may still be transitioning from pencil to keyboard, the BCPP field team uses laptops exclusively. “Going to paper is not an option,” said Erik van Widenfelt, Director of Data Operations and Information Technology at the Botswana Harvard AIDS Institute Partnership (BHP), who designed a system to capture, store, and access the enormous amount of data being generated.

Electronic & Local

In the planning stages, BCPP leaders looked into purchasing an off-the-shelf data management system, but couldn’t find an affordable system that met their needs. Erik took on the task. He recruited six local computer-science graduates to help with the software design. Using open-source code, the team developed a flexible data management system for complex clinical trials.

Research Assistants (RAs) used to gather information on paper forms. That information would be keyed into a computer by a data entry person, usually weeks later at an entirely different location. The process was vulnerable to error. In a pilot study, Erik developed a data management system that allowed RAs to enter information directly into a laptop, eliminating both the paper forms and the errors that accompany them.

The BCPP protocol is complex with lots of rules to follow. Most study interviews take place inside people’s homes, not in the controlled environment of a clinic. Babies may be crying, dogs barking, music playing. Chaos or not, RAs are tasked with following a strict protocol. Erik’s team designed an easy-to-use tool that guides RAs through the interview process.

“Our RAs have to be good at dealing with people—talking to them about the importance of knowing their HIV status or participating in the study,” said Erik. “If we find someone who’s good at counseling and dealing with people, we’ll make sure that person—as long as they’ve got enough fingers to hit the keyboard—can operate the system.”

The software itself drives the process. As an RA enters data into a laptop, the system directs next steps. If a participant answers a question one way, required information fields and follow-up questions appear. Answers must be entered before continuing to the next step. The system guides RAs through the process, allowing them to concentrate on the participant and keeping the conversation as comfortable as possible.

Fast & Accurate

After completing household visits for the day, RAs head back to two trailers parked outside a local clinic. The trailers serve as the field team’s base of operation in a village. When the RA is within a 15-meter radius of the IT trailer, the laptop automatically connects to the secure Wi-Fi network broadcasting from the trailer. Data synchronizes off the laptop and uploads onto a server. (continues on page 6)
If we find someone who’s good at counseling and dealing with people, we’ll make sure that person—as long as they’ve got enough fingers to hit the keyboard—can operate the system.

Erik van Widenfelt

At the mobile lab, the RA hands over the small tubes of blood from study participants. The Lab Assistant, viewing a screen with the data just downloaded from the RA’s laptop, reconciles the tubes with the data and prints a barcode label for each tube.

The lab is equipped with a centrifuge to separate whole blood into buffy coat and plasma. Erik’s system indicates which tubes need processing and generates a packing list for loading tubes into a cool box. Several times a week, a driver picks up the cool box and delivers it to BHP headquarters in Gaborone.

In the middle of the night, when RAs are hopefully sound asleep, data on the server in the IT trailer is transmitted to a server at BHP headquarters. The next morning, Drs. Unoda Chakalisa and Etienne Kadima, the BCPP Study Coordinators in Gaborone, review the data to see what’s going on in the field and make any necessary adjustments.

When the driver delivers the cool box to BHP, samples are again reconciled. HIV+ samples are tested for viral load. Most samples are stored in BHP freezers. Some are sent to the Essex Lab in Boston for genetic analysis.

The time difference between Gaborone and Boston is six hours. When she arrives at her Harvard office, Nealia Khan, the BCPP Data Manager, accesses new data on the BHP server in Gaborone. Data is encrypted at this and every other step of the process. Nealia cleans the data and creates reports for conference calls.

“That means that when we have weekly calls, we have up-to-date information,” said Erik. “On a Wednesday, we have Tuesday night information. That’s how good it is.”

The BCPP data management system demonstrates that high-quality research data can be collected quickly across a large geographic area. In the past, it took months or years for a study of this magnitude to have data ready for publication. The BCPP does it in days. “As we shift from paper-based to electronic collection, that interval just keeps shrinking,” said Erik.

“It’s been extremely important to modernize data collection, efficiency, and quality,” said Max Essex, Senior Principal Investigator of the BCPP and Chair of the Harvard AIDS Initiative and the Botswana Harvard Partnership.

INFO FOR GEEKS

The BCPP DMS is a suite of Python modules that extend the Django framework for clinical trials research. All code is open-source, updated daily, and available on GitHub. Researchers designing complex clinical trials are welcome to use and customize the code for their studies.

FLOW OF BLOOD AND DATA
Erik van Widenfelt

When he first arrived in Botswana, Erik wasn’t an IT guy. After graduating from the University of Michigan with a degree in cellular and molecular biology, he joined the Peace Corps in 1986 and taught science and English in Ghanzi, a dusty outpost on the edge of the Kalahari Desert. When his two-year assignment was up, he stayed on.

“I wanted to continue teaching, to grow the reading program I had started, and to give the school a bit of continuity,” said Erik, who comes from a family of teachers. He taught kids in their early teens. Many had trouble with basic reading skills. The school library was full of books—John Grisham novels, old encyclopedias, books in Afrikaans—books with little relevance to his students’ lives.

Erik worked with the headmaster to purchase books his students could read and enjoy. “I developed in them the habit to read a book successfully, even if it was easy, and let them work their way up to more challenging books.”

He taught for another three years, then moved to the capital, Gaborone, where he worked for the Botswana Book Centre, developing software for their book ordering and inventory systems. Though Erik had learned some programming at the University of Michigan, his computer skills are largely self-taught.

He got married and started a family. His oldest son is named Oarabile, which in Setswana means He has answered; his brother is Moratiwa, meaning He is loved.

A few years later, Erik left the bookstore to start his own computer business. In 2000, the Botswana Harvard AIDS Institute Partnership (BHP) hired him as a consultant. AIDS was on the rise in southern Africa. People at many of the companies Erik worked with were getting sick and dying. In 2001, as the BHP began their first large clinical trials, Erik

What is Data Cleaning?

Data cleaning is the process of detecting and correcting bad records in a data file. Much of the early BCPP data came from a baseline household questionnaire. Research Assistants (RAs) interviewed thousands of study participants and recorded their answers on laptops. The use of customized software minimized data entry errors.

As data was collected, Nealia Khan, the BCPP Data Manager, cleaned it using the following steps:

Confirm that data exists and conforms to expectations.

Does the file contain information in the right format with the approximate number of records expected? For example, does the batch of data contain information from several hundred study participants from a pair of villages in Botswana?

Reconcile discrepancies in answers from study participants.

For various reasons, study participants don’t always tell the truth. They may misunderstand a question, misremember past events, or feel obliged to offer socialy acceptable answers.

It’s not the RA’s job to question a participant’s memory or integrity.

Well-designed questionnaires include redundancy to help verify responses. The same question may be asked several times in different ways. For example, if a participant says she has never been tested for HIV, yet has her own prescription for HIV drugs, then a “logic-check” would flag her answers.

Derive variables from raw data.

A variable is derived using questionnaire answers and other available information.

Take ART status—whether a participant with HIV is on antiretroviral treatment (ART). If a participant says he’s not on ART, but records at the local clinic show he once had a prescription for ART and a suppressed viral load, it’s possible he stopped taking his medication. The team investigates further to determine if he’s a treatment defaulter.

After the data has been cleaned, investigators begin their analysis.
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.

Answering important questions often necessitates the creation of new tools and systems. Because they work at the forefront of AIDS research, HAI scientists must invent and adapt and repurpose on a daily basis. This issue of Spotlight delves into the infrastructure behind the studies, as well as notable findings from the Botswana Combination Prevention Project.

(continued from page 7)

was offered a full-time position. Since then, he’s been responsible for coordinating all research data.

“He understands what’s needed for large field studies when you don’t have access to internet or electricity,” said Max Essex, who has high praise for the data management system Erik created for the BCPP. “He understands the importance of collecting high-quality data and then assuring that it’s accessible and analyzable by a variety of people with varying degrees of expertise.”

“I’m grateful to Max for giving me a lot of space and support to run with my ideas,” said Erik. “Peace Corps was similar. We were expected to be creative and trusted to be productive with limited resources.”

Because all BHP research projects depend on access to data, Erik’s job can be exhausting, with long and stressful days. To balance work, he plays drums, often performing with bands around Gaborone. “Music requires thought and effort, but is different enough from my work that it’s a wonderful distraction,” he said. “No circuits or software in a drum set!”

Yet there are similarities between computer science and percussion. As Erik explained, “Data management, like drumming, is a supportive activity. People don’t usually appreciate how important these efforts are until something goes wrong.”