From Terrorist Cells to Sexual Networks: Modeling Complex Systems

Fresh out of the University of Pennsylvania, Ravi Goyal was recruited by the National Security Agency (NSA) for its rapidly expanding Counter-Terrorism Unit. The year was 2002. Ravi went to work as an Applied Research Mathematician, using his exceptional math and computer skills to analyze how information flowed within and between terrorist networks.

But it wasn’t all sitting at a desk. During the Iraq War, he was embedded in an intelligence unit in Baghdad, assigned to find new ways to utilize information. “It was important to see not just data, but how it was coming in,” said Ravi. “That really impacts how you view it and how you want to use it and the uncertainties and errors that come with various kinds of collections.”

In the Botswana Combination Prevention Project (BCPP), researchers led by Max Essex are conducting a large-scale evaluation to determine if combining several HIV (continues on page 4)
What does it mean to control HIV at a ‘community level’?

Within an individual, we know the processes by which cells get infected, virus replicates, and antiretrovirals (ARVs) interfere with that process. We need similar kinds of models at the community level that describe transmission across individuals. The goal is to learn at the community level what we’ve learned over the decades about individual therapy: how to optimize treatments and tailor them to individual characteristics. We need to know what the community-level factors are that affect the impact of prevention interventions in order to use the results of BCPP in designing prevention strategies for Africa.

How is the BCPP different from previous clinical trials to prevent HIV infections?

Individual-level trials have produced a lot of very important information, but don’t tell us all we need to know. They provide useful information about reduction of an individual’s risk of HIV infection (or transmission), but the trials don’t tell us how to control the HIV epidemic at a community level. It’s like if you’re fighting a war, you need to know how individual weapons work and what they’re useful for, but to win, you have to know how to put them all together.

What will we learn from the BCPP?

By the end of this study, we should be able to say whether combination prevention methods, including treating all highly viremic patients, can bring about a major reduction in HIV infection in villages in Botswana. We’ll also learn what level of coverage of interventions is needed at the community level to achieve targets for HIV incidence reduction. We know that at the individual level HIV treatment works well. But we also know that if patients don’t take their ARV medications as directed, it can do them more harm than good. We need to understand what kind of community-level compliance with an intervention program is needed for the program to succeed, and how this level depends on the HIV dynamics within the community.

What is the definition of success for the BCPP?

The study is designed to have an impact of reducing HIV incidence [new infections] by 50% in the intervention communities compared to the control communities. But what’s most important is that the epidemic be made unsustainable in the communities where the intervention is offered. In other words, the community by itself could not sustain an epidemic. New cases will arise from contacts outside the community. But if the epidemic were not sustainable within a community, and if all surrounding communities got the intervention as well, then we should be able to control the epidemic in ever-larger geographic units, and ultimately in entire countries that receive interventions. This must be the primary goal of HIV prevention research.
Growing up, Victor wanted to be a physicist. “When I was young, I saw a movie by Frank Capra about cosmic rays and became fascinated with radiation. When I was a little older, I found a book about special relativity written by a Russian physicist. All of the examples were about a train going from Moscow to Leningrad. Between the exoticism of Einstein’s ideas and the exoticism of the train between Moscow and Leningrad, I was hooked.”

After majoring in physics at Brown, though, Victor realized he didn’t want to spend the rest of his life in a physics lab. He earned a graduate degree in bioengineering, tried medical school, and taught high school math for a year. He came to HSPH in 1976 to pursue a Master’s in Epidemiology, found his calling, and never really left.

Victor started work on his ScD in Biostatistics at HSPH just as the AIDS epidemic was taking hold. He graduated, and after a Fulbright year in France and a postdoc, he joined the HSPH faculty in 1987. He now works on HIV/AIDS research in the U.S. and internationally.

Victor’s research focuses on developing statistical methods to address the natural history of HIV and the impact of treatment and prevention methods. He served as the Director of the Statistics and Data Analysis Center of the Adult Project of the AIDS Clinical Trials Group (ACTG) during the crucial period in which highly active antiretroviral treatment (HAART) was developed. He is the Co-Principal Investigator on the Botswana Combination Prevention Project (BCPP), a clinical trial that combines several HIV prevention methods to try to significantly reduce the rate of new infections within communities.

“Victor’s great strength is statistical techniques, but he also knows how to ask important questions,” said Max Essex, Chair of the Harvard AIDS Initiative and Principal Investigator of the BCPP.

Victor bikes to his office at HSPH and spends his days teaching, meeting with students, and conducting research. He also contributes to the design and analysis of Harvard AIDS Initiative studies and clinical trials, ensuring they are statistically rigorous.

The most rewarding aspect of his job, he says, is training doctoral students, “getting them involved in real-world problems and in identifying and addressing the statistical challenges that arise in solving them.”

Biostatistics seems to be the perfect fit for Victor— it’s mathematically challenging, but also involves a lot of collaboration. “I guess I like it in the same way that I prefer bridge to chess,” said Victor. “It just seems to be a lot more social.”
prevention measures can significantly reduce the number of new infections within a community.

As part of the project, Ravi and his colleagues are building a computer model that creates a simulation of how the AIDS virus spreads within a village. This new model, one of the many innovative aspects of the BCPP, will allow researchers to measure how effectively their interventions are working.

Gathering information is the first step in building a model. In the BCPP, information will be collected from tens of thousands of people over the course of several years, resulting in billions of bits of data. The data comes from a number of sources, including extensive testing for HIV and lab tests from people who are infected.

Demographics, such as the fact that about 25% of the adult population of Botswana has HIV, are fed into the model, as is knowledge gained from previous HAI studies like the Mochudi Prevention Project.

Most new HIV infections in Botswana are from sexual contact. Though researchers can’t actually observe the sexual network, they use several methods to get a glimpse of it.

Questionnaires from study participants provide detailed information, such as number of sexual partners, length of relationships, and knowledge of partner’s HIV status. Participation in the study is voluntary and all information is confidential.

As enormous amounts of data are collected, the model gives researchers a way to organize and interpret it. Members of the BCPP biostatistics team, led by Dr. Victor DeGruttola, use algorithms and mathematical techniques to simulate the complex biological evolution of a disease within an individual, while simultaneously modeling how the HIV virus moves from one person to another along an evolving sexual network.

The BCPP model must deal with a constantly changing situation on the ground. In the clinical trial, two processes are operating over time. One is the spread of new HIV infections throughout the community; the other is the roll-out of HIV prevention interventions within the community.

As the trial unfolds, more and more people will be tested for HIV. Testing will get more people on antiretroviral treatment (ART). Once an individual is on treatment, his or her viral load drops,
as does the chance of transmitting HIV to a partner.

Along with increased testing and treatment, there will be a roll-out of voluntary male circumcision, which has been shown to reduce transmission of HIV by over 50%. Condom distribution and other prevention measures will also be increased.

As information is added, the model evolves. It will be able to provide preliminary assessments about the effectiveness of the interventions. “We want to know early on whether or not the trial looks as though it’s succeeding,” said DeGruttola. “The model will allow the team to make mid-course corrections if necessary.”

Researchers are also using viral genetic sequencing of new infections to learn how closely related new infections are to other infections within a community. This is somewhat like a paternity test for HIV, showing whether new infections are related to known infections. Viral genetic sequencing will not only provide information for the model, it will also serve as a check to measure how accurately the model reflects what’s actually happening on the ground.

Conducting the BCPP on the ground in Botswana is an enormous scientific and logistical challenge. The project involves tens of thousands of participants and hundreds of doctors, nurses, counselors, and staff to follow them over the course of several years.

Using the model, researchers can explore a number of options that would be too expensive to test in the real world. “It wouldn’t be practical or ethical to run a whole bunch of experiments over and over again on a group of people,” said Ravi, “but a model allows us to test different kinds of interventions and how they would work under various conditions.”

The results of the BCPP could provide the first real example of how to systematically end the AIDS epidemic in Africa.

The state-of-the-art computer model being developed will be adaptable for use in other countries that have different HIV infection rates or different social conditions.

Ravi is just finishing his PhD and will stay on as a postdoc. It turns out that working on the AIDS epidemic is not entirely different from working on terrorist networks. “You want to see how they evolve,” said Ravi, “and you want to see how you can break them apart.”

The results of the BCPP could provide the first real example of how to systematically end the AIDS epidemic in Africa.
Cell Phones & Sexual Networks

Harvard AIDS Initiative researchers are hoping to use data from cell phones to better understand sexual networks in Botswana villages.

The Botswana Combination Prevention Project (BCPP) will deliver a combination of HIV/AIDS prevention measures to 15 villages in Botswana to try to dramatically reduce new HIV infections. Villages receiving the intervention will be compared to 15 control villages that are similar, but receive standard HIV care. The goal of the BCPP is to significantly reduce new HIV infections at a community level. Success will be measured by how sharply the rate of new infections declines within entire villages.

Unlike a laboratory experiment in which conditions can be tightly controlled, the BCPP is a large clinical trial in the real world. And the real world is messy. Though people are more likely to have sexual partners within their own village, a certain fraction of relationships will likely occur across the villages, potentially leading to relationships that couple individuals from treatment and standard of care villages. If lots of people have relationships across the villages, the effect of the BCPP interventions will be diluted and become harder to measure. Researchers have to estimate how much social and sexual mixing takes place between villages and adjust their statistics accordingly.

In an innovative study, Dr. J.P. Onnela hopes to examine data from cell phone companies to measure how much mixing occurs between villages. Onnela has a PhD in Computational Science and did a postdoc at Harvard under Dr. Nicholas Christakis, a leader in social network research.

Botswana has one of the highest cell phone usage rates in Africa—about 115%. In other words, the number of cell phones is greater than the number of citizens. Onnela, working with Drs. Vlad Novitsky and Tianxi Cai, plans to use phone data to investigate the social integrity of the villages in the BCPP. Two major cell phone operators have agreed to share data if the project gets funded.

The phone companies would turn over anonymous information about phone calls and text messages; no personal identifiers would be included. “We would know that person A lives within a certain geographical area and makes phone calls to 15 other people, 10 of whom reside within that area and 5 outside of it,” explained Onnela.

Though obviously people don’t have sex with everyone they call, phone usage is a good proxy for quantifying social interactions. “We’re not predicting sexual relationships at the level of individuals,” said Onnela. “Rather we want to understand to what extent two villages are socially intermixed.”

“We hope the project can give us the tools to understand how closely and how strongly different groups of individuals are connected and intermingled,” said Onnela. “If we can understand the extent of mixing, we can learn how effective different treatments really are.” The idea of using cell phone data to study social networks in an HIV cluster-randomized trial is a new idea. Like most untried

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Seven Steps to End the Epidemic

To continue the conversation beyond the AIDS@30 meeting last December, symposium leaders wrote Engaging to End the Epidemic: Seven Essential Steps Toward an AIDS-Free Generation. The authors, all experts in their fields, offer provocative recommendations for a global AIDS response.

Published in JAIDS, the supplement was launched at the AIDS 2012 conference in Washington, D.C this July.

Email us at EngagingtoEndtheEpidemic@hsph.harvard.edu for a free copy.

President of Liberia Visits BHP

This May, President Ellen Johnson Sirleaf of Liberia visited the Botswana Harvard AIDS Institute Partnership (BHP) as part of a five-day official visit to the Republic of Botswana. She met with the BHP leadership team and was given an overview of HIV/AIDS treatment and prevention in Botswana. She praised BHP’s work as a model for how African nations can successfully address the AIDS epidemic. President Sirleaf received an honorary Doctor of Laws from Harvard in May 2011. In October 2011, she was awarded the Nobel Peace Prize.

Alexander McCall Smith Advocates on Behalf of HAI

“Max and his people have changed the lives—saved the lives—of so many people. Anybody here who’s in a position to support the Harvard AIDS Initiative, I can think of no greater cause, no worthier cause, than that.”

Alexander McCall Smith, best-selling author of The Ladies No.1 Detective Agency Series, at a benefit reading for HAI at the Brattle Theatre in Cambridge.

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

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Here’s the likely story: One hunter in central Africa got an infection from butchering chimpanzee meat just as colonization was changing the social structure of Africa. The infection spread to others, slowly at first, until it expanded into today’s worldwide HIV/AIDS epidemic, with over 33 million people currently infected.

HIV spreads through social/sexual networks. To end the epidemic, researchers must understand how the virus moves within a community and use that knowledge to prevent new infections. In this issue of Spotlight, we look at how the Botswana Combination Prevention Project is taking an innovative, community-wide approach to AIDS prevention.