HIV testing model first adopted in Botswana is now being recommended in the US

Only a few years ago Botswana had one of the highest HIV prevalence rates in the world. It was estimated that 57% of adults ages 15 to 49 in the country were HIV infected. In 2002 the government started a national treatment program to provide free antiretrovirals (ARVs) to all HIV-infected individuals in need, yet very few people were benefiting. By 2004 only 17,500 of the estimated 110,000 people in need—a mere 16%—were receiving treatment. Part of the reason for the poor uptake was that most people were never tested for HIV, so didn’t even know they were infected.

This all changed dramatically after Botswana introduced a routine HIV testing program, the first of its kind in Africa. Now a similar strategy is being recommended in the US as a way to identify those who are already infected and to enhance HIV prevention efforts.

Everyone agrees that conducting more HIV testing will have many benefits, the most obvious of which is identifying those who are HIV infected and promptly referring them to treatment and care services. Most researchers also concur that people who know their HIV status will be more likely to change their behaviors to protect either their partners or themselves from future infection. Such behavioral modification should result in fewer new infections. But many researchers, clinicians, and activists are carefully considering whether there is enough money and manpower in the US to ensure that the HIV-infected individuals identified through widespread testing will be connected with treatment programs. “We have to measure our success not just on the number of tests or diagnoses, but on how many people receive care and treatment,” says Jeffrey Levi, executive director of the public policy association, Trust for America’s Health.

Overcoming barriers

One of the greatest barriers to HIV testing in sub-Saharan Africa is the pervasive stigma associated with the virus. Another is the limited availability of life-saving medications. Research has shown that more people are willing to undergo HIV testing if they know they could be placed on ARV treatment. Fortunately, as ARVs become increasingly available in developing countries, more and more people are being tested for HIV infection. In South Africa the number of people undergoing voluntary counseling and testing (VCT) doubled between 2004 and 2005 when the government’s treatment program was introduced. Other African countries, including Lesotho and Malawi, are also expanding their VCT efforts. By the end of this year Lesotho will have completed an ambitious door-to-door VCT campaign that aims to offer each and every citizen an HIV test.

But in Botswana the link between treatment and testing did not seem to be working. Despite the government’s provision of free ARVs, only 70,000 HIV tests were performed in a country of 1.7 million people through mid-2003. In response President Festus Gontebanye launched a routine HIV testing initiative in January 2004 that meant everyone seeking healthcare received an HIV test unless they specifically refused. It was hoped that this approach would encourage more people to be tested by erasing some of the stigma associated with the disease. Making testing more commonplace also helps prepare communities for HIV prevention trials, like those for vaccines and microbicides, where volunteers must first be screened for HIV infection.

In Botswana, conducting more testing was also a way for healthcare workers to link HIV-infected individuals in need to the national treatment program. In just two years this initiative spurred significant progress. Shelia Tlou, the country’s health minister, reported that as of August 2006, 70% of those who need ARVs are receiving them from the government. Studies also indicate that routine testing is widely supported by the citizens of Botswana. Of 1268 adults interviewed for one study, 81% favored routine testing and the majority (89%) thought this approach would help eliminate the barriers to HIV testing.

Botswana’s dramatic turnaround was hailed as a great achievement by public health experts and many started touting this routine testing program as a model for other African countries. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) modified their HIV-testing guidelines, partly based on the results from Botswana, to recommend that other countries with high HIV infection rates introduce similar testing initia-
viral infection with the routine battery of medical tests reflects how far AIDS treatment has progressed in wealthy countries over the last 25 years. Although taking ARVs is still difficult because of unpleasant side effects, drug regimens are now much simpler and have, for the fortunate minority who have access to ARV therapy, turned AIDS into a chronic disease. Public health workers in the US are hopeful that treating the diagnosis of HIV/AIDS like other chronic diseases will help remove some of the stigma associated with the virus, as it seems to have in Botswana.

**We have to measure our success not just on the number of tests or diagnoses, but on how many people receive care and treatment**

Jeffrey Levi

Another reason for introducing a routine testing paradigm now is that testing more people has never been easier or cheaper. The advent of rapid HIV tests, many of which only require a drop of blood or a small sample of saliva, has made it easier for clinics to conduct more HIV tests and results can be provided much more quickly, sometimes in only about 20 minutes. Rochelle Walensky and her colleagues at the Epidemiology and Outcomes Research Group at the Center for AIDS Research, based at Harvard University, have shown that introducing routine HIV testing is now a cost-effective approach in all areas with HIV prevalence greater than 0.1%, which is true throughout the US.

**Counseling?**

A key concern among critics of the routine-testing model is that less emphasis will be placed on the pre- and post-test counseling that is a cornerstone of the VCT model. This counseling helps people learn more about HIV, how it is transmitted, and how they can reduce their risk of becoming infected or transmitting the virus to others.

Some argue that without pre-test counseling a person will be ill-prepared for the consequences of an HIV diagnosis and, since post-test counseling will probably only be provided to those who test positive for HIV infection, people who are not already infected would receive little education on how to reduce their risk in the future. Bernard Branson of the Division of HIV/AIDS Prevention at the CDC says the CDC’s initial goal is to target those who stand to benefit the most from HIV counseling. Research studies have documented how HIV counseling affects individual risk behaviors in those who test positive. The CDC itself conducted Project RESPECT in 1998, which found that consistent use of condoms was more likely in groups that received pre- and post-test counseling. Those who received counseling also had a marked decline in the rate of other sexually-transmitted diseases. There is little known, however, about the behavior differences between those who test positive or negative. “It’s very hard to find studies that look at the impact of counseling in people who test negative for HIV,” says David Holtgrave, professor in the department of health, behavior, and society at Johns Hopkins University.

Counseling for those who are not already HIV infected will become even more important in the future as other HIV prevention tools become available. If other options, like microbicides or drugs that can be taken to prevent HIV infection (see VAX May 2006 Spotlight article, Treatment as Prevention), are found to be effective, counseling will be an essential way to introduce the benefits and limitations of these approaches.

Even in the absence of other prevention tools, having people know whether or not they are HIV infected can help reduce the number of new HIV infections. Data indicates that HIV transmission rates among those who are aware of their HIV status (knowing whether or not they are infected) are around 2%, compared to 9-11% amongst people who are unaware they are infected. Consequently, routine testing has won praise by many in the public health field as a way to not only connect people to treatment and care services but also to improve HIV prevention efforts.
Treatment access

Ultimately, as in Botswana, the success of the CDC’s routine testing initiative will be measured by how many people are linked to treatment and care services. But many question whether clinics and the current funding systems in the US, like the Ryan White Care Act and the AIDS Drug Assistance Programs, are prepared to handle an influx of HIV-infected people. Statistics indicate that the majority of people with HIV are considered low income and are less likely to have private insurance, which might cover the yearly cost of ARV treatment—around US$12,000 to $15,000.

“We have a problem already,” says Levi. “We already have a lot of people diagnosed with HIV who aren’t receiving care.” He estimates that about 250,000 individuals in the US, who are known to be infected, are currently not receiving treatment. Adding another quarter of a million HIV-infected people into the system, many of whom may need treatment immediately, would require significantly more capacity and funding. The CDC argues that just identifying HIV-infected individuals isn’t in itself adding to the problem. “HIV infection eventually declares itself,” says Branson. “People need treatment whether or not they’re diagnosed.”

Without more funding some clinicians worry that the connection between testing and treatment will not be made and therefore more testing will do little to stem the number of new infections in the US. “We shouldn’t be looking for the needles in the haystack if we’re only going to throw them back in,” says Walensky.

Global News

Two new preventive AIDS vaccine trials initiated in Africa

In December researchers at the Karolinska Institute in Stockholm, Sweden and colleagues at the US Military HIV Research Program (USMHRP) and the Muhimbili University College of Health Sciences in Tanzania began a second vaccine trial to evaluate the safety and immunogenicity of administering immunizations of two vaccine candidates sequentially. This Phase I/II trial will enroll 60 volunteers in Dar es Salaam, Tanzania.

The first vaccine candidate is a DNA plasmid comprised of several HIV genes. This candidate is given as a prime immunization and then is followed by a booster immunization with a modified vaccinia Ankara (MVA) vaccine candidate also containing HIV genes. Neither candidate can cause HIV infection. The DNA vaccine candidate was developed at the Swedish Institute for Infectious Disease Control and is based on HIV strains circulating in Tanzania. The MVA candidate, known as MVA-CMDR, was developed by the US National Institute of Allergies and Infectious Diseases (NIAID) and is manufactured by the Walter Reed Army Institute of Research (WRAIR). The Karolinska Institute is also conducting another Phase I trial in Sweden evaluating the safety and immunogenicity of the MVA candidate alone in 38 volunteers.

Last year at the 2006 AIDS Vaccine Conference in Amsterdam, Eric Sandström of the Karolinska Institute presented preliminary results of another placebo-controlled, Phase I trial in Sweden where volunteers received the DNA and MVA candidates in a prime-boost manner. This combination induced promising immune responses in the volunteers without causing serious safety issues.

More recently the South African AIDS Initiative (SAAVI) and the HIV Vaccine Trials Network (HVTN), which is part of NIAID, initiated a second Phase Ib test-of-concept trial in collaboration with Merck to evaluate the company’s adenovirus-based vaccine candidate (MRKAd5). The trial is being called Phambili, which means ‘going forward’ in Xhosa, and will recruit 3000 volunteers in four South African provinces, including trial sites in Soweto, Cape Town, Klerksdorp, Medunsa, and Durban.

Another test-of-concept trial, known as the Step study, with the MRKAd5 candidate is currently ongoing at HVTN sites in the US, Canada, Peru, Dominican Republic, Haiti, Puerto Rico, Australia, Brazil, and Jamaica. South Africa is currently hosting other AIDS vaccine trials as well as other HIV prevention trials; however, the Phambili trial is the country’s largest AIDS vaccine trial to date. It also marks the first time Merck’s leading vaccine candidate is being evaluated in a population where the predominately circulating strain of HIV is not genetically matched with the antigens in the vaccine candidate (see VAX July 2006 Primer on Understanding HIV Clades). The epidemic in South Africa is primarily clade C HIV and the candidate is based on clade B. For more information about these or other ongoing preventive AIDS vaccine trials, visit the IAVI Report clinical trials database (www.iavireport.org/trialsdb) and the January 2007 Special Issue of VAX at www.iavireport.org/VAX/VAXJanuary2007.asp.
Why are HIV-specific neutralizing antibodies so difficult to induce with vaccination?

The human immune system uses many different types of defenses to combat pathogens such as viruses and bacteria, and these can be divided into two broad categories known as innate and adaptive immunity (see VAX February and March 2004 Primers on Understanding the Immune System). The innate immune responses are the first responders on the scene when the body encounters a new pathogen. They can either prevent an infection or limit it until additional help from the immune system can be rallied. Often this additional help is necessary and this is where adaptive immunity kicks in. Adaptive immune responses are customized to act upon a particular pathogen, such as HIV. These adaptive immune responses are further divided into two main branches—cellular and humoral immunity. Cellular immune responses are carried out by cells known as CD4+ T helper cells that orchestrate the activities of another group of cells known as cytotoxic T lymphocytes (CTLs) that can kill cells infected with a particular virus. Humoral immunity consists of cells called B cells that generate antibodies, which are Y-shaped protein molecules that can latch onto specific viruses and thereby block them from infecting cells.

Why are antibodies important?

Many types of human cells need to replicate or make copies of themselves. When a virus first enters the body it infects human cells and hijacks the machinery the cell normally uses to replicate and instead creates more copies of the virus. These viruses can then infect even more cells, setting off a vicious cycle of infection. With HIV, this has an especially disastrous effect because the primary cells infected by the virus are those of the human immune system and as they are infected and destroyed the immune system begins to break down.

Both cellular and humoral immune responses can stop this cycle by preventing HIV from infecting more cells, but they act at different stages. CTLs target cells that are already infected with the virus, while antibodies act on the virus before it enters the cell. A virus and a cell are like two puzzle pieces that fit together, but when an antibody attaches to the virus it comes between the two, blocking them from connecting. The HIV puzzle piece is the virus’s envelope protein, also known as gp120. The cellular piece of the puzzle is the CD4 receptor protein on the surface of the CD4+ T helper cells, the primary target of HIV. The receptor protein is what HIV attaches to and uses to gain entry into the cell.

Since antibodies could stop a virus like HIV in its tracks, or neutralize it, they will be a particularly important component of a future AIDS vaccine candidate that could prevent people who are exposed to HIV from becoming infected. Many existing vaccines—including those against measles, hepatitis A and B, and polio—work because they induce virus-specific antibodies that are capable of protecting against infection.

Not all antibodies are created equal

To learn more about the types of antibodies that are produced in response to HIV, researchers have closely analyzed the immune responses in HIV-infected individuals at various times during the course of their infection. They have found that many types of HIV-specific antibodies are produced by the humoral immune system, but very few of them are capable of actually binding to the virus and neutralizing it. Those select few antibodies that can successfully stop the virus from infecting cells are known as neutralizing antibodies. Antibodies that can effectively neutralize many different strains of HIV are called broadly neutralizing antibodies. These are very rare and so far only a handful have been identified.

HIV has several tricks it uses to avoid being neutralized by antibodies. One is that the virus can change itself, or mutate, very rapidly. This mutation can be a slight change in the virus’s shape or structure. Most HIV-infected individuals produce HIV-specific antibodies soon after becoming infected. But even in the short amount of time it takes for the adaptive immune system to gear up and start producing HIV-specific antibodies, the virus can alter itself so dramatically that the antibody no longer recognizes the majority of the virus in the body and is therefore ineffective.

Another reason why there are so few broadly neutralizing antibodies against HIV is that the virus itself is coated in bulky sugar molecules that act as a shield, effectively blocking the antibodies from reaching their target. In fact the region of the HIV envelope protein—gp120—that antibodies would latch on to is the most heavily protected viral protein scientists have ever studied.

Vaccine strategy

There has been little success to date in inducing broadly neutralizing antibodies through vaccination. Recently however a team of researchers in the US has discovered a possible chink in HIV’s protective armor. When studying the exact site where one of the already-identified broadly neutralizing antibodies binds to the virus, researchers found it was the precise place where the virus would connect to the CD4 receptor protein on cells, blocking the two from fitting together. Another promising finding is that this CD4-binding region on gp120 is highly conserved—meaning it doesn’t mutate as much—since this region of the virus is needed to attach to human cells. This means that this site should be similar in most strains of HIV. This exciting news provides a new window of opportunity for AIDS vaccine researchers to design vaccine candidates that can induce antibodies to target this vulnerable point on the virus.