Welcome to a new edition of the HVTNews, the newsletter of the HIV Vaccine Trials Network. Our newsletter’s mission is to provide timely updates on the science of HIV vaccines, and the science of the HVTN. To that end, this issue features discussions that include innate immunity studies at the HVTN, the possible impact of the RV144 Correlates Analyses on future vaccine trials, and the Network’s ongoing commitment to its study participants via our VISP testing service.

Our featured article in this issue is a look back at the Network’s achievements in 12 years of operation, and the impact it had on the HIV vaccine field.

The search for an HIV vaccine is as relevant and urgent today as it was at the outset of the epidemic. We hope this issue gives you a glimpse of the myriad ways in which the HVTN pursues our ultimate goal -- eradication with vaccination.

The development of an effective HIV vaccine is one of humanity’s greatest scientific challenges. In acknowledging that the path to an effective HIV vaccine will likely require numerous iterative steps, the HVTN has aimed to improve the process of designing, implementing, and analyzing HIV vaccine clinical trials. Over the last decade, while conducting numerous clinical trials, the Network has made significant scientific contributions to the field and set precedents in community engagement. These and other major achievements are discussed below (see Figure 1).

Streamlined Protocol Development Process

Before a clinical trial can begin, a trial protocol outlining the protocol’s objectives, target population, and conduct must be approved. Defining and compiling the required information is performed by the protocol team, which comprises a diverse group of stakeholders. They include community members, product experts, clinicians, laboratorians, statisticians, researchers, regulatory experts, and representatives from the Division of AIDS (DAIDS), which usually sponsors the trial. A major Network achievement has been streamlining the protocol development and implementation process. This has been achieved largely through efforts to bring stakeholders to the table at the appropriate time and ensure that all support operations are in place at the projected trial opening date.

A standard protocol template has also improved efficiency. A standardized template saves considerable time and effort by allowing the focus to stay on the unique aspects of the particular trial. The current template represents over a decade of historical learning by the HVTN.

The HVTN: Strategic Accomplishments of the First Decade and Beyond

Tracey Day, Cecilia Morgan, Adi Ferrara, and Jim Kublin

Streamlined Protocol Development Process

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CALENDAR [back cover]
The protocol drafting process culminates in a “face to face meeting” in which every team member signs off on a final protocol document that is then submitted to DAIDS for review, and ultimately for regulatory submission. Together, the measures outlined above significantly improve the protocol development process and thus minimize the time to trial opening.

Commitment to Community Engagement

To successfully conduct vaccine clinical trials, it is necessary for trial sites to communicate with and educate the community about HIV prevention and clinical trials. Community advisory boards (CABs) provide a means for community members and vaccine researchers to interact and thereby give a voice to the communities where trials are conducted. The HVTN involves CAB representatives throughout the life of a trial from protocol development through trial implementation, and CAB members also sit on HVTN committees. Community education programs are also conducted at trial sites to enhance the enrollment and retention of trial participants.

Another example of the HVTN’s strong commitment to community is the provision of treatment for trial participants who become infected with HIV. The Network ensures these individuals have access to antiretroviral treatment, and maintains funds to provide this treatment in the event that it is not available. Following through on this commitment required strong community partnerships, especially in developing countries where treatment may not be easily accessible.

Preventive HIV vaccine candidates should be tested in a wide range of individuals to ensure that a developed vaccine is protective in diverse populations. In the U.S., African American and Hispanic populations are among those at highest risk for HIV infection, but are under-represented in clinical trials, in part because of mistrust in medical research due to historical abuses. To improve representation of these cohorts, the HVTN pioneered the Legacy Project. This project’s mission is to build trust between researchers and minority populations, and its success led to expansion into all DAIDS-supported HIV research networks (http://www.hanc.info/legacy/Pages).

Generation of Robust Immunogenicity Data

From the beginning, the importance of a centralized laboratory program that provides standardized, high quality immunogenicity data was recognized. A major HVTN accomplishment has been the establishment of a laboratory program endowed with standardized processes, comprehensive quality assurance measures, and robust data management systems that ensure data integrity for complex immunogenicity assays.

The Laboratory Program invests significant effort in assay development and optimization, as well as training in specimen handling at all trial sites. A large number of assays are performed in HVTN trials, including multiple “validated” assays for which stringent pass/fail criteria are defined, “qualified” assays, for which optimization studies have been completed, and several exploratory assays are conducted as well.

Management of such vast and complex laboratory data poses a number of challenges. For example, early phase trials place high priority on rapid access to safety data. The data management system must also function among trial sites which vary in their ability to support such systems. To meet these varied challenges, programmers at the Statistical Center for HIV/AIDS Research and Prevention (SCHARP) created an

STRATEGIC ACCOMPLISHMENTS ACHIEVED BY THE HVTN
integrated web portal system that allows incoming data to be monitored daily from any computer. This allows laboratory staff to respond immediately to any deviations in specimen or assay data at specific sites, and allows clinical development staff to assess safety data in a continuous manner.

Thus far, immunogenicity data typically serves as the driving force for critical decisions on advancing products through clinical phases, since the majority of products tested by the HVTN to date have not generated adverse safety concerns.\textsuperscript{2,3} The Network’s efforts to generate robust immunogenicity data, therefore, provide the HVTN with the best possible means with which to drive vaccine development. In addition, these measures yield a wealth of valuable resources to the field through assay methodology, reagent sharing, and the provision of high quality specimens to collaborators conducting ancillary studies.

**Statistical Leadership**

The HVTN has been extremely fortunate to work with statisticians that are leaders in the field. SCHARP statisticians and programmers contribute to many aspects of HVTN vaccine testing, providing key input into trial design and assisting in data analysis and management. Additionally, SCHARP statisticians are well known for their achievements in developing novel trial designs. For example, statistical parameters have been developed to provide earlier efficacy evaluations through phase 2b trials and for adaptive trial designs in which vaccine candidates failing to meet predetermined criteria are abandoned, thus conserving resources and allowing only the most promising candidates to proceed.\textsuperscript{4-7}

SCHARP statisticians are also well known for developing “sieve analysis” methods. This novel approach determines whether and how vaccine efficacy selectively blocks HIV acquisition with certain HIV genotypes, and/or drives the evolution of infecting viruses.\textsuperscript{8} In a collaborative effort that included SCHARP statisticians, sieve analysis methods were carried out for the Step study, and provided the first evidence that a T-cell-based vaccine can have an effect on HIV-1.\textsuperscript{9}

Identification of immune responses that reliably predict vaccine efficacy is a primary goal of vaccine research. The RV144 HIV vaccine regimen, in a trial conducted by the U.S. Military HIV Research Program (USMHRP) and the Thai Ministry of Health, offered a modest vaccine efficacy of 31.2\%, but provided, for the first time, an opportunity to examine potential immune responses correlating with infection risk.\textsuperscript{10} SCHARP statisticians and the HVTN Laboratory Program participated in a large collaborative effort to investigate potential vaccine induced immune responses that correlated with HIV infection risk in the RV144 study. The group’s successful identification of two such correlates of risk was a major highlight of the recent AIDS Vaccine conference held in Bangkok, Thailand.\textsuperscript{31} These findings represent a milestone in HIV vaccine development, and have the potential to significantly affect future HIV vaccine trials.

**Significant Scientific Contributions**

The Network’s successful completion of many HIV vaccine clinical trials has provided a wealth of information on the safety and immunogenicity of a large number of diverse products and regimens (Table 1). Vaccine candidates that progress into efficacy trials have the greatest potential to advance the field and generate immune correlates of protection. The largest ongoing HIV vaccine clinical trial, known as HVTN 505, is...
a phase 2b trial testing a vaccine regimen developed by the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID). The regimen, a DNA prime followed by a recombinant adenovirus type 5 (Ad5) boost, was found to be the most immunogenic in any HVTN study to date. The results of this trial together with the large amount of immunogenicity data being collected are expected to provide valuable information for future vaccine development.

Significant scientific advances are also made by collaborative research. The HVTN has made a concerted effort to reach out to the entire HIV vaccine research community for ancillary studies. These studies provide a novel means for research to be conducted in conjunction with vaccine trials, which differs from typical industry-run trials. Examples include the HVTN laboratory oversight of over 25 studies by investigators around the world on samples from the Step study.

Collaborative research conducted by the HVTN Laboratory Program also serves as a valuable resource to the HIV vaccine field in developing and evaluating vaccine concepts and efficacy signals. The program's standardized approaches and years of experience serve the vaccine community well in the ability to rapidly assemble collaborative teams that carry out state of the art immunological and virological analyses, which clarify findings in efficacy studies worldwide.

**Future Directions**

A primary focus of HVTN activities is improving on the efficacy and durability of the RV144 vaccine regimen. Toward this effort, the HVTN is participating in a novel collaboration between pharmaceutical companies and non-profit organizations, known as the Pox Protein Public Private Partnership (P5). P5 is a partnership between NIAID, the Bill & Melinda Gates Foundation, HVTN, the U.S. Military HIV Research Program, Sanofi Pasteur, and Novartis Vaccines. A primary aim is to extend and confirm the RV144 findings in other geographical locations, such as South Africa, and to prepare a path to eventual vaccine licensure.

Completion and follow up analyses of the numerous ongoing HVTN clinical trials, in particular HVTN 505, are expected to provide insight into future vaccine development strategies. These and future trials also provide a valuable opportunity to perform behavioral research on aspects of clinical trial participation. The HVTN recently launched its social science initiative, to identify facilitators and barriers to trial participation, and improve recruitment and retention of participants in HIV prevention clinical trials.

After over a decade in existence, the HVTN has become known as an efficient, high quality network with processes and infrastructure that optimize HIV vaccine development. While still maintaining its intense focus on HIV vaccine development, the HVTN is exploring ways to leverage its strengths through collaborations with other HIV research networks.
and through work in other disease areas. By incorporating the expertise of leaders in the scientific, clinical, laboratory, and statistical arenas, and actively engaging local communities, the HVTN generates a forceful synergy, propelling the field ever closer to its goal of developing an effective HIV vaccine.

Acknowledgements

For helpful discussions and input: Peter B. Gilbert, Steve G. Self, M. Juliana McElrath, Lawrence Corey, Steve Wakefield, John Hural, Niles Eaton, Carter Bentley, Yunda Huang, Cristine Cooper-Trenbeath, Fatima Laher, Michael Keefer, Gail Broder, Elizabeth Adams, Mary Allen, Alan Fix, and Philip Renzullo.

Tracey Day is Senior Science Writer; Cecilia Morgan is Associate Director, Scientific Development, Adi Ferrara is Technical Editor, and Jim Kublin is Executive Director, HVTN.

References


Table 1: Table of HVTN Trials by Year. *Reflects numbers available at time of submission.

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Table 1: Table of HVTN Trials by Year.
The HVTN Fall Conference took place in Seattle last November. The meeting focused on several pertinent issues in the HIV vaccine field, including updates from the RV144 correlates analyses, a session on lessons learned from viral sieve analyses, and a discussion on how pre-exposure prophylaxis (PrEP) may impact HIV vaccine efficacy trials. As promised by HVTN PI Dr. Larry Corey during his welcoming comments, the conference was a data-rich meeting representing current and forward thinking.

**RV144 Correlates Updates**

The first of several RV144-related plenary sessions began with Dr. Jerome Kim (U.S. Military HIV Research Program [USMHRP]), providing a quick summary of salient lessons learned from this study conducted by the USMHRP and the Thai Ministry of Health. This large efficacy trial, which was held in Thailand, is the only preventative HIV vaccine trial to date where a reduced HIV infection risk was observed. Although the vaccine offered only a modest benefit, with a vaccine efficacy of 31.2%, the results have significantly affected the field. During the last two years since publication of the primary study results, an enormous collaborative effort has taken place to identify correlates of risk (ie, immune responses that correlated with HIV infection). The initial results of this analysis were recently presented at the AIDS Vaccine 2011 Conference in Bangkok, Thailand. The HVTN Fall Conference provided an opportunity for researchers to share these results with HVTN members in more depth.

Based on a series of pilot studies, the collaborative team selected six assays measuring specific immune responses for the correlates analysis. Responses from vaccine recipients who became infected were compared with those from recipients who remained uninfected. A statistical analysis plan, developed by Dr. Peter Gilbert (Statistical Center for HIV/AIDS Research & Prevention [SCHARP]) and colleagues, identified two correlates of risk.

The first correlate was the presence of IgG antibodies targeting a highly variable region, called V1/V2, on the HIV Envelope protein (Env). Vaccine recipients who generated the highest levels of these antibodies had the greatest reduction in HIV infection rate. These results were presented by Dr. Susan Zolla-Pazner (NYU School of Medicine). Dr. Corey asked Dr. Zolla-Pazner how her group knew to look at the V1/V2 region. The response was that they didn’t know but they should have, based on historical evidence indicating that antibodies targeting conserved variable regions can be broadly cross-reactive. Pilot studies suggested that V1/V2 was a region of interest, which led to its selection for the correlates analysis. It was also noted that one advantage of binding antibodies (such as these IgG antibodies) is that they are more easily induced via vaccination than the broadly neutralizing antibodies.

The second correlate was the presence of plasma IgA antibodies that bind to Env. In contrast to the Env-specific IgG antibodies, presence of these antibodies correlated with an increased HIV infection rate. Importantly, the IgA antibodies did not increase a person’s risk for HIV infection, but rather interfered with the ability of the vaccine to decrease HIV infection. Exactly how an IgA antibody might interfere with an otherwise protective immune response is not known, but one hypothesis is that the IgA antibody could block antibody-dependent cellular cytotoxicity (ADCC), a mechanism by which other antibodies promote destruction of HIV in infected cells. One way that IgA antibodies could do this would be by binding to the same site that IgG antibodies bind to when triggering ADCC. Dr. Georgia Tomaras (Duke University) presented unpublished data that support this hypothesis. She also suggested that IgA antibodies could block other kinds of protective IgG functions, a topic that is the focus of ongoing research. Dr. Tomaras emphasized the need for future trials to examine IgA responses not only in plasma, as was done in RV144, but also in mucosal specimens where HIV infection takes place, and where antibodies could have different effects.
Thus far, the correlates analysis identified only antibody responses as being potentially associated with protection; however T cell responses were also assessed. Dr. Julie McElrath (Fred Hutchinson Cancer Research Center [FHCRC]) summarized these results. The vaccine reliably induced CD4+ T cell responses, which was encouraging, and analyses of several exploratory assays, such as gene expression from individual T cell subsets, are still pending. Results from these analyses may point to T cell responses that also correlate with infection risk; for example, those that promote antibody production by B cells.

While the first correlates analyses were performed using each of the primary assays independently, subsequent research has examined the potential for pair-wise interactions between assays to correlate with risk of HIV infection. Dr. Holly Janes (SCHARP) presented these studies, which found numerous interactions between assays. All of these interactions correlated inversely with IgA levels, suggesting that IgA antibodies can interfere with multiple protective mechanisms provided by IgG antibodies. These findings suggest that considering multiple assays may better predict infection risk. The ideal, however, is to identify immune responses that do not just correlate with infection risk but rather can predict vaccine efficacies. These so-called surrogates of protection are ultimately needed to drive vaccine development; methods to identify them face a major hurdle, however, as identification requires comparison of vaccine induced immune responses between vaccine recipients and placebo recipients. Placebo recipients, however, have no “vaccine induced” immune responses. Janes described how future trials could facilitate surrogate discovery by evaluating baseline immune responses, and incorporating trial designs in which placebo recipients are vaccinated after trial completion to obtain the missing data.

**Viral Sieve Analyses in Vaccine Trials: What Are They Teaching Us?**

Viral sieve analysis is an approach developed by Dr. Peter Gilbert and colleagues to determine whether a vaccine is having an impact on the virus. In the case where vaccine efficacy is observed, such as the RV144 trial, this information may also support hypotheses on the mechanisms of protection.

In order to perform sieve analysis, the nucleic acid sequences of virus isolates from infected participants are determined. The viral sequences from both the vaccine and placebo recipients are then compared to the sequences in the vaccine. If, for example, the virus sequences of vaccine recipients are less similar to the vaccine than those of placebo recipients, it suggests that the vaccine had a sieve effect -- the immune responses produced by the vaccine were able to “sift out” a specific kind of infecting virus (an acquisition effect), and/or affected viral evolution during the course of infection (a postinfection effect).

One of the first applications of sieve analysis involved the Step (HVTN 502/Merck 023) study. It found that although no efficacy was observed, the vaccine did exert immune pressure on the virus. More recently, sieve analysis was conducted for the Phambili (HVTN 503) trial, which utilized the same vaccine regimen as Step. Unlike the Step study, only very weak effects were found on viral sequences of infected vaccine recipients in this trial. Dr. Tomer Hertz (SCHARP) explained that this discrepancy could be due to the small number of infections occurring in the trial (only 43 vs. 66 in Step). Another possible explanation for the difference is that the vaccine in the Phambili trial utilized immunogens from HIV clade B in a region where clade C is predominant, whereas the Step study vaccine matched the predominant clade.

Dr. Morgane Rolland (USMHRP) presented results from a global sieve analysis of the RV144 trial in which no acquisition effects were observed, but post-infection effects were noted. A follow-up study, presented by Dr. Paul Edlefsen (SCHARP), sought to focus the sieve analysis on the V1/V2 region of Env identified in the correlates analysis. Two viral amino acid sites within the V2 region of Env were found to be affected, lending credence to the notion that the immune responses identified in the correlates analysis are indeed associated with the observed vaccine efficacy.

In the roundtable discussion, Dr. McElrath noted that there is a pressing need to identify how best to collect samples for viral sequencing analysis because the next efficacy trials are currently being planned. It was generally agreed that early and frequent samplings are essential for determining acquisition effects. However, there were differing opinions regarding how comprehensive the sequencing should be. McElrath then concluded the session applauding the synergy achieved between the various sieve analysis experts representing the divergent fields of statistics, molecular biology, and virology.
Post RV144 Selection of gp120

In general protein immunogens are the most effective method of eliciting antibody responses. Based on the encouraging RV144 correlates results, suggesting the importance of antibodies binding to the gp120 portion of Env, there is intense interest in including similar or improved gp120-derived immunogens in future efficacy trials. Dr. Antu Dey (Novartis) described the selection process for HIV-1 clade C gp120 proteins for use in South Africa, a predominantly clade C region. Based on immunogenicity, RV144 correlates results, and production considerations, two proteins, TV1.C (Novartis) and 1086.C (CHAVI/Duke) were selected and will be used with the MF59 adjuvant in future trials conducted via the Pox Protein Public Private Partnership (P5; a partnership between the National Institute of Allergies and Infectious Diseases [NIAID], Bill & Melinda Gates Foundation, HVTN, USMHRP, Sanofi Pasteur, and Novartis Vaccines). This novel collaboration aims to extend and confirm the RV144 findings and to prepare a path to eventual licensure.

HIV virus isolates that succeed in infecting a new host differ from the viruses that persist in chronically infected individuals. A vaccine that prevents HIV infection will need to generate immune responses against the types of viruses that are able to infect, also known as transmitted/founder viruses. Dr. Tomaras spoke on behalf of Dr. Bart Haynes, also of Duke University, regarding comparative studies of Env proteins from transmitter/founder viruses versus chronic phase viruses. This research aimed to identify gp120 proteins that may be able to improve upon the efficacy observed for RV144. Tomaras reported that the TV1.C and 1086.C candidate proteins show the desired profile, based on the RV144 correlates findings, of inducing high IgG and low IgA Env-specific antibody titers in non-human primates.

The following presentations focused on the generation of broadly neutralizing antibodies that bind to Env. Dr. Leonidas Stamatakos (Seattle BioMed) presented ongoing studies aimed to identify Env variants that elicit the broadest cross-neutralizing antibody responses. His group sequenced numerous Env sequences from transmitter/founder viruses from the Phambili trial, and has identified some promising candidates. Dr. Jason McLellan (Vaccine Research Center [VRC], NIAID) described the 3-dimensional structure of a broadly neutralizing antibody, PG9, showing how it is able to bind a highly variable region among so many viral isolates. Dr. Marie Pancera (VRC, NIAID) described an ongoing study utilizing a new method of high through-put sequencing (deep sequencing) to track PG9 development in B cells during the immune response. The ultimate goal of all of these studies is to identify vaccination strategies to induce these potent antibodies.

Pox Vector Programs

In this plenary session, two major programs developing pox viral vectors for HIV vaccines were highlighted.

Dr. Giuseppe Pantaleo (Centre Hospitalier Universitaire Vau- dois) described the development of NYVAC-C, a EuroVacc consortium pox virus vector. NYVAC-C is based on a vaccinia virus strain that was attenuated by the deletion of 18 genes. By adding back a few of these genes, a replication competent yet still attenuated version of the vector, called NYVAC-KC, was also generated. Pantaleo presented data from nonhuman primate studies comparing the immune responses induced by each of these vectors plus a gp120 boost, with or without a DNA prime containing the env, gag, pol, and nef genes. The vaccines induced T cell responses and antibody responses, including ADCC activity and IgG responses to V1/V2. In addition, Pantaleo’s data showed that waning antibody responses could be strengthened by including an additional protein boost at 12 months.

Yiming Shao of the Chinese Center for Disease Control and Prevention presented an overview of a large HIV vaccine program ongoing in China. Multiple pox virus vectors are under development, including several derivatives of a smallpox vaccine widely used in China (vaccinia Tiantan). Shao presented data from a phase 1a trial utilizing a replicating but highly attenuated version of this vector, called rTV. rTV contains the env, gag, and pol genes. He also showed results from a phase 1b trial utilizing rTV with a DNA prime. These studies indicated that the vaccine is safe and well tolerated. When the DNA prime was included, binding antibody responses were induced in all recipients and T cell responses in most. The HIV-specific immune responses were somewhat reduced in those who had been previously exposed to vaccinia virus. A phase 2 trial evaluating this regimen is underway, with additional phase 1 trials and a phase 2b trial planned for 2013. Liking the quest for an HIV vaccine to another seemingly insurmountable barrier, the Mount Everest North Face, Shao ended his presentation with an image of a ladder installed by Chinese climbers, which enabled thousands of people to reach the summit via this route.
The RV144 Immune Correlates Analysis: Implications for Vaccine Evaluation

Holly Janes

The RV144 immune correlates analysis, which identified IgG V1V2 and IgA binding antibody responses as significant correlates of risk, was the first study of its kind. This analysis was a follow-up study within RV144, the first HIV vaccine efficacy trial with evidence of partial efficacy. The statistical analysis was prespecified and focused on six primary immunological variables. These variables were selected by an international consortium of investigators based on pilot studies of 17 assay subtypes. The study demonstrated the feasibility and importance of a prespecified analysis plan to preserve data integrity. Its primary focus on a very limited number of immunogenicity variables enabled the analysis team to avoid spending power over a larger set; had all 165 variables been analyzed together, the multiplicity adjustment would have lowered the required significance level substantially, and the V1V2 and IgA antibody correlates would not have been detected.

The correlates analysis also demonstrated the importance of examining potential correlates jointly as well as individually. Analyses of interactions among the six primary variables raised the hypothesis that the V1V2 antibody response is an independent predictor of vaccine-induced protection, while the IgA antibody response acts by abrogating the protective effects of the ADCC, neutralizing antibodies, IgG avidity, and CD4+ T cell responses.

This study illustrated the role of a correlates analysis within the broader context of the search for surrogates of protection. An immune correlates study can only evaluate the extent to which immune markers are correlated with risk of infection in vaccine recipients, since immune responses are not observable in placebo recipients. Therefore it cannot distinguish between markers that are correlated with risk, regardless of vaccination, and markers that measure the degree of vaccine-induced protection (ie, surrogates). Additional studies are needed to discriminate between these two hypotheses. In RV144, the hypothesis that the V1V2 antibody response measures vaccine-induced protection is currently being evaluated in the sieve analysis and in analyses of vaccine efficacy by HIV genotype. It will be further assessed in follow-up non-human primate studies. Questions remain about what additional studies are needed to confirm or refute the IgA abrogation hypothesis.

The results of the correlates study will impact the design of future phase 1 vaccine trials, particularly in the choice of immune assays. IgG and IgA binding antibody responses are now being considered as primary immunogenicity endpoints. Yet there is some consensus that these should not be the exclusive focus given that much additional research is needed to determine if the V1V2 and IgA antibody responses actually measure the degree of vaccine-induced protection. It is possible that these correlates of risk are, in reality, measures of susceptibility to infection, regardless of vaccination. Moreover, these responses may not have any ability to predict protection afforded by different types of vaccines. Related to the 2 considerations above is the question of what role the V1V2 and IgA antibody responses should play in go/no-go rules for determining whether future vaccine candidates should be advanced for further study based on phase 1 data.

The design of future efficacy trials will also be influenced by the correlates analysis. Increased attention is being paid to ensuring that designs have adequate power for correlates assessment, by having at least as many breakthrough infections in the vaccine arm as were observed in RV144. There is also discussion of novel trial designs that would facilitate more complete vetting of putative correlates, such as vaccinating all trial participants at baseline with a non-HIV vaccine. Such a design modification would allow the missing HIV vaccine immune responses in placebo recipients to be filled in, or “imputed”, under the assumption that the responses to the two vaccines are correlated. Importantly, this design would allow markers that are simple correlates to be distinguished from markers that are true surrogates.

The RV144 correlates analysis set a precedent for future correlates studies. The results will impact the design of future trials, although exactly how remains unclear. As is typical of exploratory studies, the study raises more questions than it answers.

Holly Janes is a Statistician at the HVTN Statistics and Data Management Center
Two distinct parts of the immune system protect the body from pathogens. The first line of defense is the immediate, short-lived and non-specific innate immune response. It is followed by the long-lasting adaptive immune response, consisting of B and T cells that produce antibodies and kill infected cells in a pathogen-specific manner. Thus far, vaccine development efforts have primarily focused on analyzing the vaccine-induced adaptive immune response. However, we now know that the type and strength of the early innate response dramatically affects the nature of the ensuing adaptive response. Thus, there is currently an intense interest in learning how best to manipulate innate responses, in order to induce optimally protective adaptive responses for vaccine development.

Certain types of immune responses are better for ridding the body of some pathogens than others. For example, antibodies are more effective in clearing parasites that reside outside the cells, while T cells can be better for killing bacterial pathogens that reside inside the cells. One important role of the innate response, in addition to alerting the body that an infection is in progress, is to identify the nature of the infecting pathogen and orchestrate the most appropriate kind of immune response.

To detect and identify invading microbes, the innate immune system takes advantage of the fact that pathogens contain several types of common components, such as cell wall fragments and nucleic acids that distinguish bacterial, parasitic, fungal, and viral pathogens from host cells and from each other. These common microbial components are known as pathogen-associated molecular patterns (PAMPs). Different cells of the innate immune system, such as dendritic cells (DCs) and macrophages, are positioned at ports of pathogen entry and detect invading microbes by recognizing their PAMPs. Innate immune cells contain numerous receptors known as pattern recognition receptors (PRRs), which allow them to bind to and recognize PAMPs. These receptors in concert read the different types and combinations of PAMPs like a barcode, and allow the cell to classify a pathogen.

To date, five major families of PRRs are known: toll-like receptors (TLRs), nucleotide-binding oligomerization domain-containing protein (NOD)-like receptors (NLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), C-type lectin receptors, and cytosolic DNA detectors (see Figure 1).

Upon binding a PAMP, PRRs signal to other molecules in a cascading response that leads to the activation of the immune cell. As a result, the cell will upregulate its expression of stimulatory surface molecules and release signaling molecules, such as cytokines and chemokines. In this way, information about the infection is passed on to other surrounding immune cells, which then impact the developing adaptive response.

To illustrate the role of innate immunity in vaccinology, we provide an overview of the localization of the five different PRR families and their corresponding ligands in different compartments (cell membrane, endosome, or cytosol) of innate immune cells. TLR = Toll-like-receptors; NLR = Nucleotide-binding oligomerization domain-containing protein (NOD)-like receptor; RLR = retinoic acid-inducible gene I (RIG-I)-like receptors.
of the adaptive immune system (Ag-specific T and B cells). If cells of the adaptive immune system recognize the presented antigen, an antigen-driven and pathogen-specific adaptive immune response begins. The DCs therefore connect the innate and adaptive immunity by delivering the microbial information from the site of infection to the secondary lymphoid organs, the home of the adaptive immune cells.\textsuperscript{1,2,4,5}

Recent advances have begun to unravel how the initial stimulation of the innate immune system via PAMPs, as well as the resulting activation of the dendritic cells, can direct the adaptive immune response.\textsuperscript{3} This is of particular interest for vaccine development, in which a pathogen-specific antigen is introduced along with an innate immune system stimulant, such as an adjuvant. One such adjuvant is potassium aluminum sulfate (Alum), a synthetic compound used in several commercial vaccines, and another is an oil-in-water emulsion adjuvant developed by Novartis, called MF59. Precisely how these synthetic adjuvants work is unknown, but they are thought to mimic PAMPs by engaging with PRRs and thereby succeed in inducing an innate immune response.\textsuperscript{6,7} In the case of protein antigens in vaccines, inclusion of an adjuvant is considered critical for generating an immune response. In contrast, antigens that are introduced via a viral vector do not typically require adjuvants, because they contain virus-derived PAMPs.

Vaccine development for pathogens with an as-yet-unknown mechanism of protective immunity (eg, HIV) is hampered by the lack of knowledge of which type of immune response, and therefore which adjuvant/antigen combination, would result in effective protection. While HVTN trials ultimately seek vaccines that effectively protect against HIV, it is also important that we understand how we can vary adjuvants and vaccination schedules to improve upon vaccines that show partial efficacy, such as the regimen used in the Thai trial (RV144), which had a 31% vaccine efficacy.\textsuperscript{8,9} To achieve this aim, we must first determine how the individual facets of various vaccine induced immune responses correlate to vaccine efficacy.\textsuperscript{9-14}

To address these requirements, we established a suite of procedures that measure early activation of the innate immune response upon vaccination in peripheral blood and mucosal surfaces in humans. To investigate the innate immune response to vaccination, we have strategically chosen key sampling timepoints, such as 1 and 3 days post vaccination, reflecting the different stages of innate immune activation as well as feasibility for the participants and the clinic and laboratory personnel. In several recently initiated studies, we compare these data across trials to identify factors associated with successful vaccination (see Table 1). The long term goal of these studies is to improve our understanding of the innate immune response to vaccination, and its influence on the ensuing adaptive immune response.\textsuperscript{12}

Table 1: Summary of different HVTN HIV vaccine trials conducted or planned that includes innate immunity assessments. rVSV = recombinant vesicular atomatitis virus; rMVA = recombinant modified vaccinia Ankara virus; rAd5 = recombinant adenosine serotype 5.

Key data that we record (see Figure 2) include changes in the frequency and phenotypes of various immune-cell populations categorized by the use of multicolor flow cytometry and fluorescence-activated cell sorting (FACS), changes in gene expression (microarray analysis), functional analyses, and the release of soluble factors (multiplex analysis).

The peripheral blood contains lymphocytes and several soluble factors. Changes in their phenotype as well as in quantities reflect the impact of an infection or vaccination on the host. For example, we observed transient but dramatic changes in the peripheral blood lymphocyte populations 24 hours after vaccination with the Merck recombinant adenovirus serotype 5 (rAd5) HIV vaccine (HVTN 071) and with the GeoVax recombinant modified vaccinia Ankara (rMVA)/HIV62 vaccine (HVTN 205/908). We also observed that the abundance of inflammatory monocytes in the peripheral blood peaks three days after vaccination. Our data demonstrate that these vaccines have an instant influence on the behavior of innate immune cells within the peripheral blood.\textsuperscript{12}
Since mucosal surfaces reflect the primary site of HIV transmission, they are of great interest for assessing vaccine-induced immune responses. Synchronized collection of mucosal specimens and peripheral blood samples at peak time points of the innate as well as the adaptive immune responses have been included in our study protocols, and will provide comprehensive information of vaccine-induced immune responses at key sites of immune reaction.12, 15

Our studies comprehensively evaluate innate and adaptive immune responses on the cellular and molecular level. In the long term, we aim to correlate the types of adjuvants used with the observed initial innate immune response. We would also like to correlate them with the adaptive immune response to a vaccine, and with its efficacy. This will enable better prediction of vaccine success and ultimately facilitate development of a truly protective HIV vaccine. 11

Erica Andersen-Nissen is a Staff Scientist within the HVTN Laboratory Program; Antje Heit is a Research Associate working with the HVTN

References

Fig 2: Overview of key specimens and assays used by the HVTN to measure innate and adaptive immune responses

<table>
<thead>
<tr>
<th>PERIPHERAL BLOOD:</th>
<th>MUCOSA:</th>
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<tr>
<td>Whole blood</td>
<td>Cells from Cytobrush</td>
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<td>Serum/Plasma</td>
<td>Soluble factors from wick/sponge</td>
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<tr>
<td>PBMCs</td>
<td>Tissue from biopsy</td>
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- FACS (cell counts, phenotype, isolation of cell subsets)
- RNA (microarray analysis/qPCR)
- In vitro functional assays (ICS, B & T cell ELISPOT, proliferation assay, viral inhibition assay, epitope mapping)
- Multiplex assay (cytokine/antibody concentrations)

ELISPOT = enzyme-linked immunosorbent spot; FACS = fluorescence-activated cell sorting; ICS = intracellular cytokine staining; PBMC = peripheral blood mononuclear cells; qPCR = quantitative real time polymerase chain reaction.
## Auxiliary Research Projects 2011

The HVTN, having data and specimens available from multiple trials, is well-suited to collaborate on studies going beyond the primary analyses in our clinical trials. The HVTN encourages these auxiliary studies to address novel scientific questions. The following table includes an overview of over 35 auxiliary studies with activity in 2011, involving over 35 institutions in 9 countries.

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<tr>
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<th>Project Title</th>
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<tr>
<td>Matyas G.</td>
<td>ELISA assay of serum samples from volunteers who were immunized with liposome-encapsulated MPL with alum from the AIDS Vaccine Evaluation Group (AVEG) Protocol 015, for antibodies to lipids used in the immunizations</td>
<td>WRAIR</td>
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<tr>
<td>Cooper-Trenbeath C, Hertz, T.</td>
<td>Antigen microarray pilot study to assess utility for identifying novel antigens for HIV diagnostics</td>
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<tr>
<td>Jin X.</td>
<td>Antigen microarray pilot study to assess utility for identifying novel antigens for HIV diagnostics</td>
<td>University of Rochester</td>
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<tr>
<td>Tomaras G, Seaton K, Robinson H, Goepfert P, Lan A, Munir Alam S, Parekh B.</td>
<td>Comparison of avidity index to HIV-1 Env gp41 immunodominant region using MVA prime/boost strategy vs DNA prime MVA/boost (HVTN 065)</td>
<td>Duke University School of Medicine/ GeoVax Inc/University of Alabama/CDC</td>
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<td>Kobie J, Keefer M, Jin X, Sanz I,</td>
<td>Identification of multi-clade HIV reactive B cells at the single cell level following vaccination</td>
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<td>Frahm N, Montefiori, D, Tomaras, G.</td>
<td>Assessment of HIV-specific IgG-producing B cells induced by vaccination with DNA, Ads and MVA</td>
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<tr>
<td>Goepfert P.</td>
<td>Induction of cryptic epitopes by HIV-1 vaccines</td>
<td>University of Alabama</td>
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<tr>
<td>Baden L., Metch B.</td>
<td>Defining antivector immunity to MVA</td>
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<td>Janes H., Kallas E., Friedrich D., McElrath M., Frahm N., Krambrink A.</td>
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<td>KIR - The effect of KIR genotype on the course of HIV-1 infection among Step participants</td>
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<td>Bekker LG., Gray G., Metch B., Moodie Z.</td>
<td>Phambili risk behavior modification: Did unblinding affect HIV risk behaviour and the perception of risk in the HVTNS03/Phambili study?</td>
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<td>Adamson B.</td>
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<td>Perla M, Lama J, Sanchez J.</td>
<td>Genital tract infections, bacterial vaginosis, HIV and reproductive health issues among Lima-based clandestine female sex workers</td>
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<td>Peut V, Thomas E, Adams D, De Rosa S, Framh N, McElrath MJ.</td>
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<td>Extended follow-up Step study participants</td>
<td>FHCRC/University of Washington/San Francisco Dept of Public Health/Asociacion Civil Selva Amazonica/Emory University/IMFACTA Peru/Merck</td>
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<td>Jin X.</td>
<td>Design of optimal multi-epitope vaccines to elicit CD4 T cell immunity to HIV</td>
<td>University of Rochester</td>
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<td>Rolland M, Herbeck J, Janes H, Mullins J.</td>
<td>Multiplicity of HIV-1 founder variants and viral load setpoint</td>
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<td>Young K, Bekker LG, Gray C, Frahm N, Moodie Z, Andersen-Nissen E, Riou C.</td>
<td>A pilot study to evaluate baseline immune activation in HIV vaccine trial participants and the impact this has on immune responses to vaccination (HVTN 204, HVTN 073)</td>
<td>Desmond Tutu HIV Center/University of Cape Town/ FHCRC</td>
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**PrEP: Implications for HIV Vaccine Efficacy Trials**

Pre-exposure prophylaxis (PrEP) is an HIV prevention strategy in which HIV-negative people take antiretroviral drugs. Several recent studies have shown that PrEP decreases HIV infection rate in specific populations. These results represent an exciting advance for reduction of HIV infections. Although many questions remain, this approach may eventually be adopted by individuals at high risk for HIV infection, in combination with other prevention methods such as condoms and the use of sterile needles. This session addressed several key questions regarding PrEP and its impact on HIV vaccine trials.

While the majority of studies thus far have found PrEP to reduce HIV infection risk, a wide range of efficacies (40-80%) has been observed, and some PrEP methods have not shown any effect. One important question then is what led to the different results across studies? A possible explanation is the large number of differences among the studies. These include different drug formulations (eg, oral pill versus topical gel) and different participant populations (eg, men who have sex with men versus heterosexual women at high risk). However, speakers focused on evidence suggesting that adherence is the key factor affecting efficacy. Several possible reasons were suggested for adherence differences between individuals. These included differences in the participant’s perception of their own risk and their willingness to take a pill as opposed to use a gel on a daily basis.

Another possible explanation cited for the discordant study results was that the amount of drug reaching rectal versus vaginal tissues could be different, and these could also vary for a pill versus topical gel. Thus far only a few of the PrEP studies have examined drug levels in these tissues; however in one study, 10 times more drug from an oral pill was found to accumulate in rectal tissue compared to vaginal. These results were presented by Dr. Craig Hendrix (Johns Hopkins University). Dr. Hendrix acknowledged that the minimum drug levels required for efficacy in tissues and more importantly, within the cellular targets of HIV, are currently unknown and thus confound dose selection. In general, investigators agree that the products would most likely be used intermittently rather than daily, and therefore the ideal PrEP regimen would involve a drug that is immediately active in the appropriate anatomical location, rather than one requiring a loading phase to reach sufficient levels in tissues.

One major concern for PrEP is the potential for viral drug resistance to develop if an individual becomes infected and continues to use the drug. Hendrix reported that resistance has not yet been a problem and proposed that variable adherence was one reason for this. His data suggested that individuals with high adherence maintained high drug levels, which prevented HIV infection and thus also prevented development of viral resistance; in individuals with poor adherence no drug was detected and thus, although some became infected, there was no drug pressure to drive viral resistance. PrEP trial participants undergo frequent HIV testing and are told to stop the regimen if they become infected. This level of support likely contributes to the lack of viral resistance developing in the trials.

Until a preventative HIV vaccine is available, PrEP usage will likely increase. The impact of such increase on HIV vaccine efficacy trials was discussed by a panel of experts. Although it is not yet known how widespread PrEP usage will be, it is expected that its utilization by trial participants will reduce the number of HIV infections occurring during an HIV vaccine study. This is a positive outcome on one hand; however, it will result in the need for a larger number of participants to prove vaccine efficacy. Dr. Corey suggested there is a potential for a beneficial synergistic effect between PrEP and a vaccine. This synergy could benefit the partial efficacy thus far achieved by each strategy alone.
NHVREI, Social Sciences, and RAMP Scholars

This session highlighted the accomplishments of the NIAID HIV Vaccine Research Education Initiative (NHVREI) in assessing and increasing awareness of HIV vaccine research. Cornelius Baker of FHI 360 (a global development organization), summarized the initiative's formative research and reported that in general, there was very little public awareness of HIV vaccine research, and a significant amount of stigma related to HIV/AIDS still exists. Among those expressing an interest in trial participation, the desire to help their community was a key motivator; however, concerns over safety and general public distrust of medical research was a significant barrier to participation. In addition, Baker emphasized the importance of engaging the community over time, rather than just once. These findings have been incorporated into the next phase of NHVREI followup effort, known as the “Be the generation bridge project.” “Be the Generation” is a NIAID supported interim project run by the Legacy Project and FHI 360. (The Legacy Project is a national effort run by the HIV/AIDS Network Coordination [HANC].)

HVTN social scientist, Dr. Michele Andrasik, described her work researching HIV vaccine trial recruitment strategies for U.S. men who have sex with men (MSM). She cited concerns about vaccine induced seropositivity (VISP) and its impact on participants as a key impediment to recruitment. VISP refers to cases of reactivity in standard HIV tests in HIV vaccine trial participants as a result of vaccination. This reactivity result may be interpreted as an HIV infection, even when a participant is uninfected. The HVTN provides access to accurate HIV tests for trial participants, to reduce the risk and resulting impact of VISP.

The following plenary session featured presentations from Research and Mentorship Program (RAMP) scholars. This effort aims to increase the numbers of black and Latino researchers in the HIV prevention field. The program supports short term research projects by U.S. medical students under the mentorship of HVTN-affiliated investigators.

John Chiosi (Mount Sinai School of Medicine) presented a study assessing the feasibility of HIV education programs conducted in neighborhood taverns in Cape Town, South Africa. He reported that both tavern owners and patrons expressed a willingness to utilize HIV education materials, indicating that these may be good locations for targeted HIV educational campaigns and clinical trial recruitment.

Cesar Angel (Stanford Medical School) discussed his work identifying methods to enhance Latino MSM participation in HIV vaccine trials. His study, involving several focus groups around the San Francisco Bay Area, observed that the poor understanding and specific connotation of the term vaccine are key barriers to participation. The focus group feedback indicated that campaigns should engage in grass roots efforts, particularly those evoking feelings of empowerment and community support.

In the final presentation, Daniel Gonzalez (Commonwealth Medical College) discussed his work on the parameters affecting U.S. MSM participation in HIV vaccine trials. This study sought to identify specific versus common themes across several major cities. Common facilitators included altruism and compensation. Safety fears and mistrust appeared as common barriers.

Larry Corey asked the scholars to report on what they got out of their research experience, what they planned to do next in their careers, and whether the experience had been fun. The scholars unanimously agreed that it had been an enriching experience that had influenced their future plans. They also agreed it was fun.

Tracey Day is Senior Science Writer and Cecilia Morgan is Associate Director, Scientific Development, HVTN.
The goal of an HIV vaccine is to induce an anti-HIV immune response; while an effective vaccine has not yet been found, many of the experimental HIV vaccines have induced immune responses that include anti-HIV antibodies. These antibodies may react on common HIV serologic tests, causing the test to appear positive even in the absence of actual HIV infection. This phenomenon is known as vaccine-induced seropositivity or VISP (this is also referred to as vaccine-induced seroreactivity or VISR). As part of every HIV vaccine clinical trial conducted by the HVTN, study participants undergo HIV diagnostic testing throughout the trial, and participants are encouraged to only have their HIV testing done through their study site. This testing follows an algorithm that can distinguish true infection from VISP through RNA polymerase chain reaction (PCR), Western blots, enzyme immunoassay (EIA), chemiluminescence assay (CIA), or Rapid serology tests along with knowledge of the different vaccine delivery systems and HIV inserts. At the conclusion of a participant’s scheduled study visits, end of study testing is performed to determine whether or not the HIV vaccine has induced antibodies that would result in a positive test on standard HIV antibody tests.

After more than 12 years of research, the HVTN has data on a number of HIV vaccine candidates. Among the individuals who received an HIV vaccine product in 27 phase 1 or 2a trials, VISP occurred in approximately 42% (908 VISP participants at the end of the studies out of 2176 non-HIV-infected vaccine recipients). These trials were conducted in a total of 9 countries between December 14, 2000 and January 15, 2010. VISP was determined by HIV EIA.1

Recent data suggest that VISP is a “common but highly variable” outcome of preventive HIV vaccine trials. Once a participant tests VISP, the duration of the response may be highly unpredictable. Some participants have a transient response, while other participants’ responses last longer than 15 years.2

The HVTN is currently conducting a long term follow-up observational clinical trial (HVTN 910) to collect data that better characterizes the persistence of VISP, by routinely testing former trial participants.

The effects of a false diagnosis because of VISP may include difficulties in obtaining medical or disability/life insurance, donating blood or organs, finding or keeping employment, filing for immigration, obtaining student or travel visas, enlisting in the military, or disruption of personal relationships with family or friends. For participants in later phase efficacy trials, who are often at higher risk for HIV infection, this becomes an even more complex problem. In addition to emotional stress, participants could be subjected to inappropriate treatment with antiviral drugs.

Test results with a false diagnosis could also have serious implications related to HIV surveillance and future program planning. In areas where HIV infections must be reported to the public health authorities, a false diagnosis could have implications on HIV epidemic estimates data.3

The HVTN, with the support of the Division of AIDS (DAIDS), has worked to develop policies, procedures, and materials to support study participants prior to joining a trial, as well as during and after completing a trial. Study sites educate their participants about VISP and the implications of requesting HIV testing outside the study site via discussion and supplementary resources. These resources include participant brochures, information sheets, and a publicly accessible website with VISP-related information. The HVTN provides accurate HIV testing free of charge for as long as the HIV vaccine-induced antibodies persist. Individual study sites have taken the lead in developing mechanisms to provide testing and counseling to fulfill this commitment. In addition, the HVTN developed the VISP Testing Service to support participants who may have moved away from their study site or for those whose study site is no longer open. The Testing Service includes a toll-free phone service that study participants can call to request HIV testing. Currently, this service is only accessible for participants living in the United States but there are future plans to expand it internationally.

In addition to the VISP Testing Service, a voluntary VISP Registry was developed to support former study participants. The Registry’s intent is to enable the Testing Service to identify participants in DAIDS--funded HIV preventive vaccine trials, and provide support to such participants for possible social harms resulting from testing VISP. The Registry allows the centralized VISP Testing Service to access information about a participant’s involvement in a trial, and identify whether or not they received an HIV vaccine which might put them at risk for VISP. Sites will offer the opportunity to be part of the
VISP Registry to all participants following enrollment in an HIV vaccine clinical trial. This Registry is solely intended to facilitate a participant’s request to get post-study HIV testing, and cannot be used for any other purpose, including research. If a participant is unwilling to join the VISP Registry, HIV testing will still be provided; however, the ability to mitigate social harms may be limited since the HVTN may not be able to attest to their participation in a trial, nor verify whether they received an experimental HIV vaccine or placebo/control.

Participants are sometimes tested in the community without their knowledge, particularly with the recent adoption of “opt-out” HIV testing recommended by the Centers for Disease Control and Prevention. For this reason, beyond the education of the participants, it is also imperative that the surrounding communities and healthcare service providers, especially in places where HIV community testing is prominent, understand the issues of testing current and former HIV vaccine trial participants. For example, as part of the VISP education outreach program, the Fred Hutchinson Cancer Research Center/University of Washington Vaccine Clinical Research Site located in Seattle, WA worked with the public health authorities in Washington State to incorporate VISP education into state-mandated health care provider training. This included adding information about VISP into the health department’s training sessions on HIV testing and counseling, and the addition of VISP information into HIV educational training required for Washington State licensure of all health care providers. These efforts are designed to improve provider awareness of VISP and, thereby allow them to better identify HIV vaccine recipients when these individuals seek community HIV testing. An awareness of VISP and its implications is extremely important in HIV vaccine research, especially given the stigma associated with HIV/AIDS.

The development of more immunogenic HIV vaccine regimens, with particular interest in increasing antibody responses following the RV144 trial results, may increase the potential for VISP outcomes. Unfortunately, with this, the likelihood of participants with VISP testing outside the study site or the HVTN Testing Service may be elevated, as more participants enroll in trials, and “opt out” testing procedures are becoming increasingly common.

In the past, the differentiation between HIV infection and VISP has been manageable at the study site level; however, as the number of participants in HIV vaccine clinical trials increases, and the opportunities for HIV testing increase, it becomes more important than ever to ensure that health care providers and testing centers are educated about VISP.

The HVTN values the critical role clinical trial volunteers play in the effort to develop an effective preventive HIV vaccine and remains committed to support those volunteers in many ways, including the provision of accurate HIV testing for as long as necessary. For more information about VISP, please visit our web site: http://www.hvtn.org/visp.

Carissa Karg is a Clinical Trials Manager and Margaret Wecker is Director, Scientific Operations, HVTN

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2. Reported by clinic staff at HVTN Nashville Clinical Research Site, 2011.


The HIV Vaccine Trials Network is an international collaboration of scientists and educators searching for an effective and safe HIV vaccine. Support for the HVTN comes from the National Institute of Allergy and Infectious Diseases (NIAID) of the U.S. National Institutes of Health, an agency of the U.S. Department of Health and Human Services. The Network and NIAID have a close, cooperative working relationship, with shared attention to intellectual and scientific issues.

MISSION OF THE HVTN

To enhance the discovery and drive the development of a safe and globally effective vaccine to prevent HIV.

We do this through well-designed clinical research trials that objectively and ethically address the critical questions of the field.

Our objective clinical trial platform lets us evaluate safety, immunogenicity and efficacy of candidate vaccines, as well as design clinical trials that will provide clues on ways to enhance the effectiveness of new vaccines.

We promote the use of new innovations, which may help us get closer to a safe and effective vaccine more quickly.

CALENDAR

CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS
MARCH 5-8, 2012
Washington State Convention Center
Seattle, Washington

HVTN EXTERNAL ADVISORY COMMITTEE MEETING
MARCH 9, 2012
Seattle, Washington

KEYSTONE SYMPOSIA, HIV VACCINES
MARCH 21-26, 2012
Keystone Resort
Keystone, Colorado

HVTN CONFERENCE
MAY 30-JUNE 2, 2012
Renaissance Mayflower Hotel
Washington, D.C.

INTERNATIONAL AIDS CONFERENCE 2012
JULY 22-27, 2012
Walter E. Washington Convention Center
Washington, D.C.

AIDS VACCINE 2012
SEPTEMBER 9-13, 2012
Boston Convention and Exhibition Center
Boston, Massachusetts