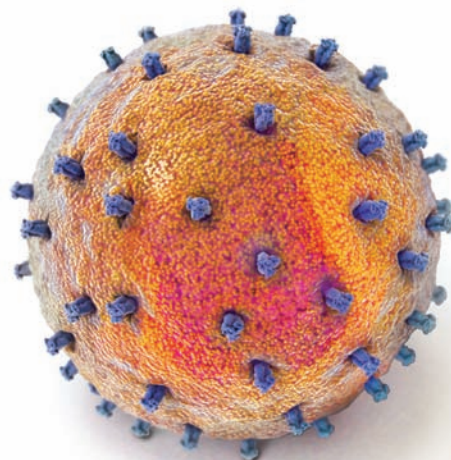


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The Bulletin on AIDS Vaccine Research



[SPOTLIGHT]

First Evidence of Efficacy from Large-Scale HIV Vaccine Trial

Results from a trial in Thailand show that the combination of two vaccine candidates provides some protection against HIV infection
By Regina McEnery and Kristen Jill Kresge

RESULTS FROM AN AIDS VACCINE trial known as RV144 involving more than 16,000 participants from Thailand show that a combination of two vaccine candidates administered sequentially in what is called a prime-boost regimen lowered the rate of HIV infection by about 31%. This is the first time an AIDS vaccine candidate has shown any efficacy in preventing HIV infection, prompting excitement among many researchers.

“To be clear, the level of efficacy demonstrated by this vaccine is a modest one. However, it is the first time that we have ever seen a positive signal of efficacy in a human trial of any HIV vaccine—a welcome and exciting result in a field that has been characterized by many disappointments for more than two decades,” says Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases (NIAID). His agency paid for the bulk of the US\$105 million trial. The US Army Surgeon General was the official sponsor of the study and the Army funded the remainder of the trial costs. “This study represents a major scientific achievement and is the result of an outstanding international and inter-agency collaboration involving many partners from the Thai and US governments,

private companies, non-profit organizations, and Thai volunteers,” says Eric Schoomaker, surgeon general of the US Army.

Of the 8,198 volunteers who received injections of an inactive placebo, 74 became HIV infected during the course of the three-year study through natural exposure to the virus. Among the remaining volunteers who received the prime-boost combination of the two vaccine candidates, 51 became HIV infected. Statisticians can do multiple calculations, including a test of statistical significance, to determine how meaningful the difference is between vaccine and placebo groups. In this case, the difference of 23 infections between the two groups was statistically significant, which means that as long as the trial was designed and conducted properly, there is only a small chance (3.9%) that the actual efficacy of the vaccine candidates is zero.

So far, limited data has been reported by trial investigators. “Right now all we have is a number,” says Mitchell Warren, executive director of the AIDS Vaccine Advocacy Coalition. “Activists as much as scientists want and need to know more to make strategic decisions about what should happen next.” Investigators say data from RV144 is being readied

for publication in a major medical journal, and will also be presented next month at the AIDS Vaccine Conference in Paris (October 19-22). This will likely stimulate more discussion about how these results may impact the future direction of AIDS vaccine research. “Nothing is going to change the field like a positive signal,” says Seth Berkley, president and chief executive officer of IAVI.

In the absence of additional data, many researchers are urging caution in interpretation of the results. “I think the tone to take is cautious optimism,” says Alan Bernstein, executive director of the Global HIV Vaccine Enterprise. But for a field that has been trying to prevent the spread of a virus that infects 2.7 million new people annually, the results from

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this trial were energizing. “This is a huge shot in the arm for the field,” says Warren. “This is the first evidence from a clinical trial that a vaccine is possible.”

Interpreting the results will take time and researchers agree there is much work still to be done to try to decipher how this prime-boost regimen afforded some level of protection. “RV144 is the largest HIV vaccine trial to date [but] it’s just the first step in a longer journey to a globally effective HIV vaccine,” says Jerome Kim, deputy director of science at the US Military HIV Research Program (MHRP).

Digging for clues

Indeed, RV144 may have raised more questions than it answered. The prime-boost regimen evaluated in RV144 consisted of six shots of two vaccine candidates over a six-month period. Four injections were

administered of the prime, known as ALVACHIV (vCP1521), which used a modified bird virus that cannot cause disease in humans as a vector to shuttle non-infectious fragments of HIV into the body (see VAX September 2004 *Primer on Understanding Viral Vectors*). The boost was an engineered version of one of HIV’s surface proteins, known as AIDSVAX B/E.

“The question is why did the vaccine work,” says Stanley Plotkin, a veteran vaccinologist and advisor to the company Sanofi Pasteur, which developed ALVAC. “No one at this point can answer that.”

The premise of the prime-boost combination was that it might stimulate both arms of the immune system, unleashing cellular immune responses that could kill HIV-infected cells, and triggering the production of antibodies, Y-shaped proteins that could bind to HIV and stop it from infecting cells in the first place. The cellular immune responses were thought to be induced primarily by ALVAC and the antibodies primarily by AIDSVAX. However, both of these vaccine candidates had been tested before and the immune responses they induced were not that robust, at least according to the tests researchers currently use to evaluate the stimulation of immune responses by vaccine candidates.

In multiple Phase I and II clinical trials ALVAC induced only a moderate level of cellular immune responses against HIV. AIDSVAX B/E was tested previously in two Phase III clinical trials, and although it induced antibodies against HIV, the vaccine candidate had no effect on HIV infection rates in studies involving primarily men who have sex with men (MSM) or injection-drug users (IDUs). So just how the combination of these two vaccine candidates produced a 31% efficacy has some researchers scratching their heads.

Another puzzling observation is that the prime-boost regimen was able to prevent infection but had no effect on set point viral load. Viral load—the amount of HIV circulating in an infected person’s blood—spikes soon after HIV infection occurs. But once the body’s immune system kicks in, viral load usually levels off at a much lower level known as set point viral load. Viral load usually remains at this lower set point level for many years until a person’s immune system, battered and exhausted by the continuously replicating virus, becomes incapable of controlling HIV.

Many AIDS vaccine candidates that have undergone testing in recent years, including ALVAC, were designed to elicit cellular mediated immunity (CMI). The objective was that a candidate that induces CMI could help lower the set point viral load even further than the immune system is capable of doing on its own. Set point viral load is an important marker of disease progression in HIV-infected individuals. Typically, the lower the set point viral load, the longer until a person develops AIDS. Why ALVAC failed to have an effect on viral load in RV144 is a mystery.

“The absence of an effect on viral load suggests this [protective effect] wasn’t due to CMI,” says Plotkin. He, among others, suggests the protection afforded by the prime-boost combination was more likely mediated by antibodies, which is how all licensed vaccines are thought to work. If it is antibodies, it raises another intriguing question. In 1994, NIAID refused to fund a large-scale vaccine trial of an earlier version of AIDSVAX after experiments showed that the antibodies triggered by the vaccine, while effective in neutralizing HIV strains grown in the laboratory, could not neutralize strains circulating at that time.

“The speculation I would make is that it was somehow the combination [of the two vaccine candidates],” says Plotkin. Others refuse to speculate until more data is shared. “It’s very early days,” says Dennis Burton, a professor of immunology and molecular biology at The Scripps Research Institute. “From the antibody side we just don’t even know enough to comment.”

Analyzing the data from RV144 to try to answer all of these questions will now become the major focus. Investigators at MHRP and NIAID have already set up multiple committees of experts to analyze samples from this trial, as well as to conduct related studies in animal models. Whether or not RV144 proves to be the key that helps researchers unlock the mysteries of immunological protection against HIV, it provides an important clue—actually 8,000 of them. “Let’s hope we can learn something useful from this,” says Burton.

The key to protection

One goal will be trying to determine the correlates of protection—those immune responses that were present in vaccinated

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volunteers that were able to fend off HIV (see VAX November 2006 *Primer on Understanding the Immune Correlates of Protection, Part I*). An effective vaccine works by training the immune system to recognize and then eliminate a specific pathogen (either a virus or a bacterium) that a person may be exposed to in the future. For an HIV vaccine to work it must induce HIV-specific immune responses—namely antibodies, cellular (CD4⁺ or CD8⁺ T cell) responses, or other natural immune responses. Typically, a subset of these immune responses is what is actually required for protection. Researchers refer to these specific immune responses as the immune correlates of protection.

If the correlates of protection can be identified from RV144, researchers could capitalize on this to design new and improved vaccine candidates. “That would be a *huge* boost for the field, much more so even than the results of the trial,” says Peggy Johnston, director of the vaccine research program at the division of AIDS at NIAID. Mark Feinberg, vice president of policy, public health and medical affairs at Merck, agrees. “That would put the field in a totally different place than it has ever been.”

However, researchers have limited cell samples from RV144 to work with and this could limit their ability to decipher the correlates of protection. “There wasn’t a lot of material that was collected to do ancillary studies,” says Louis Picker, associate director of the Vaccine and Gene Therapy Institute at Oregon Health & Science University. However, Picker says it may be possible to use studies in nonhuman primates to help tease out the correlates of protection with this prime-boost regimen. “Trying to replicate the results in the monkey model would be of interest and would allow modifications more quickly,” added Plotkin. But Plotkin and others also point out that this trial shows the importance of conducting clinical trials. “You can only show things that are important in humans, in humans,” says Plotkin. Berkley agrees. “This validates the importance of clinical research.”

Nelson Michael, director of MHRP, says the number of cell samples from RV144 was limited because investigators amended the trial protocol to collect fewer samples from volunteers when criticism was raised by prominent scientists in the field about whether or not the trial should occur. “This goes to the

lack of enthusiasm that surrounded this trial at the start,” Michael says.

In early 2004, shortly after the launch of RV144, 22 prominent AIDS vaccine researchers (including Burton, Feinberg, and Picker, who were interviewed for this story) published a policy forum in *Science* magazine that questioned the scientific rationale for pursuing a large-scale trial of these candidates when others that, in their opinion, offered greater hope of success were in early-phase clinical trials. The scientists’ concerns were driven by how ALVAC and AIDSVAX had performed in previous clinical trials. In 2003, the HIV Vaccine Trials Network scrapped plans to conduct a Phase III trial of similar design to RV144 in the US because the immune responses it induced were considered too weak.



Principal Investigator Supachai Rerksgarm even confessed to having some hesitation about moving forward with RV144, so when this experimental regimen provided some protection against HIV infection, it caught many people by surprise. “I was stunned,” says Michael. Johnston concurred. “I expected that if we saw anything it would be a difference in viral load, not a prevention of [HIV] acquisition, so when I saw the data... I was just elated and surprised.”

Results of the trial, which was conducted by the Thailand Ministry of Public Health, were announced on September 24 in Thailand and videocast to the Rayong and Chon Buri provinces where the clinical research centers were located.

In the early 1990s, Thailand focused on a collaborative effort for HIV vaccine development and within a decade emerged as a

key player in the testing of vaccine candidates. During that same time, the country also waged a multi-faceted HIV prevention campaign that required commercial sex workers to use condoms during every sexual act. The country’s HIV prevalence dropped from 2.4% in 1993 to 1.9% in 2003 when RV144 started. The most recent data available suggest HIV prevalence is about 1.5%, according to the Joint United Nations Programme on HIV/AIDS.

Volunteers in RV144 were recruited from the general population and not specifically from groups considered at high risk of HIV infection. “This [trial] includes people at higher risk and people at very low or no risk,” says Kim. This could impact the route of HIV transmission—while some MSM and IDUs were enrolled, the majority of volunteers were heterosexual men and women—as well as the amount of virus people were exposed to. “One of the reasons people have postulated that this trial may have succeeded is that the intensity of [HIV] exposure might have been lower,” added Kim.

All volunteers received counseling on how to protect themselves from HIV infection throughout the trial. Individuals who became HIV infected during the trial received free HIV care and treatment and are being followed in a companion study, RV152, which will continue collecting information from these volunteers. Meanwhile, the study sponsors have begun notifying all volunteers in the trial whether they received the vaccine candidates or placebo.

“Before the trial started there was negativity, so I was excited by the results,” says Nimit Thien-Udom of AIDS Access Foundation, an AIDS activist group in Bangkok. “But we have many questions.” Thien-Udom says it will be important to know the specific risk behaviors of the volunteers in the trial and to educate both volunteers and the general community about what the results actually mean. “We still need to counsel people to use condoms,” he says. ■

Andreas von Bubnoff contributed reporting to this article.

It is the first time that we have ever seen a positive signal of efficacy in a human trial of any HIV vaccine.

—Anthony Fauci

Understanding Challenge Viruses

How does the choice of challenge virus affect the outcome of vaccine studies in nonhuman primates? *By Regina McEnerly*

BEFORE A VACCINE CANDIDATE can be tested in humans, it is first evaluated extensively in both laboratory tests and animal models. Animal models help scientists gain important insights into human diseases and how to prevent them. Researchers also rely on animal models to help determine if a candidate vaccine is safe to administer in people.

In AIDS vaccine research, the most relevant animal model is nonhuman primates (NHPs), especially a specific species known as rhesus macaques. No animal can be infected with HIV—it is a pathogen specific to humans. But rhesus macaques can be infected with certain types of simian immunodeficiency virus (SIV), which is the monkey equivalent of HIV, or viruses known as SHIV that are constructed in the laboratory and contain parts of SIV and HIV.

The similarity between SIV and HIV allows scientists to mimic HIV transmission and infection in NHPs. They do this by purposely infecting the monkeys with batches of virus known as challenge stocks.

Researchers can also evaluate potential vaccine candidates by first giving the candidate vaccine to the monkeys and then exposing them to one of the challenge viruses. Studying the immune responses induced in the monkeys following vaccination, and how well these responses can protect against the virus challenge, can help researchers decide which AIDS vaccine candidates are the best ones to evaluate in clinical trials (see *VAX* October 2008 *Primer on Understanding Animal Models of HIV Infection*).

Different stocks, different results?

There are several different virus challenge stocks in existence and many variations are used in experiments evaluating AIDS vaccine candidates. There are notable differences between these virus stocks. This raises concern among scientists about whether the outcomes from studies that are conducted using different virus chal-

lenge stocks can be compared. This concern has led some researchers to focus on more thoroughly characterizing many of the monkey virus stocks currently in use to better understand the differences between them. But some researchers think just knowing the differences between the multiple challenge viruses is not enough and instead suggest that all studies of AIDS vaccine candidates should be conducted with a standardized challenge virus to ensure that the results can be compared. Then, only those candidates that perform the best can be advanced to human testing.

The origin of virus challenge stocks

Most of the virus challenge stocks currently used in AIDS vaccine research are derived from a strain of SIV that naturally infected a nonhuman primate species known as sooty mangabeys. While sooty mangabeys don't typically get sick when they are infected with SIV, rhesus macaques infected with SIV from sooty mangabeys develop a disease that is similar to AIDS in humans.

Because the quantity of virus isolated directly from a naturally infected animal is limited, researchers must propagate or "grow" more of the virus. This is usually done in a laboratory. Researchers can add the SIV to cells isolated from an NHP. Because viruses naturally reproduce when exposed to animal or human cells, researchers can use this procedure to produce more of the virus. While this technique solves the supply problem, it creates another potential problem. Propagating SIV in the laboratory can alter the properties of the virus stock. New batches of SIV that are cultivated in the laboratory can have genetic and biological differences. Conditions may also vary among different laboratories that are producing stocks of virus, which may also contribute to variability. So even though some challenge viruses may bear the same name, they could behave differently biologically, affecting the results of studies

evaluating vaccine candidates.

Researchers have observed some practical differences between different virus challenge stocks. Some become more pathogenic after they've been cultivated in a laboratory, which means that they cause disease in NHPs much faster than the original challenge virus. Conversely, other viruses become more susceptible to antibodies, proteins that can bind to the virus and prevent it from causing harm, after they have been cultivated in the laboratory. Either way, these new batches of virus can impact evaluation of vaccine candidates.

While it is still unknown just how much of an effect these genetic or biological differences in virus stocks have on the outcomes of studies involving AIDS vaccine candidates, some scientists think they could be problematic. These researchers are therefore advocating for the development of a standardized challenge virus stock that everyone in the field can use to evaluate AIDS vaccine candidates in NHPs. However, even if this were to be endorsed by researchers, there is still some disagreement about what the best standard would be.

Meanwhile, researchers are also searching for new challenge strains whose biological properties more closely resemble HIV than the ones currently being used in NHP studies. For instance, one SIV strain now widely used in NHPs is harder to neutralize than HIV, making it difficult to test vaccine candidates that can induce neutralizing antibodies, so researchers have been experimenting with SIV and SHIV strains that can be neutralized more easily.

Ultimately, improving the comparability of NHP studies of AIDS vaccine candidates will help researchers prioritize candidates that should be tested in humans. ■

