ANTIRETROVIRAL THERAPY PROTECTS UNINFECTED PARTNERS

96% reduction in HIV transmission

Researchers involved in a large multinational study recently announced that men and women with HIV who take antiretroviral drugs have a 96% lower risk of transmitting the virus to their sexual partners. The study results, just published in *The New England Journal of Medicine*, were hailed by AIDS experts as a game-changer.

Until now, antiretroviral therapy (ART) was known to improve the health of HIV-infected patients, but this is the first randomized clinical trial to show that treating an HIV-infected individual with ART can reduce the risk of sexual transmission of HIV to an uninfected partner.

The clinical trial, conducted at 13 sites in Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, the United States, and Zimbabwe, was scheduled to end in 2015, but the findings were released early because the treatment worked so well.

"This new finding convincingly demonstrates that treating the infected individual—and doing so sooner rather than later—can have a major impact on reducing HIV transmission," said Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID), one of the study funders.

The study, known as HPTN 052, was conducted by the HIV Prevention Trials Network (HPTN), a global partnership dedicated to reducing the transmission of HIV. The study began in April 2005 and enrolled 1,763 HIV-serodiscordant couples (in which one partner is HIV-infected and the other is not).

The Harvard AIDS Initiative (HAI) was part of the trial and enrolled 77 couples. Dr. Max Essex, Principal Investigator for the Botswana arm and Chair of HAI, commented, "The results provide tremendous rationale for our Mochudi Prevention Project now underway that links treatment and prevention efforts. Strategies for scaling up knowledge of HIV status and increasing treatment coverage are critical next steps to realizing the public health benefits of this finding."

FIRST FULBRIGHT–FOGARTY FELLOWS IN BOTSWANA

For the first time this fall, the Botswana–Harvard Partnership (BHP) will host two Fulbright–Fogarty Fellows. The program, sponsored in partnership with the National Institutes of Health (NIH), was established to promote the expansion of research in public health and clinical research in resource-limited settings. The first two fellows are Tessa LeCuyer and Dr. Ryan Davis.

New Fellows at BHP: (left to right) Dr. Ryan Wells, Tessa LeCuyer, Victoria Maiswe, Dr. Ryan Davis. LeCuyer and Davis are the BHP's first Fulbright–Fogarty Fellows.

Tessa LeCuyer, age 26, spent her early years in northwestern New Mexico, where her parents worked as lawyers on a Navajo reservation. She attended Tufts University, where she majored in French and Biology and was captain of the equestrian team. After college she worked at the Harvard-affiliated Immune Disease Institute. She just completed her third year of veterinary school at Washington State University.

At the BHP, LeCuyer will be working on a project to validate the accuracy of tests for the incidence of new HIV infections in cross-sectional studies. "This is important because error rates in these tests vary among populations and have not yet been established in Botswana," said LeCuyer.

(continues on back page)

First Fulbright–Fogarty Fellows in Botswana *(continued from page 5)*

After her Fulbright–Fogarty year, LeCuyer will finish veterinary school and may pursue a PhD. She hopes to work as both a clinician and scientist.

Dr. Ryan Davis, age 27, received his BA in English and Chemistry from Georgetown University. His undergraduate volunteer work at the Whitman-Walker HIV clinic inspired interests in health disparities, infectious diseases, and cross-cultural medicine. He earned an MPH from Johns Hopkins Bloomberg School of Public Health and an MD from the Medical School for International Health, a Columbia University-affiliated program at Ben-Gurion University in Beer-Sheva, Israel.

At the BHP, Davis will study methods to optimize a pooled PCR technique to cost-effectively identify HIV cases in the earliest stages of infection when the viral load and risk of transmission are high but standard antibody tests can give a false-negative result.

spotlight

is published by the
HARVARD SCHOOL OF PUBLIC HEALTH AIDS INITIATIVE
651 Huntington Avenue, 6th Floor
Boston, MA 02115

Phone: 617-432-6106
Fax: 617-432-4545
Email: mshenry@hsph.harvard.edu
Web: www.aids.harvard.edu
Chair: Dr. Max Essex
Executive Director: Dr. Richard Marlink

PUBLICATIONS STAFF
Editor: Martha Henry
Print & Web Designer: Kim Dostaler
Thanks to: Kim Armstrong, Andy Redd, Iain MacLeod, Raabya Rossenkhan, Lendsey Melton, Iva Siler

In this issue...

spotlight

summer 2011

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

HAI
Harvard School of Public Health
AIDS INITIATIVE
651 Huntington Avenue
Boston, MA 02115
USA

NONPROFIT
ORGANIZATION
U.S. POSTAGE
PAID
BOSTON, MA
PERMIT NO. 53098

HAI spotlight
summer 2011
HARVARD SCHOOL OF PUBLIC HEALTH AIDS INITIATIVE

SURPRISE FINDING IN THE NEWLY INFECTED

In a paper published this April in *AIDS*, HAI researchers found that a significant number of people recently infected with HIV-1C, the HIV subtype predominant in southern Africa, maintain a high level of HIV (viral RNA) in their blood and semen for a much longer period than was expected. About 34% of people infected with HIV-1C maintain a high viral load for 100–300 days; 19% maintain a high viral load for 200–400 days. Viral load is the chief predictor of the risk of heterosexual transmission of HIV. The study subjects were from Botswana and South Africa.

The finding was a surprise. Earlier research done on HIV-1B, the subtype predominant in the U.S. and Western Europe, found that most recently infected individuals maintained a high viral load for several weeks, rather than many months or a year. After the initial infection, known as the acute stage, a person's viral load drops as the body's immune system subdues the virus and reaches what is called a viral set point. The set point can remain relatively stable for years before it climbs and a person develops full-blown AIDS.

The new finding may help explain why the AIDS epidemic is so much worse in southern Africa than elsewhere in the world.

The new finding may help explain why the AIDS epidemic is so much worse in southern Africa than elsewhere in the world. People in the early stages of HIV infection are not yet stricken with AIDS-related illnesses. If they feel healthy and don't change their behavior, "that puts them in a very hot spot for transmission of new infections," said HAI scientist Dr. Vladimir Novitsky, who led the study. "People with a high viral load are more likely to infect their sexual partners. If their viral load remains high for a longer period of time, they may infect more partners, increasing the number of new HIV transmissions."

New knowledge also brings new opportunities. Most people in southern Africa with acute HIV infection and a high viral load do not qualify for antiretroviral treatment (ART) because their other health indicators, such as CD4 count, have not fallen to dangerous levels. Antiretroviral drugs are extremely effective at dropping a person's viral load. Putting all individuals with a high viral load on ART could prevent new infections and have a profound effect on the epidemic. This is the premise behind HAI's Mochudi Prevention Project, now underway in a village of 40,000 in southern Botswana.

"The hypothesis is that a small fraction of people with a high viral load are responsible for the majority of new transmissions in the community," said Novitsky, who is working with HAI Chair Dr. Max Essex on the Mochudi Prevention Project. "If a person's viral load is dropped with ART, that person stops being a potential transmitter, which would greatly benefit the community."

Photo by Ryan Louis Hurley

Q&A | Max Essex

IS AFRICAN AIDS DIFFERENT?

Besides trying to the find the most effective methods to treat and prevent HIV/AIDS, Dr. Max Essex, Chair of the Harvard AIDS Initiative, has been trying to understand why southern Africa is the epicenter of the epidemic. According to the *2010 UNAIDS Report*, 22 million of the 33 million people living with HIV live in sub-Saharan Africa. In South Africa the adult HIV prevalence is 17.8%, with an estimated 5.6 million people living with HIV. In three other southern African countries, the national adult HIV prevalence rate now exceeds 20%. These countries are Botswana (24.8%), Lesotho (23.6%) and Swaziland (25.9%). *Spotlight* Editor Martha Henry asked Essex about what he and his HAI colleagues have learned.

(continues on page 2)

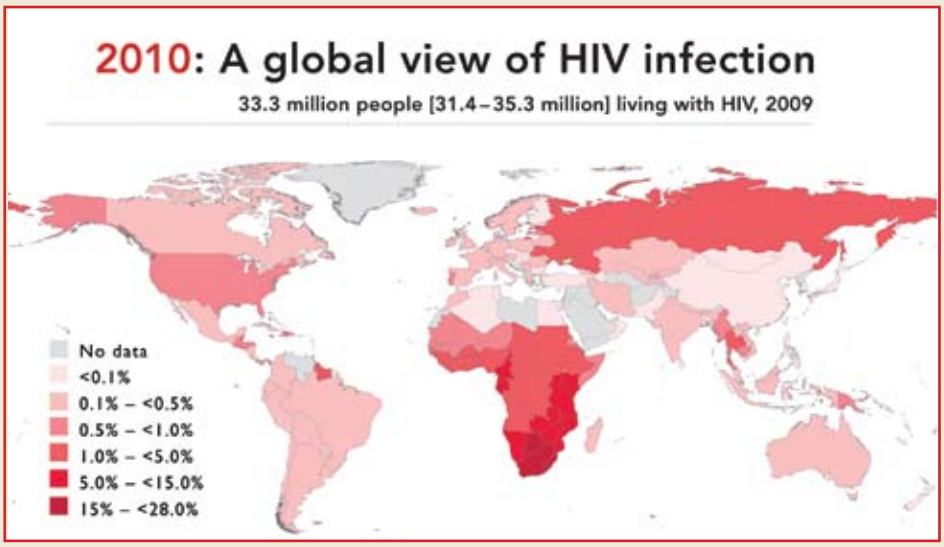
Spotlight: Your recent paper in *AIDS* showed that about 30% of people acutely infected with HIV-1C, the subtype predominant in southern Africa, maintain a high viral load for a much longer period than was expected. People with a high viral load have a much greater chance of infecting a partner. Does this finding explain why the AIDS epidemic is much worse in southern Africa than elsewhere? Is this the smoking gun that researchers have been looking for?

ESSEX: Researchers don't like to use terms like "smoking gun" because we're wary about raising expectations higher than other people might interpret as justified based on the evidence. But yes, it's certainly the most logical way to explain why the epidemic in southern Africa is much worse in terms of total number of people infected than the epidemics anywhere else in the world.

How can you tell if the severity of the epidemic in southern Africa is due to a biological difference in HIV-1C rather than behavioral differences in people, such as social migration patterns or concurrent (overlapping) sexual partners? Is it possible to tease apart whether it's biology or behavior or some combination of the two?

ESSEX: In wanting to find an explanation for the severity of the epidemic in southern Africa, we thought a difference in the virus was a logical place to look. Admittedly I'm a virologist, so I think of the virus first.

I have no doubt that behavioral issues like the absence of circumcision and multiple concurrent partnerships can contribute to higher rates of infection, but I think the explanation that makes the most sense is that those differences are in addition to the virus's ability to spread based on viral load. Behavioral factors may make spreading or transmission worse, but without this significant difference between viruses, they just increase transmission by 50 or 100%, not five-fold, the way the differences really are in southern Africa versus other parts of Africa.



Source: UNAIDS

Unlike the AIDS epidemic in the U.S., which is predominantly among men who have sex with men and are infected with HIV-1B, the epidemic in southern Africa is predominantly a heterosexual epidemic with both men and women infected with HIV-1C. Why the difference?

ESSEX: The difference in transmission ratios with respect to viral subtypes that I think is clearest to document but hardest to explain is why HIV-1B, the subtype that caused the epidemic in the U.S. among gay men and IV drug users, doesn't have much of an ability to infect women any place in the world. There's no evidence that I'm aware of anywhere—South America, Haiti, etc.—that HIV-1B has had the same degree of efficiency in infecting women as any of the major viral subtypes that have caused the heterosexual epidemic in Africa.

And so what I would predict is that, for whatever reason, HIV-1B doesn't get produced in cervical vaginal fluids or female reproductive tract fluids or infect through cells of the female reproductive tract as well as does HIV-1C, the subtype predominant in southern Africa. It's that ability, the ability of the virus to infect cells in the reproductive tract, especially the female reproductive tract, that I think would be different with the different viruses.

PROFILE

DR. VLADIMIR NOVITSKY: TRYING SOMETHING ELSE

Like a lot of boys growing up in the Soviet Union in the 1960s, Vladimir Novitsky wanted to be an astronaut. While his counterparts in the U.S. idolized John Glenn, his hero was Yuri Gagarin, the first man to successfully orbit the Earth.

Novitsky comes from a scientific family. His mother was a microbiologist and his father a gynecologist. Perhaps because of parental influence, medicine eventually won out over space exploration and Novitsky enrolled in medical school in the Ukrainian city of Odessa.

Following medical school, he worked as a virologist at an Odessa biotechnology company that produced a herpes simplex vaccine for the entire Soviet Union. After a few years, Novitsky left for Moscow to get his PhD in virology.

In 1992, he was appointed as a Senior Scientist at the new Southern Ukrainian AIDS Center, where he supervised HIV diagnostics in 33 screening laboratories and provided major contributions to HIV/AIDS epidemiology in the region. "HIV was not very prevalent at the time, but it was scary because there was no treatment and stigma was huge," said Novitsky. "In Odessa, HIV was associated with injection drug users. It exploded from almost nothing to very high because people shared injection equipment—10 to 15 people used the same syringe."

Dr. Vladimir Novitsky (right) advises PhD student Raabya Rossenkhan.

With the dissolution of the Soviet Union in the 1990s, funding for scientific endeavors was severely cut. There was little money to maintain laboratories or buy imported reagents used in the most basic research. "It was a frustrating time," said Novitsky.

In 1994 he won a local competition through the British Council to work in London for a year at the Central Public Health Laboratory. While there, Novitsky continued studying the molecular virology and immunology of HIV, as well as the management and maintenance of large HIV reference laboratories.

A young Novitsky at work in the Ukraine

He arrived in Boston in 1996 to work as a Research Fellow in the laboratory of Dr. Max Essex, Chair of the Harvard AIDS Initiative. It was an opportune time. That same year, Essex had gone to Botswana and brought back blood samples from people infected with HIV. Though AIDS was ravaging the country, until then almost no HIV/AIDS research had been done in Botswana. Back in the lab in Boston, Novitsky was involved with isolating and sequencing viral DNA from the first Botswana samples.

After an agreement was reached to establish the Botswana–Harvard Partnership (BHP), Novitsky, working with Mary Fran McLane, helped to design the Botswana–Harvard HIV Reference Laboratory in Gaborone. His experiences in Odessa and London gave him an ideal background for setting up the new lab and training the scientists and technicians who would work there.

Essex was impressed with Novitsky's quiet energy and intelligence and worked to keep him at Harvard. "Vlad is very bright, but he also has deep knowledge and commitment," said Essex. "Having him in the lab is a blessing. We learn a lot from each other."

Novitsky was appointed as a Research Scientist at the Harvard AIDS Initiative in 2000. He became a U.S. citizen in

(continues on page 4)

Profile: Dr. Vladimir Novitsky *(continued from page 3)*

2005. Today he holds the title of Principal Research Scientist and is a mainstay of the labs in Boston and Botswana.

He is working to understand why the AIDS epidemic is so much worse in southern Africa than elsewhere, as well as how to control the virus. He was the first author on HAI's recent paper on acute infection that found that about 25% of people infected with HIV-1C, the virus predominant in southern Africa, maintain an initial high viral load for much longer than expected. (See cover story.)

Like most senior scientists, Novitsky spends little time actually running experiments in the lab. His days are spent analyzing data, writing papers, and applying for grants. He supervises the lab technicians and works closely with students and visiting scientists, helping them to identify and design research projects.

Dr. Simani Gaseitsiwe received the benefit of Novitsky's mentorship when he worked as a research assistant at the BHP in 2000. Novitsky taught him the basics of biomedical research, inspiring Gaseitsiwe to pursue his PhD at the Karolinska Institute in Sweden. Gaseitsiwe now oversees laboratory research activities at the BHP; his mentor has become his colleague.

Gaseitsiwe credits Novitsky with teaching him how to deal with the frustrations inherent in laboratory research. "Part of the training is that you make mistakes. Things don't always turn out the way you expect them to—that's part of the research process," said Gaseitsiwe. "Once you reach that moment when things do work, then you really feel the joy. It wouldn't be as exciting if it worked all the time. Then what would be the challenge?"

Raabya Rossenkhan, a PhD student in molecular biology, understands those challenges. **"**Vlad helps you look at things in different ways. He'll push you to ask a question more specifically, to make your inquiry more scientifically robust," she said. "If something isn't working, he usually says, 'Try something else. And if that doesn't work, try something else.'"

For Novitsky, helping students mature as scientists is one of the rewards of his work. "I enjoy seeing their growth," he said, "and seeing them develop from being completely clueless about a problem to becoming creative thinkers."

MICHELLE OBAMA IN BOTSWANA

Photo by Ann Bookbinder

When she arrived in Gaborone on June 24th, First Lady Michelle Obama (right) visited an AIDS clinic to help children paint a mural. She then had lunch with AIDS activist and former Botswana Supreme Court Justice Unity Dow (left) and other women leaders. Dow gave Mrs. Obama a copy of her book *Saturday Is for Funerals*, co-authored with Dr. Max Essex, Chair of HAI. Mrs. Obama, accompanied by her daughters Sasha and Malia, also visited the village of Mochudi and Mokolodi Game Reserve.