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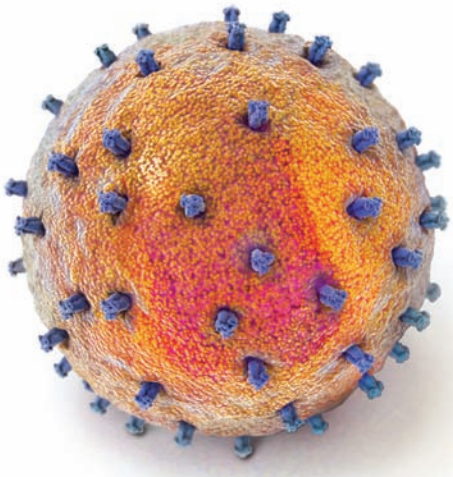

[SPOTLIGHT]

Test and Treat on Trial

A strategy to implement universal HIV testing and immediate treatment is receiving increased attention and scrutiny from HIV prevention researchers *By Regina McEnery*

Millions of lives have been saved by highly active antiretroviral therapy (HAART)—the combination of antiretrovirals (ARVs) for the treatment of HIV infection. But with an estimated 7,400 new infections still occurring every day, effective strategies for preventing the spread of HIV are still sorely needed. "With no vaccine or microbicide on the horizon, we need to look at other approaches," said Sarah Fidler of Imperial College, in a talk at the 5th International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, which was held July 19-22 in Cape Town, South Africa.

One strategy, which received considerable attention at the IAS conference, is known as test and treat. This approach calls for universal HIV testing and immediate treatment of all HIV-infected individuals. Current guidelines for initiating treatment vary by country and circumstance, but the World Health Organization (WHO) recommends treatment begin when a person develops AIDS (defined as having fewer than 200 $CD4^+$ T cells in a microliter of blood) or an AIDS-related illness. The basic assumption of test and treat is that people taking ARVs adherently will have lower viral loads—the quantity of virus that is circulating in their bodies. And since studies have shown that viral load is the chief predictor of the risk of heterosexual HIV transmission, individuals on ARVs with reduced viral loads should be less likely to transmit HIV to others. Therefore, getting more HIV-infected people on treatment as early as possible could also theoretically reduce the spread of HIV.

IAS President Julio Montaner says researchers have been confident for several years that ARVs, if appropriately employed, provide a dual benefit. "Number one, they decrease morbidity and mortality rates among HIV-infected [individuals]," he says. "In addition, adequately treated people become at the very least less likely to transmit HIV. So if you treat a larger number of people, the impact on the epidemic could be significant." Mathematical models suggest that the test and treat strategy could possibly even eliminate HIV in 50 years.

But Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases (NIAID), cautions that this approach "may not work." Speaking at the IAS conference, Fauci said, "We need to address that before we can promote it." NIAID and others are now studying the feasibility of test and treat, including how much of an effect ARVs have on reducing HIV transmission and the feasibility of implementing universal HIV testing. "We need to determine these things factually or we'll be in trouble," says Myron Cohen, director of the Institute for Global Health and Infectious Diseases at the University of North Carolina, who is also studying test and treat.

Even if shown to work, there are numerous logistical and financial obstacles to implementing this strategy. Based on the current treatment guidelines, only about a third of people who need therapy are now receiving it. Treating all people who are currently HIV infected, regardless of their disease status, would dramatically increase the number of people who qualify for ARVs, adding substantially to treatment costs. "Why are you even thinking of test and treat if you can't even get all infected people [who need treatment now] on antiretroviral

ALSO IN THIS ISSUE

therapy?" Fauci asked at the IAS conference. He answered his own question by saying these are complementary issues that need to be addressed at the same time.

The model

The mathematical model that sparked much of the current discussion regarding the viability of test and treat was developed by a quintet of researchers from the WHO, and was published in the medical journal *The Lancet* in January. The authors of the study used South Africa to model a generalized HIV epidemic and predicted that by testing all adolescents and adults at least 15 years of age every year and providing ARVs immediately to those who are found to be infected, HIV incidence would drop from slightly more than 1% a year to .05% a year, effectively ending the epidemic within 50 years. The authors suggested that the epidemic would end because no new infections would occur and those already HIV infected would eventually die.

Several assumptions were programmed into the model, including that all HIV transmission was heterosexual, that 95% of the population receiving ARVs was compliant to therapy, and that access to different drugs would be available for individuals whose first HAART regimen failed to control the virus. In many countries, availability of second-line drug regimens is limited and often prohibitively expensive. The model was also based on the assumption that the period of acute or primary infection, which occurs soon after HIV infection and is when viral load is highest, only lasts about two months, and contributes to only 10% of HIV transmissions. However, the stage of acute infection is when the risk of HIV transmission is thought to be highest.

"Their assumptions about the effect of this strategy are highly optimistic," wrote David Wilson, an AIDS researcher at the University of New South Wales in Sydney, in a commentary published three months later in *The Lancet*. "They assume that ARV therapy reduces infectiousness by 99%," Wilson wrote. "This level of reduction is unlikely."

Brian Williams, the WHO researcher who created the mathematical model and is now with the South African Centre for Epidemiological Modeling and Analysis, says the volume of emails and press coverage that *The Lancet* study generated exceeded anything he had experienced before. Many researchers have raised questions about this model. The WHO researchers acknowledge that better data on test and treat is needed, and they hope studies are done to determine if the approach is feasible. "The real obstacles are political not scientific," says Williams. "If you don't have the political will it won't work." The WHO is convening a meeting this fall to discuss test and treat.

Determining feasibility

Meanwhile, several researchers are already at work on determining the feasibility of this strategy. NIAID, along with the US Centers for Disease Control and Prevention (CDC), is developing and sponsoring pilot studies that address the feasibility of universal HIV testing and explore which voluntary counseling and testing strategies work best in specific high-risk populations. Since risk of HIV transmission is high during the acute stage of HIV infection, testing strategies would need to target individuals at greatest risk of HIV infection and provide them with ARVs very soon after they become infected. But getting high-risk individuals to undergo routine testing has proven difficult, even in countries where treatment is accessible and routine testing is recommended. A recent CDC analysis of 34 US states found 38% of individuals progressed to AIDS within a year after their HIV diagnosis, underscoring the failure to identify HIV-infected individuals soon after they became infected.

Scientists will also have to measure how effective ARVs are in actually preventing transmission. While scientists widely believe ARVs, by suppressing viral load, can help reduce HIV transmission, this has not been shown clinically. "I love mathematical modeling," says Cohen, "but the model in question is driven by assumptions that if we test everybody, treat everybody, and the therapy works well, it will prevent transmission. It's a far cry from having absolute veracity."

Cohen is leading a trial in Africa, Asia, and Latin America that is looking at whether earlier initiation of ARVs reduces the risk of heterosexual HIV transmission. The study will compare HIV transmission rates among serodiscordant couples (in which one partner is HIV infected and the other is not) based on whether the HIV-infected partner starts ARV therapy early or starts taking ARVs only when their CD4+ T cell count drops to between 200 and 250. Plans are to enroll 1,750 couples in the seven-year study.

More research will also be necessary to study the relationship between the stage of HIV infection and the likelihood of transmission. There is scant clinical data showing what percentage of HIV infections actually get transmitted during the acute stage of infection.

The financial burden

At the IAS conference, much attention was focused on the sustainability of global HIV treatment programs given the current economic crisis. The Joint United Nations Programme on HIV/AIDS (UNAIDS) and

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the World Bank reported in July that some international treatment programs are facing drug shortages, resulting in interruptions in treatment for some individuals, because the global recession prompted some public and private donors to reduce their funding. This has some researchers wondering where additional money for implementing test and treat would come from. "The proponents of this [test and treat] strategy are not being realistic and could do a lot of harm to treatment programs if there is a competition for resources," says Ron Gray, a professor of population and family planning at the Johns Hopkins Center for Global Health.

UNAIDS estimates that US$25 billion will be required to achieve universal access to HIV treatment, prevention, care, and support in low- and middle-income countries by 2010, including $7 billion for provision of treatment, based on the current treatment guidelines. In 2008, $14 billion was available for HIV programs.

The WHO researchers suggest that although implementing test and treat would require substantially more money in the short term, over time the financial burden would be alleviated as the number of new infections declined.

Kristen Jill Kresge contributed reporting to this article.

GLOBAL NEWS *By Regina McEnery*

Phase II Prime-Boost Trial Begins in the US

A Phase II trial testing the safety and efficacy of a combination of two AIDS vaccine candidates developed by the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health (NIH), recently began enrolling volunteers in the US. The trial, which is sponsored by NIAID and is being conducted by the HIV Vaccine Trials Network (HVTN), is referred to as HVTN 505. Researchers aim to enroll 1,350 men who have sex with men (MSM) at 15 clinical research centers in 12 US cities.

The two vaccine candidates being evaluated in HVTN 505 will be administered sequentially in a prime-boost regimen. Volunteers will first receive three vaccinations with a DNA-based candidate that contains non-infectious HIV fragments or immunogens, followed by a second vaccine candidate that employs an inactivated strain of the common cold virus, known as adenovirus serotype 5 (Ad5), to ferry HIV immunogens into the body to provoke an immune response against HIV. Neither vaccine candidate can cause HIV infection.

The HVTN 505 trial will evaluate the safety of the vaccine candidates as well as their efficacy; however the trial is not designed to determine whether the candidates can block HIV infection entirely. The efficacy of the prime-boost regimen will instead be determined by measuring whether individuals who receive the vaccine candidates and become HIV infected through natural exposure have lower viral loads (the quantity of HIV circulating in blood) than those who receive an inactive placebo.

Soon after a person becomes infected with HIV, their viral load is typically very high. Once a person's immune system responds specifically to HIV, the viral load usually drops to a much lower level, referred to as the set point viral load. Generally, the lower the set point viral load, the longer it takes for a person to develop AIDS. In HVTN 505, researchers will assess if volunteers who received the DNA/Ad5 prime-boost regimen have lower set point viral loads than those who receive an inactive placebo.

The prime-boost regimen being evaluated in HVTN 505 was originally slated for a much larger trial, known as PAVE 100, a Phase IIb test-of-concept trial of 8,500 HIV-uninfected men and women from North and South America and Africa. But the start of PAVE 100 was postponed in 2007, after another Ad5-based candidate, known as MRKAd5, which was developed by Merck, failed to prevent HIV infection or lower viral load in vaccinated volunteers who subsequently became HIV infected in a Phase IIb trial known as the STEP study. The PAVE 100 protocol then went through numerous revisions before NIAID settled on the current HVTN 505 trial.

Based on the STEP trial results, which showed that uncircumcised men who had pre-existing antibody immunity to Ad5 from being exposed to the naturally circulating cold virus were at increased risk of HIV infection, trial investigators for HVTN 505 decided to only enroll circumcised MSM who also have no pre-existing Ad5 immunity (see *Primer*, this issue). "We are deeply committed to the population that we are hoping to recruit for this trial," says Scott Hammer, study chair of HVTN 505. "We will do our part to provide them with counseling and education and make sure that they are fully aware of the STEP trial results."

Alan Fix, chief of the Vaccine Clinical Research Branch at the NIH, says there are a number of differences between the regimen being assessed in HVTN 505 and MRKAd5. In the STEP trial, volunteers received three doses of MRKAd5, whereas in HVTN 505 they will receive only one dose of a different Ad5 candidate, as part of a prime-boost regimen. The HIV immunogens in the DNA/Ad5 candidates being tested in HVTN 505 also differ from those in MRKAd5. "We don't know if this vaccine, with its similarities and differences from the Merck vaccine, will behave the same way," says Fix, who added that the DNA/Ad5 candidates being tested in HVTN 505 are not intended for future licensure.

The Fenway Community Health Center in Boston is one of the research centers now screening volunteers for the HVTN 505 trial. "While we hope to be vaccinating people very soon, it's been an intense screening process," says Ken Mayer, principal investigator at this research center. Community forums are being held at many clinical research centers to help potential participants understand the trial and put the STEP results in their proper context.

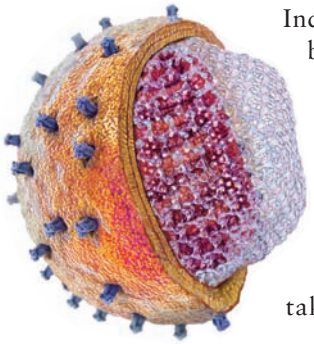
[PRIMER]

Understanding Inclusion/Exclusion Criteria

What are some of the eligibility requirements for volunteers to participate in AIDS vaccine clinical trials? ***By Regina McEnery***

Before an AIDS vaccine candidate can be tested in clinical trials, various committees comprised of scientists, ethicists, government regulatory bodies, and community members review the plans for the trial, which are known as the trial protocol. The trial protocol details such things as what vaccine candidate will be tested, the goals and design of the study, the number of visits that volunteers will be asked to make to the clinical research center where the trial takes place, when and how data will be collected, as well as many other specifics about how the trial will be conducted and how data will be analyzed once the trial is complete (see *VAX* November 2003 *Primer* on *Understanding Trial Approval*).

Another important detail outlined in the trial protocol is the eligibility criteria for volunteers interested in enrolling in the study. These guidelines for participation are referred to as the inclusion/exclusion criteria for a trial and may include many characteristics about potential volunteers, such as their age range, sex, and overall level of health. Before a volunteer is eligible to enroll in an AIDS vaccine clinical trial, nurses or counselors will collect baseline information about the volunteer from a physical examination, as well as laboratory tests such as collecting a blood sample, to determine whether the individual is healthy. For clinical trials of preventive AIDS vaccine candidates, already being infected with HIV is an exclusion criterion that prohibits someone from participation. Many vaccine trials also exclude volunteers who have a history of adverse reactions to vaccines or a psychiatric condition that could preclude compliance with the trial protocol to ensure the safety of the volunteers.



Individuals who are being treated for other health problems may also be excluded. For instance, AIDS vaccine trials may exclude volunteers who are taking immunosuppressant medications or those who are being treated for tuberculosis. Women who are pregnant or planning to become pregnant are also often excluded from participating in AIDS vaccine trials for safety reasons.

Specifying sexual risk

Some trials may also have specific inclusion criteria pertaining to the level of sexual risk activity of the volunteers. To evaluate the efficacy of preventive AIDS vaccine candidates, researchers must study the candidates in individuals who are potentially at risk of becoming infected with HIV (see *VAX* May 2008 *Primer* on *Understanding the Recruitment of Volunteers at Risk of HIV Infection)*. These individuals would also benefit most from a preventive AIDS vaccine, so it is essential they participate in clinical trials. Inclusion criteria specifically related to sexual behavior helps ensure that at-risk individuals are enrolled in the trial. For example, if an AIDS vaccine candidate is being tested in men who have sex with men (MSM), the trial protocol may specify that to be eligible to enroll in the trial, men must report having had unprotected anal intercourse with at least one partner who they knew was HIV infected in the last six months.

Specific exclusion criteria

Exclusion criteria for trials can also be informed by results of previous vaccine trials. Such is the case with HVTN 505, a Phase II trial launched recently to evaluate the safety and efficacy of two vaccine candidates administered sequentially in what is known as a prime-boost regimen (see *Global News*, this issue, for more details).

One of the candidates being tested in HVTN 505 uses an inactivated cold virus called adenovirus serotype 5 (Ad5), which is manipulated by researchers to carry non-infectious fragments of HIV into the body in the hope of generating an immune response against HIV (see *VAX* September 2004 *Primer* on *Understanding Viral Vectors*). This viral vector-based candidate cannot cause infection or disease either with HIV or with the common cold.

Other Ad5 vectors have been tested in previous trials, including one developed by Merck, known as MRKAd5, which was tested in the Phase IIb trial known as the STEP study (see *VAX* September 2007 *Special Report*). MRKAd5 was found to be ineffective. Subsequent findings also indicated that the vaccine candidate may have increased susceptibility to HIV among a certain subset of volunteers. Because Ad5 is a naturally circulating form of a virus that causes the common cold, many individuals have previously been exposed to Ad5, and therefore have developed antibodies against it. In the STEP trial, uncircumcised MSM with high levels of Ad5 antibodies who received MRKAd5 were found to be at an increased risk of HIV infection compared to individuals who received the inactive placebo. Although this result is not fully understood yet, and may have been an anomaly that occurred by chance, researchers who were involved in drafting the protocol for HVTN 505 ultimately decided to exclude uncircumcised men, as well as any volunteers who have pre-existing Ad5 immunity, from this trial. Researchers can determine through a blood test whether an individual has Ad5 antibodies and thereby exclude these individuals from enrolling.

Researchers decided to conduct HVTN 505 only in the US, where prevalence of naturally circulating Ad5 is lower, so that potential volunteers would be less likely to have pre-existing Ad5 immunity and therefore fewer potential volunteers would have to be excluded from participating based on the criteria for enrollment. ■

Guidelines for participation are referred to as the inclusion/exclusion criteria for a trial and may include many characteristics about potential volunteers.