

Hill & Knowlton
RV144 HIV Vaccine Trial Results
September 24, 2009

Presentation

Lisa Reilly: Hello, and welcome to the RV144 Vaccine Trial Results conference call and webinar. My name is Lisa Reilly, the Director of Communications for MHRP.

I will briefly introduce our speakers today. First, you will hear from Lieutenant General Eric Schoomaker, Surgeon General of the U.S. Army. Next, Colonel Jerome Kim will present the study results. Then you will hear from Dr. Tony Fauci, the Director of the National Institute of Allergy and Infectious Diseases at the NIH. And, finally, Dr. Supachai, the principal investigator for this study, will make a statement from Thailand.

In addition to our speakers we also have with us today Colonel Nelson Michael, with the Walter Reed Army Institute of Research; Dr. Jim Tartaglia, with sanofi pasteur; Dr. Sanjay Gurunathan, sanofi pasteur; and Dr. Donald Francis, Global Solutions for Infectious Diseases.

Now I will turn this over to Darren Back, who will moderate the session today.

Darren Back: Thank you, Lisa. Good morning, good afternoon, everyone.

So, following the presentations by our speakers we will move to the question-and-answer session. You have a number of options available to you to field your questions. For those who are accessing via the webinar, you may do so by typing your question into the Ask a Question box displayed below the slide. For telephone callers, you may ask a question by pressing star 1 on your keypad, where you'll enter a question queue for a moderator to take your question. You can press star 2 on your keypad at any point to remove yourself from this queue. For those people in Paris at the live event, and I can see that you are already doing this, you are able to field your questions to the facilitator, who will then field those to our speakers here.

Given the length of today's call and the number of attendees, we will do our best to address as many questions as possible. However, if we do not get to your question on this call we will do our best to contact you following.

With that, I now have the pleasure of handing over to Lieutenant General Eric Schoomaker, Surgeon General of the U.S. Army and Commanding General of the U.S. Army Medical Command.

Eric Schoomaker: Well, good morning, and thank you, Darren. I'd like to welcome all of you to this media briefing for the Phase III HIV vaccine trial that was conducted in Thailand and concluded this summer, and we would like to thank you for joining us on this very important occasion.

I'm pleased and proud to announce the results of the trial, which for the first time ever has shown

that it is possible for a vaccine to reduce the risk of HIV infection in humans. Although the level of protection is modest, at 31% efficacy, the study represents a major scientific achievement. The United States Army sponsored this study, and it's a result of an outstanding international and interagency collaboration involving many partners from the Thai and U.S. governments, private companies, nonprofit organizations, and more than 16,000 Thai volunteers. This would not have been possible without all of them, or without the leadership and strong collaboration between the National Institute of Allergy and Infectious Diseases and the Department of Defense, who had the foresight to pursue and to fund this trial.

As some of you may know, Army researchers have had a long and successful history in infectious diseases and vaccine development. It is our longstanding relationship with the Royal Thai Army, the Thai Ministry of Public Health and other Thai vaccine experts that enabled us to bring this trial to such a successful conclusion.

Military medicine is interested in research that improves global health and makes the world safer for everyone, including our soldiers, sailors, airmen, Marine and Coast Guardsmen. Although only modest, the result of this trial opens new doors. It answers some questions and poses many additional questions. This is truly a great moment for world medicine and for the global human family.

In 1986, Congress initiated the United States Military HIV Research Program, the MHRP, as a result of the military directive to develop effective preventive measures against HIV disease to protect U.S. troops from infection and reduce the impact of the disease at home and abroad. The program's global focus, along with a strong science program, has enabled MHRP to become a leader in international HIV vaccine efforts, with five research sites in Africa and Asia.

I'm honored to now introduce Colonel Jerome Kim, an infectious disease expert and the United States Army HIV vaccine product manager, who has played a crucial leadership role in the execution of this trial. He will provide you with an overview of the results. And then my colleague, Dr. Tony Fauci, the Director of the National Institute of Allergy and Infectious Diseases, will help frame for us how these results will help advance the HIV vaccine field.

Thank you very much.

Jerome Kim: Thank you, General Schoomaker, and good morning. As the Surgeon General observed, this is a day when we have the pleasure to report the results of RV144, a test of the prime boost combination of ALVAC-HIV and AIDSVAX B/E in the prevention of HIV infection, and the first time an HIV vaccine has successfully prevented HIV infection in humans.

The trial, conducted in Thailand, randomized 16,395 18- to 30-year-old HIV negative Thai men and women to either vaccine or placebo. After the six-month vaccination phase, the volunteers were followed for three years, with HIV testing done every six months. In all, 8,198 received placebo and 8,197 received vaccine. In the placebo group, there were 74 infections, and in the vaccine group there were 51 infections. This translates into a vaccine efficacy of 31.2%, with a P value of 0.039 and a 95% adjusted confidence interval of 1.1%, to 52.1%. There was no effect on postinfection setpoint viral load.

The vaccine appeared safe. The occurrence of adverse events was equal in vaccine and placebo groups. The result is a major scientific achievement and provides the first evidence that a safe and effective HIV vaccine is possible. RV144, therefore, has important implications for future HIV vaccine design and testing, a topic Dr. Fauci will address during his statement.

Additional studies are clearly needed to better understand how this vaccine regimen reduced the risk of HIV infection. The collaborators are meeting with outside experts to attempt to understand why the vaccine worked, and the data derived from these analyses should drive both the science and discussion and will hopefully allow us to move expeditiously to an effective preventive vaccine.

We'd like to emphasize that this vaccine was tested in Thailand against the types of HIV that circulate in Thailand, subtypes B and E. Whether this will work in other parts of the world with different subtypes of HIV or in populations at different risk of HIV infection is not known. The fact that this vaccine was tested in a population of community risk may have been important and warrants additional study.

RV144 is the largest HIV vaccine trial to date. It's just the first step in a longer journey to a globally effective HIV vaccine. We do not know how long it will take, but we do know that on the basis of these data we're closer to that solution now than we were yesterday. The collaborators have a lot of work to do, presenting the data to other scientists, collecting their best thoughts on a speedy way forward, and then returning to the bench to do the necessary studies.

We want to thank the 16,402 Thai men and women whose participation in this trial has given us greater confidence that a safe and effective HIV vaccine might someday be found.

Thank you.

Darren Back: Thank you, Colonel Kim.

I'd now like to hand over to Dr. Tony Fauci, Director of the National Institute of Allergy and Infectious Diseases, who will now discuss the implications of these results.

Tony Fauci: Thank you. General Schoomaker, Colonel Kim, ladies and gentlemen, I am very pleased to be here with my colleagues and partners in this endeavor this morning.

This is, as you've heard, an important day for the HIV vaccine research field. For the first time, we have an HIV vaccine regimen that has demonstrated the ability to prevent HIV infection in a large-scale human clinical trial. To be clear, the 31.2% level of efficacy demonstrated by this vaccine is a modest one. However, as you have heard, it is the first time that we have ever seen a positive signal of efficacy in a human trial of any HIV vaccine. This is a welcome and exciting result in a field that has been characterized by many disappointments for more than two decades.

Although it is a cause for some measure of celebration, it is, perhaps more importantly, a humbling reminder of how little we actually know and how much work remains to be done in

our search for an optimal HIV vaccine. This is by no means our final destination. Rather, it is an opening of a gateway to a path that now has brighter lights. Many broad questions remain. What will be the duration of the effect? Will additional boosters be needed? Will we be able to improve on this level of efficacy? Will this approach work for other clades of HIV? The study, as you heard, was performed in heterosexuals. Would similar results be seen in men who have sex with men or injection drug user or even in a higher risk heterosexual population?

Given the lack of consistently strong immunological responses in earlier trials to the products tested in the current study, we feel very fortunate that we now have a clear, albeit modest, signal of efficacy. Now we have a foundation upon which to explore potential correlative immunity and to pursue further studies to improve on these findings. We need to bring the best minds together and map the way forward, both to examine the results of this trial in more detail and also to understand its implications for the field.

Does this mean that we should now focus predominantly on clinical research more than on basic research to get the key scientific answers that we need in order to develop a highly protective HIV vaccine? No, not at all. However, there's nothing like a positive results from a clinical trial, modest as it may be, to help us focus on some critical questions and provide new opportunities for further study.

NIAID has said that we will pursue an appropriate balance between the basic science needed to understand the fundamental questions surrounding HIV and the clinical research that must be performed to test the most promising HIV vaccine candidates. This commitment to an appropriate balance has not changed. What we have now is some important new information on which to build.

In my view, one of the most important and intriguing findings of the Thai trial is that the vaccine regimen prevented HIV acquisition among a modest proportion of vaccinated participants yet failed to affect viral load in vaccine recipients who later became infected. This clearly begs the question of whether protective immune responses that prevent infection are related to those that control viral load. In fact, we do not know whether our current measures of the human immune response are even relevant to the protection that we see in this trial. NIAID and its study partners are working with scientific experts to chart the next steps forward and to determine what these new findings may mean for the field of HIV vaccine research. Those discussions will continue over the coming weeks and months.

And so we have a great deal of work ahead of us. However, today I have a renewed sense of optimism, cautious optimism, that the possibility of improving on these encouraging results and ultimately developing a highly effective vaccine to protect against HIV infection is within our reach.

I want to again thank all our partners in this endeavor and also thank the trial volunteers in Thailand for helping to move the HIV vaccine field forward.

Thank you.

Supachai Rerks-Ngarm: Good morning General Schoomaker, Colonel Jerome Kim, Dr. Anthony Fauci, ladies and gentlemen.

It has been the best experience for Thailand to participate in the global effort for HIV vaccine development. This HIV vaccine trial, in particular, has also represented Thailand's policy (inaudible) effective tool for protection of the people from HIV infection. In addition to the promotion of [risk] behavior avoidance, it has been actively implemented.

The outcome of this trial has provided the scientific community a large amount of knowledge on how HIV vaccines should be further improved. However, tremendous local capacities have also been built in the study. The capacity in clinical studies has been strengthened among [health manpower]. (Inaudible) [know-how on laboratory investigation] has been transferred, and the (inaudible) networking has been established. Most important thing is the experience of [incoming engagement], which is essentially the key contributor to high retention rates in this [Phase III] trial. All of these factors will form important basis for further HIV vaccine development.

The Thai Ministry of Public Health is committed to HIV vaccine development with strong cooperation with national and international research networks for the goal of achieving a safe and efficacious HIV vaccine. This (inaudible) trial is an excellent evidence of (inaudible) have achieved among national and international organizations to develop a safe and effective supplementary biomedical intervention for HIV/AIDS prevention.

It will not be possible for us to have reached the success of this trial if we had not obtained excellent support from our international collaborators that include the trial sponsor, U.S. Army Surgeon General; the trial funders, U.S. Army Medical Research and Materiel Command, (inaudible), National Institute of Allergy and Infectious Diseases, [NIAS]; the vaccine manufacturers, sanofi pasteur and Global Solution for Infectious Diseases; World Health Organization; the data safety and monitoring board; and all other international nonprofit organizations in the field of HIV/AIDS. Last, but not least, the contribution of the volunteers and their families (inaudible) trial activities has certainly been the most vital component of this long study. (Inaudible) appreciate it. Thank you.

Darren Back: Thank you, Dr. Supachai.

That concludes the presentation, so we'll now move on to the Q&A session.

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Darren Back: As a reminder you can submit questions via the webinar, via your telephone pads to the moderator or, in France, via your facilitator at the front of the room.

So the first question is from Javier [San Pedro], from (inaudible), and we're going to direct this one to Dr. Kim. Dr. Kim, the question is, what could be the efficacy threshold for an HIV vaccine, and what would be the (inaudible), e.g. 40%, 90%?

Jerome Kim: Thank you. The efficacy threshold may be a consideration that's specific to

individual countries, the nature of their HIV/AIDS epidemics and the performance characteristics of the vaccines being tested. This is a question for public health and preventive medicine experts as well as HIV vaccine experts and needs to be reviewed along with data in the target populations. In our own trial, we had predetermined that we would convene a consultation of the same group of people, HIV experts, preventive medicine experts, public health and policy experts, to determine our future course of action regarding the specific use of this vaccine in Thai populations.

Darren Back: Okay. Thank you, Dr. Kim.

The next question, again from Javier [San Pedro], if the vaccine mix was shown to be -- to work in other populations, would it be worthwhile to start using this directly, at least in some African countries? And we're going to pass that one to Dr. Fauci.

Tony Fauci: Well, I think you have to realize that, as was stated by Dr. Kim, that this is a vaccine, first of all, that's a clade E/B, and that is not a clade that's predominant in African countries, which are fundamentally C. So, first of all, you'd have to do some significantly additional studies (inaudible) you want to translate that, bridging studies, as we call them, as well as the fact that you have to think in terms of the capability of producing this, because the production capability is something that also is self-limiting. But the real, fundamental answer is that when you talk about different countries, as Dr. Kim alluded to, not only is the decision of whether you want to use it depending upon the rate of infection in a given country, but you also would like to have a clade match.

Darren Back: Okay. Thank you, Dr. Fauci.

The next question comes from Gus Cairns, from NAM and aidsmap. This question is going to go to Dr. Kim. What HIV subtypes did the vaccine work against, and how specific to this one group was the immune response?

Jerome Kim: Okay, thanks. The vaccines were designed for use in Thailand, and so contained components of both subtype B and subtype E, which are the two predominant circulating subtypes in Thailand. Sorry, I'm looking at the question. So, the --

Darren Back: I'll repeat the question for you. It's which HIV subtypes did the vaccine work against, and how specific to this one group was the immune response?

Jerome Kim: So, at this point we don't have any data on how specific the response was. What we do know is that the HIV vaccine did prevent infection in these cohorts, and that there was no, at the first glance, apparent difference in the distribution of subtypes between the vaccine and placebo recipients.

Darren Back: And next question, again, from Gus Cairns, and, again, this is going to Dr. Kim. Do you have data yet on whether certain groups were protected, e.g., by gender, age, nationality or risk group?

Jerome Kim: So, that's a great question, and, unfortunately, our data set is still being looked at. But we have to remember that with the 125 infections that we saw that we may have limited ability to do those specific comparisons.

Darren Back: Okay, thank you.

And the next question is, again from Gus Cairns, why did you conduct the vaccine trial in low-risk people? Their immune response might be different to high-risk patients. And, again, this one is to Dr. Supachai and Dr. Kim.

Jerome Kim: Okay, so, one of the hypotheses that is clearly indicated by this trial is the idea that people who are at community risk, that is, not at particularly high risk, a particular population, as Dr. Fauci mentioned, like MSM or injecting drug users, may have a different risk from people who are in higher risk categories. The challenge may be different. The route of acquisition may be different. And all of these things could potentially be important. And the question is absolutely right. Their immune responses may be different because the route of challenge may be different.

So, one of the reasons that some people have postulated that this trial may have succeeded is that the intensity of exposure of the individuals in this trial might have been lower. We know from work on other vaccines that if you have -- even if you have a highly effective vaccine that you can overcome that vaccine immune response with a sufficiently high dose challenge.

Dr. Supachai?

Supachai Rerks-Ngarm: The only thing that I can add is that this is a trial among the (technical difficulty).

Darren Back: Okay. Thank you, Dr. Supachai.

The next question is from Miriam Falco, CNN Medical News, and this is directed to Dr. Fauci. Dr. Fauci, you said the study was done in heterosexuals and in the community. Could you clarify what that means?

Tony Fauci: Yes, Miriam. The study clearly is a study that recruited heterosexuals. There certainly could be either identified or unidentified men who have sex with men who get into the study. We don't feel that that is a significant proportion. I'll ask Dr. Kim to also comment on that. But, fundamentally, when you recruit for a study, the recruiting is, in this case, for heterosexual, which, as was just mentioned on the last question, is fundamentally in the study a low-dose mucosal exposure as opposed to some of the other types of exposure.

But, Colonel Kim, do you want to amplify a little bit on that about the possibility of there being a very small proportion of them being men who have sex with men?

Jerome Kim: Yes, sir. We do know from baseline risk assessments that there were a small number of men who have sex with men, of people who reported commercial sex work, people

who were involved in the entertainment industry. So, and, again, I think we need to remember that what we mean by community risk is that we will include everyone in the community, and that would include people at higher risk and maybe people at very low or no risk. But that's the nature of this cohort. Rather than pick a single population with a uniform route of exposure, we accepted everyone in the community, regardless of what their reported risk was. Now, those numbers, again, are fairly small.

Darren Back: Thank you, Dr. Kim.

Next question is from (inaudible), from IAVI Report. In some of the materials on the trial it was powered to show true vaccine efficacy of 50%. The trial showed 31.2% efficacy. Please could you explain the discrepancy? And again this is going to Dr. Kim.

Jerome Kim: So, the powering calculations helped us to establish the size of the cohorts that was necessary and the length of follow-up that would be necessary. The actual vaccine efficacy was 31.2%. So it was lower than the construct that was used to do the power calculation -- that is, to help us to determine the size and length of follow-up -- but it did not -- and the efficacy, the vaccine efficacy that we saw in this trial, is an entirely separate number.

Darren Back: Okay. Thank you, Dr. Kim.

The next question is to the Surgeon General. Surgeon General, why did the U.S. Army conduct the study?

Eric Schoomaker: I think it's a very good question, and it's easily answered. The first and foremost responsibility of the Army and of Army medicine and, by extension, all of military medicine, is to protect our soldiers, sailors, airmen, Marines, Coast Guardsmen. And so we undertook this study to achieve that very, very important mission to protect our warriors at home and abroad.

We partner with other U.S. federal agencies such as the National Institute of Allergy and Infectious Diseases, which is a leader in the understanding of infectious diseases and protection against them whenever their responsibility to protect the public at large and ours to protect our soldiers and our families overlap, and in this case this is a very, very good example of when that synergy has been effective.

We've reached out to a longstanding partner of ours in Asia, the Thais, through the Royal Thai Army and the Ministry of Public Health, to assist us, because our ambitions overlap with theirs, which is first and foremost to protect our people. And so the development of an effective vaccine protects our soldiers and, indirectly, protects them by reducing the burden of disease around the world and making the world safer.

Darren Back: Thank you, Surgeon General.

The next question is from Sandra Basu of U.S. Medicine. What will need to occur from this point forward for this vaccine to gain FDA approval? How long might that be? And that question is to

Jim Tartaglia.

Sanjay Gurunathan: Okay, so this is Sanjay Gurunathan from sanofi pasteur, and, again, I want to first say that we're very pleased with the results that Dr. Kim and Dr. Fauci discussed. We do know that we have many unanswered scientific questions that still need to be dealt with over the next coming years. We will sit together with the broader scientific community, with all HIV vaccine experts, public health experts, to really define what the next steps will be. But certainly what is in the cards in order to extend the findings that we've already seen in Thailand is a series of investigations, which will take a few years, to answer some critical questions before we can make a determination whether or not this vaccine would be appropriate for licensure.

Tony Fauci: Could I just chime in, because I want to make sure that there's not misunderstanding -- not misunderstanding, but maybe a little bit of misinterpretation of a literal interpretation of the question. Because the question was, what will need to occur this point forward for this vaccine, and when you say this vaccine you're talking about a vaccine that's a B/E clade that was tested in Thailand among a specific population of people, namely low-risk heterosexual. And you're asking what would it take to gain FDA approval?

And I agree with the comments that were just made. Be careful about "this vaccine," a vaccine that's based on the principal and the approach that was taken here. This vaccine was not powered for FDA approval in the United States. So it will be that what we learn from this vaccine and the many, many studies that I alluded to in my opening remarks would have to go into the kinds of trials that would then ultimately, if indeed that is what happens, gets approved by the FDA. So we're talking about a significant period of time. We're not talking about results from this trial being presented to the FDA for approval. I do not think that that's in the cards at all. There will have to be a lot of work, probably measured in years.

Darren Back: And Dr. Francis, I don't know if you've got anything you'd like to add to that question.

Donald Francis: No, clearly there is a great deal more work to do and discussions about the specific issues in Thailand with this vaccine.

Darren Back: Great. Thank you.

Next question is from Regina McEnery, from IAVI Report. What was the rationale for establishing a co-primary endpoint after trial start? Did they measure [CDAT-cell] response? Did they take mucosal responses to tease out immune response? And that's going to Colonel Nelson - Colonel Michael, sorry.

Nelson Michael: Hi, this is Colonel Nelson Michael. So, when the trial was in its infancy, there was not as much attention in the field to the possibility that a vaccine could actually show efficacy not simply by blocking infection, per se, but if infection were to occur, the notion that a more attenuated course of infection, so a milder case of disease, might occur with a lower viral load subsequent to infection, was not as popular an idea in the late 1990s and early 2000s as it became as we got closer and closer to the trial. And so based on input from advisory groups from

NIAID and other constituencies in our field, we felt that it would be important to add the viral load set point after the possibility of infection, to look at those two major themes for pathogenesis. One, does the vaccine actually provide protection from infection? And, two, if not, might we see actually evidence for an attenuated level of virus replication in somebody that became infected?

Clearly, this was something that was becoming popular in animal model experiments, and we felt that it was very important in RV144 to develop empirical evidence that at the same time we were measuring acquisition effect that we should look at viral load. Human immunology and human experimentation trumps everything else in our field. It trumps what we do in test tubes, and it trumps what we do in animals. We're very, very glad that we added this as a co-primary endpoint.

As Dr. Fauci said in his opening remarks, I believe that it's fair to say that most of us in the field were surprised to see that a vaccine combination that some might characterize as a quote, unquote, "T cell vaccine," was to show what we've learned, that the actual acquisition of infection was diminished, but if you were to become infected your viral load was no different. So this was something that was quite humbling to me, personally, I believe to many of us, that some of our preconceived notions of what we expect to measure and what we think are important might have just been turned on their heads.

And, as Dr. Fauci and others have mentioned, we've kicked open the door to this problem, but we have a long road ahead of us to figure out exactly what these immune responses in this study will mean and how we might be able to use those immune responses to more rationally design the next generation of HIV vaccines that in our hope will be ones that will work for all of mankind everywhere in the world.

Darren Back: Thank you, Colonel Michael.

Next question is for the Surgeon General. Will the U.S. Army continue to conduct HIV vaccine research? And this one's come through from the telephone line.

Eric Schoomaker: And the simple answer there is yes. The U.S. Army, and we are privileged to serve as the lead service for really a three-service effort of the Army, Navy and the Air Force, the three principal medical services in the military, are all very keenly interested in promoting the reduction of disease burden from HIV. And we very aggressively sponsor, in association or in collaboration with the Centers for Disease Control and Preventive Medicine as well as the National Institute of Allergy and Infectious Diseases, World Health Organization and other groups, research and efforts and education in protecting populations around the world and in seeking basic science research as well as clinical trial empiric evidence for improvements in disease prevention and disease treatment. So we will continue this effort, as we are with the Thais right now and with important African partners, and appreciate this opportunity to participate.

Darren Back: Thank you, Surgeon General.

The next question is from Jeff Berry, from Positively Aware Magazine. Vaccine combination trials have been done before. What about these two vaccines do you think is causing efficacy? And this question we'll put to Dr. Fauci.

Tony Fauci: There's a real simple answer to that question. We don't know, and that's really the point that I made in my opening remarks and that Colonel Michael made in his, and that is that we have a positive signal. If you look at the classical immunological parameters that we measure when you look at vaccines -- neutralizing antibodies, the hope for a high level of HIV epitope-specific CTLs, etc., etc. -- actually, we didn't see that. We saw, at best, the modest response that antibodies that reacted against cell-adapted virus, not in wild-type virus. We saw lymphoproliferative responses. We didn't see a lot of CTLs in the classic way we're looking at it.

And that's really the point that I'm trying to make. We don't know the answer to that. But correlates really don't mean something if you can't correlate it with a positive effect. So what we have now is, and I underscore, albeit it a very modest effect, but modest effect that we can then go back and try and figure out just what it is that gave us this result. What immunological parameter gave us this result? We may not have even begun to measure that routinely. We don't even know what it is. It's an excellent question. But that's the kind of thing, as Nelson and I both said, is really rather humbling about how much we don't know.

Darren Back: Thank you, Dr. Fauci.

Question from Sandra Basu again, from U.S. Medicine. Can you tell me what the Army's contribution was to this vaccine trial effort? And I'd like to put that one to the Surgeon General.

Eric Schoomaker: Thanks for the question, Ms. Basu. I will tell you, the Army has had a longstanding interest in infectious diseases and in protecting the force, and our contribution was severalfold.

First, we've had longstanding partnerships with international partners such as the Thais, but Kenyans, Tanzanians, Nigerians, Ugandans and others in trying to get to basic causes for HIV disease as well as other infectious threats. The Army has a subordinate command, the United States Army Medical Research and Materiel Command, that has laboratories, to include the Walter Reed Army Institute of Research, with a longstanding expertise and interest in infectious diseases, vaccine development and others. And our contribution was, to very much closely align with Dr. Fauci's early comments, to strike an appropriate balance between basic science and clinical trials, specifically aimed at protecting the force.

And our infectious disease experts of our laboratory scientists as well as those who have experience in field trials all participated with our Thai partners and with our partners at sanofi and GSID and others to bring this trial to fruition. This really did require a very extensive, longstanding partnership among all of the partners that we described at the opening of this media event, both partners within the federal government of the United States, international partners with our Thai colleagues, and partnerships with the commercial and nonprofit groups that are a part of providing these vaccines.

Darren Back: Thank you, Surgeon General.

The next question is from Marilyn Marchione from Associated Press. I think it's going to be pretty obvious from the question who this is directed to, the question being for sanofi pasteur and Global Solutions, can you please explain what immediate studies are planned?

Donald Francis: Go ahead, Sanjay.

Sanjay Gurunathan: Go ahead, Don.

Donald Francis: Well, I think that that, obviously, from our chuckling, is an issue that's on the table right now with both our Thai colleagues and us about with limited amount of vaccine we have right now, and until we actually get production cranking so we have new vaccine, we've got a small number of studies that we could do, and a discussion of what to do with those is underway right now, and much discussion, obviously, of what is the best approach to answer some of the most immediate questions, and then the much larger issue of how we analyze the data to figure out where some people were protected and others were not is going to be key to expanding the protective efficacy of the vaccine to greater than 30%.

Sanjay Gurunathan: All right, Don, I fully agree, and I have just a few more things to add. I mean, as far as next steps are concerned, really, [at the field] I see two parallel tracks. One is certainly to extend the results that we've already seen from RV144, and what is needed there is a more in-depth analysis on the current studies and the samples we have, as had been said in the call many times before, to extend these findings by doing both clinical and preclinical studies with this regimen to find out how it's working and how we can make it better. I think in parallel we also need to take these results and see if we can improve on the current vaccine components and the regimen, and if necessary move novel components as dictated by these analyses and these results to move forward.

In the end, I think, taken together, we are moving as rapidly as possible with the field, with the investigators, with the scientific community, to use the information that we'll get from the study to provide a greater rationalization, if you will, for subsequent development. We must remember, as Dr. Fauci said, that the vaccine development, it's not going to happen -- vaccine licensure is not going to happen tomorrow. It will be an iterative process, and it will take time, and this is particularly true for HIV. But I think the results do give us, show us promise that this can be done.

Darren Back: Great, thank you.

The next question is from Regina McEnergy, from IAVI Report. At launch there was a lot of concern and criticism from AIDS scientists [at that time]. Did you hesitate at the time of the launch? How do you feel now that you have these results? And we'd like to put that one to Dr. Fauci and Dr. Supachai.

Tony Fauci: Yes, as people who were around then remember, there was some criticism there. There was some hesitation at the time, because we were trying to figure out the right balance

between empiricism and getting more concrete scientific information. We felt we had a commitment to our colleagues who we had partnered with in the Department of Defense as well as our colleagues in Thailand. So it wasn't an easy decision.

I don't at all resent the criticism, because I think the criticism was based on people's well intention of making sure that HIV/AIDS vaccines resources are spent appropriately. So it was not an easy time. I believe, and I think it's vindicated now, that the decision was the correct one. But I think that the points that were made by the scientists that were criticizing the decision, if you go back, there were some really valid points that they had about making sure that we understand the science better. And I think what it is is just a reflection back on what I said in my opening statement, that we try very hard to strike the proper and appropriate balance between basic science and HIV vaccinology together with empiric approach as manifested by clinical trials. So we feel good about the results. It was a tough decision. I'm glad we made it.

Darren Back: Dr. Supachai, anything you'd like to add?

Supachai Rerks-Ngarm: (Technical difficulty), but if I may add, from the Thai side, at the beginning, we actually had a feeling of hesitation a little bit because of that reason that actually [gave us a notion] to be aware of scientific point of view. But since we know that the (inaudible) of the vaccine to fight against the HIV (technical difficulty), and we have (inaudible) information on our [Phase I/II trial]. This is the reason why we decide to move forward, but not on our own decision, but we also had the consultation with many international experts, including the experts from NIH. Then we (inaudible) to move forward. And now we have learned that that decision turned out to be a very significant [outcome], at least to give the hope to the world that we can have the vaccine, actually [vaccine to prevent infection] in the future.

Darren Back: Thank you, Dr. Supachai.

Our next question is from (inaudible). Sometimes you've called this trial a Phase IIb test of concept trial, in other places a Phase III trial. Can you explain this discrepancy? We'd like to put this question to Colonel Michael.

Nelson Michael: So this is an excellent question, and I completely understand why this is confusing. The answer really is rooted in history. When we began the planning for this study, we had fully expected it to be a pivotal licensure study, or that there would be a possibility of us doing that, based on what at that time were relatively high rates of transmission in Thailand. Because of the heroic efforts of the Thai government and the king personally intervening to emphasize primary and secondary prevention techniques for HIV in Thailand during the run-up to this particular study, the incidence rates in the Kingdom of Thailand fell dramatically.

And we adjusted as we could in terms of the size of the study and the number of arms in it, but it became clear as we were approaching the launch of the study and during consultations with the FDA that the anticipated number of endpoints in the study would really put this in the category of a test of concept or a proof of concept study known as a Phase IIb. This is in fact what this study actually is.

Because of the fact that this study was about to launch, in consultation with our Thai colleagues it was determined that it might be too confusing to change the name of this study, which had already been branded as a quote, unquote, "Phase III" study. And so a decision was made at that time in 2003 to continue bearing the name of a Phase III, but when in fact this study, from its actual execution, was truly a test of concept, or a Phase IIb. This is something that the FDA has never had any confusion about, nor us as a study team. But it's perfectly understandable why this is confusing to those outside the study.

Darren Back: Great. Thank you, Colonel Michael.

Next question is from NBC News. Could you please explain the viral load results further, and what might these mean in terms of the potential to develop symptoms in the future? And we'd like to put this one to Dr. Kim.

Jerome Kim: Thank you. So, there was no difference in the amount of virus in the body of people who received vaccine and became infected compared to that of placebo recipients who became infected at a point three to six months after the diagnosis of HIV infection was made. It's entirely possible that there are longer term effects from vaccination, and these are being explored in what we call the Breakthrough Infections Protocol, known as RV152, which continues to follow vaccinated and placebo recipients for longer periods of time after the principal Phase III study, RV144, is ended. So we're looking forward to looking at those data in the near future.

Tony Fauci: Yes, let me just add and underscore -- this is Tony Fauci -- add and underscore what I mentioned in my opening brief comments is that I really think that this is really very important, because it suggests, obviously, with the modest result and the numbers of infections, we don't -- and the fact that we have not had the ability yet to really mine into anything that could be correlative immunity, it strongly suggests that there's something different going on between the immune response that blocks initial infection, what we call acquisition, and the immune response that controls viral load.

This is really very important when you start to look at correlates in any vaccine trial. We need to figure out what the particular components of the immune response were that led to this modest decrease in acquisition, and we need to try and optimize that so that we can get the 31.2% up to a much higher group. The fact that it's a bit different from the fact that viral load was unchanged in the vaccinated versus the placebo group is, in my mind, as I mentioned, a very important finding vis-v-vis our understanding of the immunology.

Darren Back: Thank you, Dr. Fauci.

Next question is from U.S. Medicine. How much was spent on this vaccine trial effort? Which agencies paid for it? And we'd like to open that again to Dr. Fauci and Dr. Supachai.

Tony Fauci: I'd say in round numbers that the trial cost approximately \$100 million. The NIAID resources in that was approximately 70% to 75% of that.

Eric Schoomaker: Right, and this is Dr. Schoomaker, the Army Surgeon General, and the Army

picked up the balance of approximately 25% of what turned out to be \$105 million. Dr. Fauci is exactly right. And, to their credit, the Thais, that did a remarkable job on this, and I think the word has been used of heroics, came in at 15% under the estimated cost of the trial, did a remarkable job of acquiring volunteers and conducting this trial almost flawlessly and did not spend as much money as we estimated it would take.

I think the question really helps to describe, too, the importance of the partnerships that are required. The development of a vaccine like this just for the trial alone, \$100 million, roughly, illustrates the burden of expense and the time required to get to an effective vaccine or effective drugs in the world today. We've not described any of the cost of the basic science and all of the product development that went into these vaccines in the first place. They're very large numbers. It means that any single collaborator in this really can ill afford to take on the burden alone, and it takes the partnership that you've seen here among so many to make it come to fruition.

Darren Back: Next question is from the phone, and we're putting this one to Dr. Gurunathan. How safe was the vaccine regimen?

Sanjay Gurunathan: Well, I'll speak for ALVAC-HIV. We have used ALVAC-HIV in clinical trials from the mid-'90s. Over 15,000 to 20,000 human volunteers have received ALVAC, and to date we have not seen any safety concerns with ALVAC.

Donald Francis: And this is Don Francis from GSID. Clearly, the recombinant boost on this has been given to thousands of individuals and still -- and have very little side effects at all to date.

Darren Back: Great. Thank you.

Time is running out, so we just have time for one final question, and this one is for Dr. Fauci. What impact will this study have on the HIV vaccine field? What doors will be opened? And that's from (inaudible).

Tony Fauci: I believe it'll have a very important impact on the field of HIV vaccinology for several of the reasons that I mentioned before. But, just to reiterate and summarize, when you have even a modest result like this, there are so many things that you need to do. You need to build on the result of this particular vaccine trial and the product that was used. I mentioned a few of those. How can you maximize it? What about additional boosters? Examining samples that we already have, getting more samples.

But overarching all of this is the fundamental questions that will now arise that have been black boxes for us, and that particularly relates to the issue of what kind of correlates of immunity were responsible for this modest effect? Can they be optimized? Can you have a vaccine that both blocks acquisition and also has an effect on viral load if it's not successful? Are there a dichotomy of immune responses, or are the immune responses really separate or overlapping? These are very important, exciting questions, actually. So they're -- to me, this -- as I mentioned, this is the beginning of the effort. It's opened up a door for us to ask some very important both fundamental basic science questions as well as some clinical questions.

Darren Back: Great. Thank you. Dr. Fauci.

Now, time's running short. That's the end of the Q&A. If anyone has any additional questions they'd like addressed, please email Lisa Reilly. Contact details are at the end of the press release at MHRP.

And with that I'd just like to hand over to the Surgeon General for some closing remarks.

Eric Schoomaker: And I just want to close by thanking everybody for joining us for this media event today and thank all of those who participated in answering the questions, all of my colleagues across the world, literally. And I want to extend appreciation and congratulations to our Thai colleagues, who showed remarkable tenacity and courage in conducting this trial, and to all of those unnamed investigators at the bench and in clinics around the world who participated in providing the insights that were required for this trial to be conducted. You all are to be commended, and I think we are grateful for your efforts and for your stamina.

Thank you again for joining us, and thank you for hosting this.

Darren Back: With that, we'll close the session.

Thank you, everyone.