

THE BEGINNING OF THE END OF AIDS?

Harvey Fineberg

To mark the 30th anniversary of AIDS, Harvard convened an international symposium in December, AIDS@30: Engaging to End the Epidemic. Leading researchers, activists and government officials from around the world gathered to discuss what we have learned from AIDS and how to apply those lessons to end the epidemic. Dr. Harvey Fineberg, President of the Institute of Medicine and former Dean of the Harvard School of Public Health, presented a summary of the first day's proceedings:

From the outset, AIDS evoked and exposed both the best and the worst in the human condition: on the one side, fear, bigotry, stigma, distrust, hatred, and despair; and on the other side, love, compassion, caring, trust, community, and hope. Over the years, the good has gained on the bad—there is greater reason for hope today than ever before. We have come to understand that a unified community is the foundation for success against even the most dreadful conditions.

You do not have to wait until success is inevitable to begin the struggle to succeed.

Over the years, the HIV experience has dissolved many traditional boundaries and separations. We heard today that prevention and treatment are no longer being distinguished, instead being viewed as one and the same in terms of ultimate purpose—to improve health. We've also seen a reduced separation between population health for rich and poor countries, thanks to the efforts of so many in this room and around the world.

We've heard that policy making in the United States has been transformed because of HIV/AIDS. AIDS activism changed the way drug policy was made in the United States, and it changed the way the National Institutes of Health embark on clinical trials. AIDS changed the way science, medicine, and public health are conducted in this country.

At a time when ideology is such a powerful divider, it is worth remembering that AIDS commands attention across the political spectrum. We heard from President Clinton at the beginning of our meeting, and we had today a wonderful announcement from President Obama, yet it was President George W. Bush's administration that inaugurated the PEPFAR Program. This is one area where, despite the ideological separation in our country, people have been able to work together toward a common goal of humanity.

But we must not let the silver linings distract us from the severity, the enormity, and the ferocity of the problem. At the Battle of Fredericksburg, Robert E. Lee remarked to his generals, "It is well that war is so terrible lest we should grow too fond of it." While we benefit from the sense of community that AIDS has created, cherish the friendships, celebrate the scientific progress, and delight in clinical advances, we must always remember that our goal is to end the need for all these things. The question this conference poses is, "Have we simply reached the end of the beginning, or are we prepared to make this the beginning of the end for AIDS as a major health threat?"



Photo by Amy Hart

You do not have to wait until success is inevitable to begin the struggle to succeed. When the Human Genome Project began in 1990, it was unimaginable, but it wasn't easy or cheap, or even certain. It took 13 years, and it consumed \$2.7 billion. By the end of the Human Genome Project, it was possible to do the same job in three to four months for \$20,000. Today, we are on the threshold of the \$1,000 genome. Yet it was the willingness to make the initial investment that made possible all of the progress in capacity and efficiency that has brought us to where we are today.

In a similar way, we must strive to end the AIDS epidemic while facing uncertainty and expecting high cost, but with the conviction that we have enough tools available to accomplish the task with a unified effort. In another 30 years, at the AIDS@60 symposium, we can dare hope that the largest group present will be historians because AIDS will be a story of the past. As we depart from this gathering, let us resolve to make the future of AIDS its history. ●

MOLLY PRETORIUS HOLME: THE NECESSARY QUESTIONS

It was in a medical anthropology class at Mt. Holyoke College that Molly Pretorius Holme began asking the kind of questions that influence her work at the Harvard AIDS Initiative (HAI).

“In our culture we take for granted scientific premises like germ theory,” said Molly in a recent interview. “You have to think about how this translates into other settings when you’re trying to initiate life-saving public health measures yet the underlying beliefs about what causes illness may be completely different from your own.”

After graduation Molly joined HAI to pursue a career in international health. She soon became Managing Editor for the second edition of *AIDS in Africa*, a comprehensive scientific book with over 100 co-authors. “It

the Vaccine Initiative, she worked in a trailer near the construction site. “We’d hear the jackhammers going, but we’d also often hear people singing as they worked,” remembered Molly. “The power went out a lot and the phones didn’t always work, so we had a lot of technical challenges.”

One of the first tasks the Vaccine Team undertook was to conduct a Vaccine Preparedness Study to determine whether it would be feasible to conduct a large-scale trial in Botswana if a promising vaccine candidate became available.

At the time, conducting clinical trials was a new concept in Botswana. “We had to answer basic questions,” remembers Molly. “Can we recruit and retain people at risk of acquiring HIV to be in a vaccine trial? Can

sure people understood that this was just the first step in a really long haul,” said Molly.

The Vaccine Team had to work out how to get informed consent from participants, making sure volunteers understood what was expected of them and what the research objectives and risks of the trial were. Generally speaking, people in Botswana are less focused on individualism than in America. There is a strong belief that “no one can be human alone.” The team had to allow for volunteers to talk to ministers, parents and families and then come back to sign the consent form. Informed consent became a community act.

Villafana, who led the work, remembers Molly’s contributions. “I thought of her as my right-hand person. She has the rare ability to multitask and both pay attention to detail and maintain quality. She’s the one who just rolls up her sleeves and gets the work done.”

Molly returned to Boston in 2002. While continuing to work at HAI, she earned her Master’s in epidemiology from the Harvard School of Public Health. Her thesis addressed the issue of how to get honest answers in a clinical trial.

Participants in research studies often lie, especially when they’re asked about high-risk sexual behavior. They lie because they’re embarrassed or afraid of being criticized. In a recent microbicide trial in South Africa, 79% of women reported they had misinformed trial interviewers at least once.

“I’m interested in ways to get more truthful answers to questions that really matter when you’re trying to figure out if your intervention worked,” said Molly. She designed a study to determine if participants would give more honest answers if a machine asked the questions, rather than a human. “You re-



Photo by Hermann Bussmann

Left: Molly with a cheetah in South Africa, 1999; Right: Molly at a scientific meeting in Botswana, 2010

was like a crash course on what’s going on in the epidemic,” she said.

In 2001 Molly moved to Botswana and became Project Manager of the HIV Vaccine Initiative. The headquarters and laboratory for the Botswana–Harvard Partnership were still being built. Along with Max Essex, Chair of HAI, and Tonya Villafana, Site Director of

we get good data when we’re asking people very personal questions about their HIV risk? And culturally, is this going to fly?”

Obtaining community trust and support was essential to the project. The Vaccine Team established a Community Advisory Board to guide researchers on how to educate the public. “We had to make

move the bias introduced by people wanting to please," Molly explained.

Molly's current job at HAI is managing the Botswana HIV/AIDS Clinical Trials Unit (CTU). The goal of the CTU, funded by the U.S. National Institutes of Health, is to answer as many research questions as quickly and efficiently as possible. Clinics in the Botswana cities of Gaborone and Molepolole conduct several clinical trials at once, while similar clinics in other countries conduct the same HIV/AIDS trials.

Working closely with Max Essex, Principal Investigator of the Botswana CTU, Molly provides logistical and operational oversight for all trials. The Botswana CTU is currently conducting eight clinical trials and working to open four more this year on topics ranging from the safety of drugs for treating HIV-infected children to how best to treat people co-infected with HIV and TB.

Molly keeps everything running, from funding, to complying with federal regulations, to communicating with Botswana's Ministry of Health, to coordinating weekly conference calls where researchers determine which trials to do next. "Molly is one of the most capable people I know," said Essex. "She has a unique combination of personality, intelligence and energy."

"Each study has a completely different cost-per-patient," said Molly. "Working with an annual budget of several million dollars to pay for a fluctuating number of trials, each with different requirements for personnel, lab testing, and technology, I'm doing a juggling act all the time. How do we react when one study enrolls more, or fewer volunteers than anticipated? I'm constantly trying to figure out how to move the money around to make it match what's actually happening on the ground."

Though the doctors and scientists are usually the ones in the spotlight, the success of HAI's clinical trials program is largely due to Molly Pretorius Holme. She asks the necessary questions, and often, through dedication and hard work, provides the answers herself. ●

USING HIV VIRAL LOAD TO GUIDE TREATMENT-FOR-PREVENTION INTERVENTIONS

In a paper published in the March issue of *Current Opinion in HIV & AIDS*, HAI researchers Max Essex and Vlad Novitsky provide evidence that HIV-1 RNA load can guide treatment-for-prevention interventions to slow the AIDS epidemic.

Some HIV-infected individuals maintain increased levels of HIV-1 RNA load after acute infection for an extended period of time. These people can disproportionately contribute to the spread of HIV in the community. The level of HIV-1 RNA load is the major predictor of HIV transmission. HIV-infected individuals who maintain increased levels of HIV-1 RNA transmit the virus at higher rates.

Antiretroviral treatment (ART) decreases HIV replication, thus reducing rates of virus transmission. The recent HPTN 052 study demonstrated a 96% efficacy for initiation of early ART in HIV-1 serodiscordant couples (in which one partner is infected with HIV and the other is not).

Identifying people with a high viral load

JOSEPH E. BROOKS

We sadly note the passing in January of Joseph E. Brooks, a longtime supporter of HAI and a member of our International Advisory Council (IAC).

According to his obituary in *The New York Times*, Mr. Brooks "doubled the size of the Lord & Taylor chain and made its flagship New York store a showplace of spectacle, including elaborate retail stagecraft and a daily morning rendition of 'The Star-Spangled Banner.'"

Victoria Brooks Stafford, his daughter who now serves on the IAC, said that Mr. Brooks' commitment and dedication to finding a cure for HIV/AIDS is best summarized by a quote from Winston Churchill, whom he loved. "A man does what he must—in spite of personal consequences, in spite of obstacles and dangers and pressures—and that is the basis of all human morality." ●



and placing them on ART could be an effective strategy that has the potential to achieve both individual benefits by lowering the risk for early onset of clinical AIDS and public health benefits by reducing HIV transmission.

The Botswana–Harvard Partnership is currently conducting a clinical trial in the Botswana village of Mochudi to test the effectiveness of identifying and treating individuals with a high viral load. If successful, the approach used in the Mochudi Prevention Project could be used widely to control the HIV/AIDS epidemic. ●

spotlight

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Excerpt from *The Genome Generation*

In her new book, *The Genome Generation*, journalist Elizabeth Finkel explores what we've learned in the ten years since the complete sequencing of the human genome. Her chapter on HIV/AIDS features Dr. Max Essex, Chair of HAI, and his work examining the genetics of the people of southern Africa, where the epidemic has hit hardest.

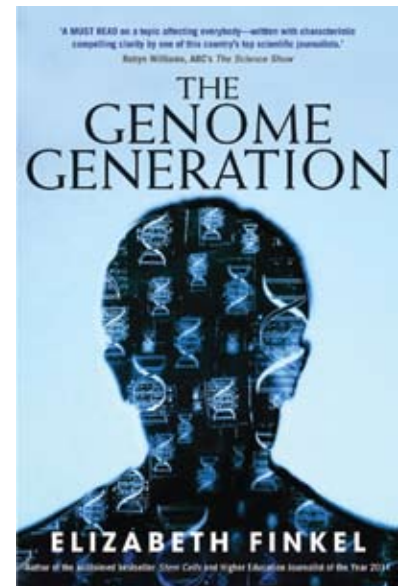
When it comes to human genetic variation, nowhere is it greater than across Africa.

This is where the family of man began some 200,000 years ago. The diverse races of Africa represent thick gnarled branches growing out in different directions from the trunk of the family tree. They have had hundreds of thousands of years to diversify. By contrast, the people who populate the rest of the world are all recent offshoots of one branch. They show far less genetic diversity.

So it is not hard to imagine that the genes of Africans might be very different from those of Europeans or Asians when it comes to susceptibility to HIV. Small-scale studies from Harvard Botswana and others have already shown that to be true. For instance, the CCR5 $\Delta 32$ gene variant that Steve O'Brien found to reside in about 10% of Europeans is entirely absent from the African population. Africans also miss out on the HLA C protective variant and another one called ZNRD1. And it turns out that a gene variation that protects them from malaria—DARC—may predispose them to HIV infection.

Given these inklings of difference, Essex told me, 'I think it would be derelict not to examine the genetics of the people.' His notion that genes hold part of the answer to AIDS in Africa has already started to provide some dividends for people in Botswana, as I discovered on my visit to Harvard Botswana in February of 2008. ●

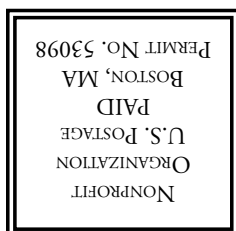
To read a longer excerpt, visit our website: www.aids.harvard.edu.



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