The Thai Trial: Where Do We Go From Here?

Gail Broder, US Project Manager, HVTN Community Relations & Education

Attending the AIDS Vaccine 2009 conference in Paris was an exciting experience, perhaps most memorable for the presentation of data from RV144, commonly known as the Thai Trial. The accomplishment of enrolling over 16,000 participants and maintaining a 90% retention rate is just astounding, and truly provides a benchmark for future efficacy trials.

Regardless of which statistical analysis one uses, the trends in the data were similar. Although only one analysis showed efficacy of statistical significance (see Table 1), there is clearly something happening that is biologically significant, noted Dr. Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases (NIAID) in his presentation at the close of the conference. Just as the HVTN did following the surprising results of the Step Study, the leaders of RV144 have established a scientific steering committee and four subcommittees to guide continued analysis of the data. These groups will look at how best to use the limited blood samples stored from study participants, as well as what other kinds of studies in animal models or people should be done to determine the correlate(s) of immunity that were elicited in this group of participants, and to maximize what can be learned overall. (Correlates of immunity are the specific immune response(s) that are needed to protect the body against initial infection or to control an infection, and since there is no evidence of any people who have “recovered” from AIDS and cleared the infection from their bodies, researchers aren’t entirely certain what they are searching for.) These four subcommittees will examine Humoral and Innate Immunity, T-Cell Immunity, Animal Models, and Host Genetics. The HVTN’s own Dr. Julie McElrath will chair the T-Cell Immunity group, so we can be certain that the HVTN will have an opportunity to share lessons we have learned as well as provide input into how further research is conducted.

In his presentation in Paris, Dr. Nelson Michael of the US Military HIV Research Program noted that two new research questions have already emerged from RV144. First, was the modest protection of the vaccine linked in some way to the fact that participants were at lower risk of being exposed to HIV?

Khorb Koon – Thanks for the Lessons in Community Engagement

By Steve Wakefield, Associate Director for Community Relations & Education

Buddhism teaches generosity. According to Buddhist doctrine, Dana or giving, is the very first and the easiest practice of making merit. Another moral instilled in the mind of Buddhists is Metta, the desire to make others happy. Metta, according to the Lord Buddha, is the virtue which sustains the world. Unquestionably, each of these teachings contributes to the charitable nature of Thai society and to the successful community engagement that took place during RV144. These monumental efforts cannot be measured adequately and we thank the people of Thailand for their role in changing the HIV vaccine field.

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Since this trial enrolled participants on a community-wide basis and not because of particular risk profiles, the overall risk for HIV infection was much lower than what previous efficacy trials have observed. Second, how long does the vaccine’s effectiveness last? The data that has been presented shows trends toward efficacy waning after one year. It will be important for future research to address how long any observed efficacy lasts, so that we can better understand the need for follow-up booster shots.” An example of this is the vaccine for tetanus, where boosters are needed every 10 years to maintain the efficacy.

“Science knows no country, for science is the light that illuminates the darkness in the world.”

Alan Bernstein, Director of the Global Vaccine Enterprise, quoting Louis Pasteur at the 2009 AIDS Vaccine Conference in Paris

It is also interesting to note that just as the HVTN continues to report new data learned from the Step Study and Phambili two years after these trials stopped vaccinations, we can expect to hear continued reports of information learned from the Thai Trial going forward.

But what does this mean for us in the short term? First, the Thai results support the rationale for moving forward with HVTN 505. Just as the Thai Trial was designed to elicit both T-cell and antibody responses by using two vaccines in prime-boost combination, HVTN 505 also uses two vaccines in a prime-boost combination in order to stimulate stronger responses. More specifically, HVTN 505 is designed as a study focused on discovery, helping researchers to better understand how to design vaccines to stimulate more powerful T-cell responses. Since both vaccines used in HVTN 505 contain a synthetic version of the HIV protein env, and we know from past trials that participants who receive the vaccine have strong antibody responses, it is also possible that we could see some protection against new HIV infections, and this is being analyzed as one of the secondary research questions. The information we learn about T-cell responses in HVTN 505 can then be carried forward in other trials with additional populations and in other regions of the world.

Additionally, the changes that the HVTN made to its scientific agenda following the Step Study continue to inform the field. For example, we have just begun a trial using electroporation (HVTN 080) which will tell us about the potential for improving responses to DNA vaccines. HVTN 906 and 907 are in progress and will provide valuable information about women at high risk in the US and Caribbean and how best to reach them. The network is also engaged

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**Table 1: Explanation of the three analyses of the RV144 results**

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<th>Analysis Type</th>
<th>Description</th>
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<tr>
<td>Intent to treat (ITT)</td>
<td>Includes all 16,402 people enrolled, including 7 people who were determined to be infected pre-vaccination. This showed 26.4% efficacy, which is not statistically significant.</td>
</tr>
<tr>
<td>Modified Intent to Treat (mITT)</td>
<td>Excludes those 7 people infected at baseline (16,325 participants). This is the statistically significant result, with efficacy at 31.2%. Trial leaders described this as the analysis that is preferred, because it is the most rigorous and least likely to have bias. mITT makes no assumption that getting every single dose is relevant, or that getting every dose on time is relevant. It includes those that may have missed a dose, or those who got a dose off schedule. This is thought to be the most “real world” view of what people under typical conditions (not in a clinical trial) might do.</td>
</tr>
<tr>
<td>Per Protocol (PP)</td>
<td>Looks at those who adhered exactly to the protocol (12,542 participants), and excludes those who became infected with HIV during the 6 month vaccination period (because they did not get the complete series of vaccinations). Efficacy in this analysis was 26.2%, which is also not statistically significant.</td>
</tr>
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SOLVING THE NEUTRALIZING
ANTIBODY PROBLEM

HIV IMMUNOGENS

SOLVING THE PROBLEM OF HOW TO CONTROL HIV INFECTION

TECHNICAL FEASIBILITY

SMALL ANIMAL MODELS
Safety and Immunogenicity

NHP STUDIES
Safety, Immunogenicity, and Efficacy

PHASE I-II CLINICAL TRIALS
Safety and Immunogenicity

PRIORITIZATION OF CLINICAL CANDIDATES

INTERMEDIATE GOAL
PROOF OF EFFICACY IN HUMANS

ULTIMATE GOAL
SAFE AND EFFECTIVE PREVENTIVE VACCINE FOR USE AROUND THE WORLD

Roadmap courtesy of IAVI, Samuel Velasco/5W Infographic

So where is the HVTN on this map?

Here are some of the questions currently being looked at through HVTN research

Will HVTN 505 (ongoing) be effective in eliciting an antibody and/or T-cell response?

How does genetic background affect vaccine responses?

What can be learned from the Vaxgen study, which was designed to elicit an antibody response?

What can be learned from RV144 (the recent Thai study), which was designed to elicit both an antibody and T-cell response?

How can we recruit & retain members of high-incidence communities?

How can we induce broadly neutralizing antibodies?

How do different vaccine vectors influence vaccine effects?

How does the location of injection affect the vaccine (i.e. intradermal, intramuscular or multi-site)?

What can be learned from continued analysis of the Step and Phambili trials (HVTN 502 & HVTN 503)?

How does the route of mucosal transmission impact vaccine effects?

Which immunogens should be targeted? When and How?

(This is what an effective T-cell based vaccine could do)
What Does “Community Advocacy” Mean in Your Community?

By Carrie Schonwald, International Project Manager, HVTN Community Relations & Education

What is community advocacy?

**Community**, according to the Encarta World Dictionary, is defined as a group of people with a common background or with shared interests within society. **Advocacy** is defined as active verbal support for a cause or position.

Simple, right? Well, not really. Those are each only one of several different definitions of those words and neither of them accounts for human elements. Human diversity, politics and emotions can cause an idea to play out very differently in different settings. Just as no two communities are exactly the same, community advocacy is not exactly the same in any two places. While defining exactly what community advocacy is within the HVTN context may not be that simple, we can say what it is not. HVTN community advocacy should not be equated with political advocacy involving lobbying lawmakers for policy change or funding allocation.

During this November’s HVTN Conference General CAB Session, all who were present began to explore the question, “What does community advocacy look like in your community?” To kick off the conversation, Cape Town Community Educator Ntando Yola and adolescent CAB member Nombini Nofemele gave a presentation that examined this issue for Cape Town. One key point that Nombini made was that one cannot advocate for someone well unless he or she has had real face-to-face interaction with that person; relationship building is a crucial part of community advocacy.

We then looked at various definitions submitted by HVTN CAB members prior to the conference and discussed them at our tables. Below are some of the definitions that were submitted:

*Advocacy can be seen as a deliberate process of speaking out on issues of concern in order to exert some influence on behalf of ideas or persons.*

In terms of HVTN studies we have to raise and stand in the gap for participants and community at large to make sure that they know their rights as to the trial and what is good for them.

A community advocate is someone who is there not to take sides, but to strive to make scientists and traditional healers, together with the community, understand the basic health needs for all.

Community advocates serve as a resource to the intended community to assist them in understanding the importance of a trial, the risks of participation, explaining why it’s important to participate and what questions will be answered.

I believe Community, in this case, pertains to the people affected by our HIV vaccine research footprint and their unique needs as a group. Advocacy is a process aimed to attend to those community needs.

However you define it and whatever it looks like in your community, community advocacy is at the very core of what CAB members, Community Educators, and Recruiters do in their HVTN work, and merits greater discussion. During the HVTN Conference, CAB members were just starting to have very animated conversations about this subject and we would like to continue the conversation, so please let us hear from you: what is community advocacy in your community? Please email your ideas to me by **January 15th, 2010** and we will publish them in the next CAB Bulletin.
A community perspective from the November HVTN Fall Conference, Strategic Planning Forum

By Jim Thomas, CAB representative to the Concept Working Group and Rick Church, GCAB co-chair

On Thursday, November 19, 2009, immediately following its semiannual conference in Seattle, the HVTN held a strategic planning session with representatives from scientific, operational, clinical, and community groups (community members included the authors and Miko Robertson, GCAB representative to the Scientific Steering Committee). The meeting presented scientific and logistical updates and concluded with extensive discussion among attendees. The meeting began with introductory remarks by Dr. Lawrence Corey, principal investigator of the HVTN.

Dr. Corey outlined a set of broad goals and strategies for the group’s consideration, many focused on extending the findings from the Thai study, RV144.

- The Thai Trial results indicate that more research is needed to understand vaccine efficacy among general population enrollment.

- Quick enrollment of eligible, at-risk participants for vaccine trials will likely put a greater emphasis on recruitment at clinical sites in South Africa and the Caribbean.

- There is a need to broaden the vaccine portfolio beyond T-cell vaccines to give greater emphasis to antibody-eliciting vaccines, particularly those that include env.

- Continued study of adenovirus vector vaccines is important, while also focusing on pox-based vectors.

Drs. David Montefiore, Georgia Tomaras and Julie McElrath followed with presentations on current assays used by the HVTN and offered new assay approaches for consideration. (Assays are types of laboratory tests)

These include:

- Better measuring of binding and neutralizing antibodies
- Measuring possible antibody activity in mucosal tissues
- Examining whether a vaccine can elicit more robust activity in mucosal tissue
- Examining whether a vaccine can induce better cellular responses, including innate immunity.

Steve Self, Principal Investigator of the Statistical Center for HIV/AIDS Research & Prevention (SCHARP), presented possible new approaches to trial design that may result in greater efficiency. He illustrated how running several vaccine trials concurrently with a shared control group (placebo arm) could be more efficient.

Dr. Jim Kublin presented an outline of the availability and clade variety of HIV vaccines including vectors and proteins for assay and clinical evaluation. He followed with a call for production of new cross-clade proteins.

Dr. Glenda Gray presented on recruitment abilities of the South African trial sites in Cape Town, Durban, Klerksdorp, Medunsa, and Soweto. Dr. Gray illustrated the capacity of these sites to quickly enroll large numbers of study participants, including large cohorts of women, who are at high risk based on the high HIV prevalence rates in the region.

Finally, a lengthy and open discussion ensued. Community concerns were raised regarding provision of clear lay language to explain any new approaches to be pursued by the HVTN. A clear take-home message for us as community members at this meeting is the need for CAB discussions regarding potential trial populations at local sites, and the capacity for large and small vaccine trials distributed throughout the global network.

HVTN Community members: CAB members, CERs, NHVREI Partners and Advocates gather on the final day of the Conference for a wrap-up lunch.

Community engagement for HIV vaccine trials is “never enough, and never finished.”

—Dr. Nelson Michael
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in discussions about how we can build on the Thai results. Our leaders and investigators are considering new trial designs, additional lab assays, as well as what can be learned from different participant populations and different geographic regions (see image on page 3 and “Strategic Planning” on page 5).

While the results of RV144 may not have taken us all the way to the destination of a licensed HIV vaccine, they have opened up many new potential routes, pointed us down new paths, and given us a big sign to guide us on our way. These are exciting times, and I for one am looking forward to where the journey takes us!

To hear webcasts from the AIDS Vaccine Conference in Paris, visit the Global HIV Vaccine Enterprise’s website: http://www.hivvaccineenterprise.org/conference/2009/webcasting.html
Khorb Koon  continued from page 1

It is easy to stand in awe of the Rayong and Chon Buri communities when you realize that more than 16,000 volunteers from these two provinces participated in the testing of an HIV vaccine. It can be a little more challenging to think about community engagement for such a large segment of these communities. Screening of participants began in September 2003 with the first enrollment in October of that year. Yet Thai collaborators had begun coordinated efforts to ensure the project’s success almost two years before the trial opened. Let’s take a moment to look at the enormous efforts required to enroll and support so many people.

Preparation of the informed consent materials began while the protocol was still being finalized. Many vaccine trial informed consent documents are created in English then translated into other languages. However, for this trial the process was different. In order to ensure the most thorough understanding possible, the information was drafted in Thai and then translated into English for collaborators, ethicists and review boards. A decision was made that the informed consent process would involve group and individual discussions, time for questions and answers, booklets and video presentations. Community understanding would be as important as individual agreement to participate in the trial.

Dr. Supachai Rerks-Ngarm, the trial’s principal investigator, told all 350 staff members to listen to the voices of the communities for without the community there would be no study. Building on his experiences with the successful national 100% Condom Programme of the 1990s, he invited CAB members and community educators to visit the two provinces and meet with individuals to help think about what it would take to conduct this trial. Rio de Janeiro Community Educator Monica Barbosa de Souza, Soweto Community Educator Mama Matilda Mogale, Chiang Mai GCAB member Udom Likhitwonnawut and I joined this meeting, during which we identified three key principles of community engagement:

- Honest, straightforward awareness campaigns,
- Social marketing, not public relations, and
- The final decision whether to volunteer in the study rests solely with each individual.

Nusara Thaitawat, the Communications Manager for this study, worked with Dr. Chirasak Kahmboonraung to engage and train media and community leaders. An important focus was addressing fears about being used as guinea pigs. The message was that key opinion leaders needed to serve as “watch dogs” and to truly help people understand the research.

These early activities led to more than 400 community health forums and volunteer relations activities, such as booth presentations with factory workers and in shopping areas, conducted by village health volunteers and over 300 recruitment and education staff. There was also extensive use of local radio and video to increase community understanding about research participation, individual rights and responsibilities, and the nature of the scientific questions being asked in this study.

More than 26,000 persons were screened at over 40 health centers. Mr. Nimit Thein-Udom, former Director of the Thai NGO Coalition on AIDS (TNCA) noted that the responsibility for trial education does not rest solely with AIDS vaccine researchers and health authorities, “but [that] they have an important role to play by making the subject and themselves accessible.” The 90% retention rate of over 16,000 participants demonstrates just how successful these education efforts were.

Now that the trial has ended, some people are starting to ask “What comes next?” This question is as important in the context of community education as it is in defining future scientific studies. CAB members and the RV144 research team have identified “sustainability” as one of the largest challenges for the future. How can communities utilize the understanding of research, the community expertise, and the sense of commitment during the next few months or years? What educational campaigns, interactive games, dialogues and discussions are appropriate for two provinces that have given so much to the world? We welcome your suggestions on this concept of post-trial sustainability as this is a challenge shared by many communities at the end of a trial.

The HVTN wants to express its gratitude to the thousands of Thai citizens who made this trial such a success. The people of the provinces of Rayong and Chon Buri have made scientists and community members happy through their important contribution to the field of HIV vaccine research. We may not be able to measure the trial’s effect in the next few months, but we can watch closely as knowledge grows and questions are answered in the future. Khorb Koon.
CAB Conference Calls

If you are interested in joining one of these calls, please email Genevieve Meyer (gmeyer@hvtn.org)

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<td>Thurs., January 21st, 9 a.m. PT/12 p.m. ET</td>
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Announcements


Slides from the HVTN Conference, including the layperson’s “Science Tutorial” can now be found online: http://hvtn.org/meeting/nov09.html

U.S. National HIV/AIDS Awareness Days
http://www.hhs.gov/aidsawarenessdays

February 7 – National Black HIV/AIDS Awareness Day
March 10 – National Women & Girls HIV/AIDS Awareness Day
March 20 – National Native HIV/AIDS Awareness Day
May 18 – HIV Vaccine Awareness Day
May 19 – National Asian & Pacific Islander HIV/AIDS Awareness Day

About CABs

Community Advisory Boards (CABs) are one way that the HVTN involves community members in the research process. CABs consist of volunteers from diverse backgrounds who work with local research units and advise the site from a community perspective. Community input has been invaluable to the broad community education efforts, as well as to the development of this bulletin.

Translation of the CAB Bulletin from English to Spanish and French provided by Infinity Translation Services. www.infinitytranslations.com

Send suggestions, questions, and articles submissions for the CAB Bulletin to:

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