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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

More Surprises Stem from RV144

At AIDS Vaccine 2011 investigators presented the much anticipated results of a two-year effort to elucidate how the RV144 vaccine regimen protected against HIV *By Kristen Jill Kresge*

TWO YEARS AGO, THE PREVAILING sentiment in the HIV vaccine field was surprise. The source of the surprise was the results of the RV144 efficacy trial that provided the first evidence of vaccine-induced protection against HIV. From the start, many leading researchers opposed the trial, involving more than 16,000 volunteers in Thailand, because they thought the candidates being tested were unlikely to work. Many were also skeptical when the results were released because the trial demonstrated only a 31.2% reduction in HIV infection risk.

Now, after a two-year hunt to try to determine just how the prime-boost vaccine regimen tested in RV144 provided this modest level of protection against HIV infection, the trial has once again yielded surprising findings (see *VAX* Nov. 2009 *Primer* on *Understanding the Hunt for Immune Correlates of Protection from RV144*). At the AIDS Vaccine 2011 conference that, symbolically, took place in Bangkok, Thailand, from Sep. 12-15, investigators presented the much anticipated results of their massive effort to identify the specific types of immune responses that were induced by the vaccine candidates that led to the observed protection. The analysis showed that two different types of antibodies—infection-fighting proteins that are generated in response to spe-

cific pathogens—were correlated with the risk of HIV infection among volunteers. The first surprise was that they identified any correlates of risk. Given the lack of public support for RV144, the trial was a scaled-back version of what was originally planned. This meant researchers were left with few samples to analyze in the correlates analysis, making it very much a needle-in-a-haystack search.

The second surprise was that while one specific type of antibody response was correlated with a reduced risk of HIV infection, the other was correlated with an increased risk of HIV infection. These intriguing findings provide valuable clues about how this vaccine regimen might have worked and help bolster the credibility of the RV144 results. “The findings lend credence to the vaccine efficacy seen in the RV144 trial,” said Barton Haynes, who led the RV144 correlates of protection analysis team comprised of four teams of researchers, adding that these results are “intriguing clues.”

Haynes was careful to warn that the antibody responses they identified as correlates may or may not actually be related to the HIV infection risk among volunteers in RV144, and are merely hypothesis generating, not conclusive. “Without this we had uninformed hypotheses,” said Haynes. “Now we have informed hypotheses and

directions that come from a trial.” Jerome Kim, deputy director of science at the US Military HIV Research Program, which was a key collaborator on RV144, also urged caution in trying to extend these findings to other vaccine candidates. “Any results may be unique to this vaccine. We have to bear that in mind as we look to the next step in HIV vaccine development,” said Kim.

However, the findings presented in Bangkok give investigators the opportunity to study these specific antibody responses more closely in both human and non-human primate studies, as well as in previous trials to determine if there is a causal relationship between these immune responses and HIV infection risk. Researchers will ultimately

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use the information generated by these studies and analyses to try to improve upon the 31% protection seen in the trial. “The RV144 correlates work is clearly going to guide us on the future of HIV vaccine development,” said Giuseppe Pantaleo, chief of the division of immunology and allergy at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland.

On the hunt

The goal of the correlates analysis team for RV144 was to determine what immune responses, if any, predicted the HIV infection risk of RV144 volunteers over a three-year period. To do this, the team of investigators carefully analyzed the immune responses present in blood samples collected from 41 volunteers in the vaccine group that eventually became HIV infected through natural exposure, as compared to the immune responses in blood samples from 205 volunteers in the vaccine group that remained HIV uninfected and 40 volunteers who received placebo.

After a series of test runs, researchers settled on six primary assays, or tests, and approximately 30 secondary assays to measure immune responses in this collection of samples. The assays were carefully selected based on several selection criteria. The assays were all run in July, and statisticians at the Fred Hutchinson Cancer Research Center in Seattle then analyzed the results. The final results were shared with the investigators in late August and presented publicly for the first time at the conference in Bangkok.

The statisticians found that the correlation between two of the immune responses and HIV infection risk was statistically significant, a measurement scientists use to give credibility to a finding (see *VAX* Oct. 2009 *Primer on Understanding the Statistical Analysis of Clinical Trial Results*). The first immune response that was significantly correlated with HIV infection risk was antibodies known as immunoglobulin G or IgG that

bind to a specific portion of HIV’s outer coat, a protein structure known as HIV Envelope, or Env. Vaccinated volunteers in RV144 who had this antibody response at week 26 of the trial (which corresponds with two weeks following all six vaccinations that were administered over a six-month period, and was the time when the immune responses peaked) were 43% less likely to acquire HIV than volunteers who did not generate this specific antibody against HIV.

When researchers compared vaccinated volunteers with low versus high levels of this type of IgG antibody they found that those with a higher level of IgG were 71% less likely to become HIV infected than vaccinated volunteers with either low or mid levels of IgG antibodies.

The second immune response that was significantly correlated with HIV infection risk was a different class of antibody that binds to HIV Env. This type of antibody, known as IgA, is most commonly generated in mucosal secretions, such as genital secretions, but can also be found in serum, a component of blood. The responses evaluated for RV144 were all from serum samples because no mucosal secretions were collected in the trial in an effort to cut costs. Vaccinated volunteers who developed IgA antibodies that targeted HIV Env at week 26 of the study were actually 54% more likely to subsequently become HIV infected. While these antibodies were significantly associated with an increased risk of infection among vaccinated volunteers, Haynes reported that vaccinated volunteers with high levels of this type of IgA antibody became HIV infected at the same rate as placebo recipients, suggesting that presence of this type of an antibody response did not enhance an individual’s risk of acquiring HIV. Rather, these antibodies reduced the protective effect of the vaccine candidates, which meant the vaccine efficacy was actually higher among volunteers with low levels of this type of IgA antibody.

Although it is unclear precisely how this

IgA antibody could increase the risk of HIV infection among vaccinated volunteers, Haynes presented one hypothesis to explain this finding. Antibodies can act against viruses, including HIV, in many ways. One of the ways is through something called antibody-dependent cellular cytotoxicity or ADCC (see *VAX* Jan. 2010 *Primer on Understanding Antibody Functions: Beyond Neutralization*). In ADCC, antibodies bind directly to cells infected with HIV and facilitate the killing of these cells by other cells of the immune system. There is evidence from other diseases, such as cancer, that IgA can block ADCC immune responses against tumors. Haynes said this type of blocking activity would be explored in the RV144 follow-up trials as well as animal studies.

What next?

Now that these two correlates of risk have been identified, researchers are planning several analyses and studies to determine if they are causally related to protection against HIV. Or, in the case of the IgA antibody, causally related to a lack of protection. This of course will be a major focus of the post-RV144 trials with the same or a similar vaccine regimen.

Other clinical trial data will come from analyzing previous trials in which one of the same vaccine candidates as was used in RV144 was administered. This includes the two Phase III trials known as VAX003 and VAX004 that tested AIDSVAX gp120 alone in either men who have sex with men in the US or injection drug users in Thailand. There was no protection against HIV infection observed in either of these trials; however, the populations differed greatly from the RV144 volunteers—both the mode of transmission and the level of risk were different in the VAX003 and 004 trials. It is possible that the same responses were induced in volunteers in these trials but the level of exposure to HIV and the diversity of the viruses that infected these volunteers

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overcame the vaccine's effect. A similar observation has been made in non-human primates. Genoveffa Franchini, who led the animal models scientific working group as part of the RV144 correlates team, has been able to reproduce the RV144 results in non-human primate studies, but found the protection is dependent on the amount of virus the animals are

exposed to. "If you're using too much virus, you can't see the vaccine efficacy," she said.

Researchers are now analyzing samples from the VAX003 and 004 trials, which are available in a repository, to see if this vaccine candidate alone induced similar immune responses to the prime-boost regimen tested in RV144.

Researchers are also planning studies in non-human primates to see if administration of antibodies of the type that were elicited by the RV144 vaccine regimen are capable of protecting monkeys against infection. All of these studies will inform the design of future vaccine candidates that might be able to improve on the efficacy seen in RV144. ■

GLOBAL NEWS

By Regina McEnery

HVTN 505 Expanded to See if Vaccine Candidates Can Block HIV Acquisition

A PHASE II AIDS VACCINE TRIAL known as HVTN 505 will expand enrollment to determine whether two vaccine candidates administered sequentially in a prime-boost regimen are capable of protecting against HIV infection. The two candidates—a DNA-based vaccine and a candidate that employs an inactivated strain of the commonly circulating cold virus adenovirus serotype 5 (Ad5)—were developed by the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID).

The HVTN 505 trial, which was launched in 2009, was initially designed to determine whether individuals who become HIV infected through natural exposure, despite vaccination, have lower viral loads (the quantity of HIV circulating in blood) than those who receive placebo (see VAX July 2009, *Global*

News). With only this endpoint, the trial was slated to enroll 1,350 circumcised men or transgendered women who have sex with men. Adding protection against infection as an additional endpoint requires expanding enrollment to 2,200 volunteers, who will be enrolled at 21 sites in 18 US cities. So far, investigators have enrolled 1,344 volunteers and are on track to enroll the remaining volunteers by mid-2012, according to Scott Hammer, principal investigator of the HVTN 505 trial.

Carl Dieffenbach, director of the Division of AIDS (DAIDS) at NIAID, says the expanded trial is a positive step for the field, but he cautioned observers to keep the scope of the trial and where it might lead in perspective. "We have to be careful that we continue to put this forward without trying to over-promise," he says.

One Oral PrEP Arm Discontinued Early in VOICE Trial

ONE ARM OF A LARGE CLINICAL TRIAL known as VOICE that was designed to test the safety, efficacy, and acceptability of one topical and two oral pre-exposure prophylaxis (PrEP) regimens in more than 5,000 women was discontinued in September after the trial's independent data safety monitoring board (DSMB) concluded that the study would be unable to show any difference between a daily dose of the antiretroviral pill tenofovir (TDF) and placebo in preventing HIV infection. About 1,000 of the volunteers were randomized to the oral TDF arm. The DSMB found no safety concerns with oral TDF.

Unlike other large-scale PrEP trials that were recently completed or still ongoing, the VOICE study is the first to evaluate both oral and topical PrEP regimens in the same trial. The remaining arms of the trial, which are testing daily administration of the antiretroviral pill Truvada—a combination of TDF and emtricitabine—and the topical administration of a 1% tenofovir microbicide gel will continue in order to determine if they are safe and effective at preventing HIV infection as compared to pill and gel placebo groups.

The US\$100 million VOICE trial, which is being conducted at 15 clinical sites in South Africa, Zimbabwe, and Uganda, began in 2009 and is sponsored by the US National Institute of Allergy and Infectious Diseases; the Microbicide

Trials Network; Gilead Sciences (the maker of tenofovir and Truvada); and CONRAD, a reproductive health research institute.

The trial is scheduled to conclude in June, at which point investigators will be able to determine whether volunteers in the oral TDF arm were less adherent to the daily PrEP regimen than women in the Truvada or microbicide arms. Michael Chirenje, a principal investigator of the trial in Zimbabwe, says it would be speculation at this point to say what accounted for the failure of oral TDF to show any effect in this trial. "Obviously we are all disappointed and perplexed by the recent results," says Chirenje. "But in science, we have to accept reality."

Three other trials have found both oral tenofovir and Truvada to be effective at preventing HIV infection in men who have sex with men and serodiscordant couples—in which one partner is HIV infected and the other is not (see VAX July 2011 *Spotlight* article, *An Antiretroviral Renaissance*). However, one trial, known as FEM-PrEP, evaluating oral Truvada in women, was discontinued ahead of schedule after the DSMB concluded that it would be highly unlikely to demonstrate efficacy (see April 18, 2011, *IAVI Report blog*, *Oral PrEP Trial in Women Stopped Early*).

Understanding the Rationale for Combination Prevention Trials

What are the potential benefits of and complications with studying multiple prevention strategies in combination? *By Regina McEneary*

OVER THE LAST FEW YEARS, several strategies have demonstrated success in preventing HIV infection. These strategies include adult male circumcision, pre-exposure prophylaxis (PrEP; the administration of anti-retrovirals [ARVs] either orally or topically to HIV-uninfected individuals to prevent HIV infection), and the first evidence of vaccine-induced protection against HIV (see VAX July 2011 *Spotlight* article, *An Antiretroviral Renaissance*; Jan. 2011 *Spotlight* article, *Prepping for the Future*; Sep. 2009 *Spotlight* article, *First Evidence of Efficacy from Large-Scale HIV Vaccine Trial*).

However, all of these strategies are only partially effective at protecting against HIV infection (see table at right), with efficacies ranging from 31% for the vaccine regimen tested in the RV144 trial in Thailand to 73% for the use of oral PrEP in serodiscordant heterosexual couples (couples in which one person is HIV-infected and the other isn't). This has led researchers to consider the feasibility of designing clinical trials to evaluate some of these prevention strategies in combination to see if a combination approach would be more effective at preventing HIV infection.

Vaccines plus PrEP

One combination of partially effective prevention strategies that some researchers believe might be worth testing is the use of PrEP along with a partially effective vaccine such as the prime-boost combination tested in the RV144 trial. Data from the trial showed vaccine efficacy was as high as 60% during the first year (although the efficacy at one year was not part of the pre-specified data analysis plan) but then waned over time. Researchers are still investigating the mechanisms that led to this protection (see *Spotlight*, this issue), and planning vaccine trials to try to improve upon this modest efficacy. Meanwhile, some researchers think that oral PrEP might boost vaccine-induced immune responses, based on evi-

dence from studies in non-human primates. Therefore, they suggest, clinical trials of this combination should be conducted.

The combination of a partially effective vaccine and topical PrEP, which is most commonly delivered as a vaginal microbicide gel, is another combination strategy under consideration. The ARV-based microbicide gel and the vaccine candidate could even be administered in the same gel

Study	Efficacy
HIV vaccine (RV144)	31%
1% Tenofovir gel (CAPRISA 004)	39%
Truvada in men who have sex with men (iPrEx)	44%
Circumcision (Orange Farm, Rakai, Kisumu)	57%
Tenofovir (TDF) or Truvada in serodiscordant couples (Partners PrEP)	62%, 73%
Truvada in heterosexual men and women (TDF2)	63%

Results from recent HIV prevention trials.

formulation. Researchers speculate that administering the vaccine candidate directly into the vagina along with an ARV-based microbicide might help strengthen immune responses at the site where transmission occurs, thereby boosting efficacy of the combined approach.

Another option, which is currently being explored as a delivery method for microbicides, is the use of intra-vaginal rings. These rings could deliver steady dosing of ARVs over a three-month period and also deliver the vaccine candidate over a period of hours or days.

The use of oral or topical PrEP in combination with a partially effective vaccine has another potential advantage. ARV prophylaxis would likely help lower HIV incidence in the clinical trial population, making it more likely that the vaccine candidate would have an effect. In the RV144 trial in Thailand, volunteers were predominantly

heterosexuals at low-risk of acquiring HIV, and several researchers suggest that the low-risk population may have been key to the observed efficacy in the trial.

Challenges to combination prevention trials

Although it is theoretically possible that combining partially effective prevention strategies would result in a higher overall efficacy, this can only be determined by studying these approaches in clinical trials. However, there are many challenges to designing such trials. Because the trials will involve multiple interventions, the size, cost, and complexity of conducting such trials will increase. The duration of trials might also be greater.

For instance, should a trial be set up to evaluate the efficacy of a partially effective vaccine candidate combined with oral PrEP, the trial would need to involve multiple arms to determine whether the overall efficacy of this combination strategy is greater than that of PrEP alone, the vaccine candidate alone, or a placebo.

Monitoring the outcome of a combination prevention trial would also be more complicated. For instance, in a trial combining a partially effective vaccine candidate with oral or topical PrEP, the use of ARVs might alter the immune responses induced by a vaccine, making it more difficult to tease out how much the vaccine actually contributed to overall efficacy.

Different biomedical interventions may also present different safety concerns, which could complicate the process of informing volunteers about the risks of trial participation. And daily adherence to oral and topical PrEP could impact the outcome of combination prevention trials just as it has in previous PrEP-only trials, making it difficult to determine actual efficacy of the combined strategies. Despite these concerns, several researchers argue that clinical trials of different partially effective prevention strategies should be designed and conducted. ■