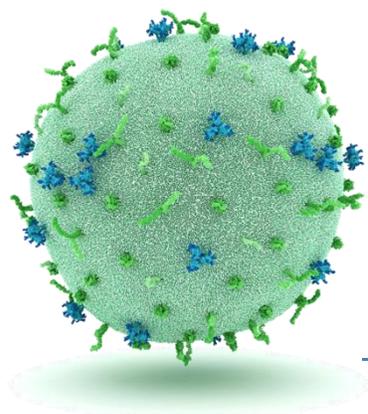


Timely Topics In HIV Vaccines

MEETING REPORT

Vaccine-Induced Sero-Positivity/Sero-Reactivity (VISP/R)



A Global HIV Vaccine Enterprise and NIH –NIAID Consultation

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Background

Clinical testing of HIV candidate vaccines in volunteers continues to be a critical component of HIV vaccine research and development. Most vaccines are designed to elicit anti-HIV antibodies and those designed to induce T cell responses also frequently elicit antibody responses as well. Vaccine-induced antibodies may confound the interpretation of serological HIV diagnostic tests that are based on the detection of serological responses to viral infection and thus, can lead to misclassification of HIV infection status. The impact of vaccine-induced antibodies on the performance of standard diagnostic tests presents a considerable technical challenge during HIV vaccine clinical trials and to local health care systems after a study has been completed. The degree, profile, and specificity of vaccine-induced antibodies vary by vaccine, but in some cases, the responses have been shown to persist for over fifteen years. Trial participants with durable Vaccine-Induced Sero-Positivity/Reactivity (VISP/R) face the potential for delays in determining their true HIV status after possible HIV exposure, as well risk of various social harms, and will require long-term support in all countries where vaccine trials are being conducted. As candidate vaccines become increasingly more immunogenic and progress to larger efficacy trials, the incidence and durability of VISP/R is certain to increase in the coming years and pose significant challenges to the field.

The Global HIV Vaccine Enterprise with support from NIH-NIAID, Division of AIDS (DAIDS) brought together representatives from academia, government, private institutions, and biotechnology companies from around the world to address the challenges brought on by the presence of antibodies in participants of HIV vaccine clinical trials. The consultation, part of the Enterprise's *Timely Topics in HIV Vaccine Series*, occurred over two days and consisted of plenary sessions, one roundtable panel discussion, and four breakout discussion groups (*). Organizing Committee members were: **Mary Allen** (National Institute for Allergy and Infectious Diseases - Division of AIDS) **Michael Busch** (Blood Systems Research Institute, US), **Hana Golding** (Food and Drug Administration), **Pat Fast** (International AIDS Vaccine Initiative), **Uli Fruth** (World Health Organization), **Surender Khurana** (U.S. Food and Drug Administration), **Joseph Mulenga** (National Blood Transfusion Services, Zambia), **Sheila Peel** (US Military HIV Research Program), and **Marco Schito** (Henry M. Jackson Foundation for the Advancement of Military Medicine, US).

Barney Graham (VRC-NIAID) noted that current efforts in the HIV vaccine field focus on antibody induction, mostly a result of the Step and RV144 trials and recent excitement around the discovery of a large number of broadly neutralizing antibodies in HIV-infected subjects. It is very likely in this context that many vaccinees from upcoming trials will develop vaccine-induced HIV antibodies and may retain these over long periods of time. Another development in the field is the increased use of antiviral drugs for pre- and post-exposure prophylaxis and the increasing availability of treatment, which suppresses viral replication and makes RNA-based PCR diagnostic tests potentially less reliable for diagnostic

purposes. Studies in SIV/monkey model systems suggest that some vaccines may significantly suppress viral load, further complicating the definitive diagnosis of infection in vaccinated volunteers. Dr. Graham concluded that as a vaccine developer, he is optimistic about the potential of serological tests that detect a specific part of the virus not included in the vaccine composition. However, development of such tests would require concerted action and continued interaction between vaccine developers and researchers, test developers and regulatory agencies, which is not currently happening. For example, information on the composition of many diagnostic tests is not available, while vaccine developers tend to frequently change their vaccine composition.

Specialized testing: algorithms, assays, and devices

Algorithms

HIV infection status is determined by assaying biological samples collected from the individual. Since the biology of people vary from person to person and the sensitivity of assays are variable, it is currently necessary to run several types of tests in parallel or in succession to accurately assign an individual's HIV status. Investigators and clinicians establish the choice and combination of assays to be performed in a testing algorithm. Routine testing algorithms for HIV include Enzyme Immune Assays (EIA), Western blots, and Nucleic Acid amplification based Tests (NAAT). In the case of vaccine trial participants, algorithms must differentiate between HIV-antibodies induced through infection and antibodies induced by immunization without infection. Making an accurate distinction between these two outcomes in trial studies is particularly challenging because the reactivity varies both with the test kits used and the composition of each candidate vaccine.

Sheila Peel of the U.S. Military HIV Research Program provided an overview of HIV diagnostic algorithms used in the clinic, global public health settings and in the U.S. Military. In the context of HIV infection status determination, it is important to combine tests with different mechanisms of detection and/or different targets (referred to as test orthogonality) to improve accuracy of specimen classification, e.g., EIA, WB, and NAAT assays. Supplemental confirmatory tests are useful in mapping the evolution of HIV sero-conversion versus durable VISP/R and are useful for mapping immunologic responses to a vaccine. While RNA assays are highly sensitive, they may yield “non-detectable” results if individuals exhibit a high degree of control over their infection (ELITE Controllers), are on Pre-exposure Prophylaxis (PREP) or Post-exposure Prophylaxis (PEP), or if an HIV candidate vaccine suppresses viral RNA levels, and thus may result in misclassification of HIV infection status. Elucidation of infection status in volunteers with VISP/R will require more complex algorithms. Dr. Peel believes that VISP/R-specific algorithms will need to include quantitative DNA as a marker for HIV infection. Studies of DNA integration events in the eclipse phase of infection as well as in acute and early infection are required. She pointed out the crucial caveats that there are currently no FDA-approved HIV-1 DNA tests available and that infection with HIV-2 will be missed if detection assays for HIV-1 alone are included.

John Hural described the HIV Vaccine Trials Network's HIV diagnostic program. This includes algorithms used for in-study testing, evaluation of sero-reactivity at the end of study (EOS) and post-study testing. He also described the HVTN process for endpoint adjudication in efficacy studies, as well as the protocol being established for long-term follow-up of volunteers with VISP/R (HVTN910). Dr. Hural showed data demonstrating that different commercial test kits show extreme variability in the level of detection of induced HIV-antibodies in a single specimen obtained from a vaccine recipient. He also showed data from HVTN studies (such as HVTN204, HVTN091) indicating that the different vaccine products induce very different levels and characteristics of vaccine-specific antibodies. Routine clinical laboratories, especially in resource-constrained settings, may not be able to implement all the steps required by complex algorithms with orthogonal testing. The appropriate algorithms for HIV testing in resource-limited regions will ultimately be dictated by the testing platforms accessible locally rather than by the application of a universal algorithm. Local investigators will have to mitigate risk of misclassifying VISP/R as true HIV infection by using available point of care (POC) technologies. Therefore, there is a need to survey testing practices in all areas where HIV vaccine studies are being conducted to gain a clear understanding of how responses to a vaccine interact with the assay kits used in the community; this is particularly true in international settings.

Commercially-available Tests and Devices

Christopher Bentsen of Bio-Rad Laboratories showed that commercially available EIA and WB assays had variable success in distinguishing VISP/R from infection-induced responses in HIV vaccine recipients. Newer 3rd and 4th generation HIV screening tests using recombinant proteins and peptides (such as the GS HIV-1/HIV-2 *PLUS O* EIA, the Multispot HIV-1/HIV-2 rapid test, the GS HIV Combo Ag/Ab EIA) appear to have better specificity for true infection in the presence of VISP/R than older assays based on viral lysates.

Opportunities to explore the technical challenges associated with VISP/R and true infection diagnosis included a discussion panel on the technology needed to address VISP/R in trial participants, as well as the break-out group session concentrating on 'Technical Feasibility at Trial and Public Health Levels' (*). Discussions focused on the usefulness of the Western Blot assay. Some investigators feel that the WB should not be overlooked as it may meet all criteria for the orthogonal assessment of antibodies to specific HIV epitopes induced by newer vaccine candidates that express multiple or mosaic antigens. However, its applicability in resource-limited settings is questionable given the resources needed and cost involved. Newer assay platforms like the Bio-Rad *Genius* may be useful in lieu of the Western Blot as this platform provides quantification of band intensity with electronic capture for each protein band thus offering an opportunity to develop a specific response profile for each vaccine. Such a database can be interrogated in the EOS testing to distinguish VISP/R from true HIV infection.

There is a great need to develop more accurate assays able to differentiate true infection from vaccine-induced responses. However, Dr. Bentsen explained that there is low impetus for large diagnostic

companies to invest in the development of such specialized tests. The overall operating and FDA regulation costs fall equally on all products being developed, approved, and manufactured by a company and make the development of low-volume tests typically not cost-effective. Despite this deterrent, and with support from public funding, some companies have chosen to engage in the development of tests designed to differentiate VISP/R. Immunetics, Inc. is developing *Selectest*, an assay based on research conducted by Surender Khurana and Hana Golding of the U.S. FDA. It is a sero-diagnostic enzyme immunoassay (EIA) targeting HIV-1 Env (gp41) regions that are not currently present in most candidate vaccines, or are not immunogenic when included. Thus far, the *Selectest* demonstrates fewer misclassifications of specimen test results due to VISP/R in HIV vaccine trial specimens than existing commercial assays in head to head comparisons.

Developing *Selectest* was not easy and came with several challenges as described by **Andrew Levin** from Immunetics, Inc. Principal issues noted:

- Selecting the right test reagents required sustained efforts. The peptide antigens to be incorporated into the test needed to show no natural immunogenicity and many antigen designs had to be considered and tested. Each redesign of peptide antigens required redevelopment of other assay reagents and chemistry as well as redevelopment of a cut-off algorithm.
- Getting access to the various vaccine trial samples required to evaluate *Selectest* specificity from vaccine trial groups has proved difficult.
- Regulatory approvals are complicated by the fact that there is no precedent for this type of test. The level of assay performance expected to justify commercial use and inclusion in diagnostic algorithms is not known. Approval for use in other countries will require procedures yet to be defined.

The makers of *Selectest* believe that if the product received approval for commercial use, it would be accepted for use in vaccine trial algorithms as well as POC sites since the assay would provide a time and cost-efficient way to determine true HIV infections from non-infected vaccine recipients. So, while the efforts needed to develop an effective VISP/R-resolving assay are not perceived as being cost-effective by many companies, it is clear that such a test could have a global impact on public health systems as well as on vaccine development efforts. It would also help to standardize the VISP/R status assignment and help prevent social harms

Mark Ware spoke on the role of the Clinton Health Access Initiative (CHAI) in supporting access to new diagnostic technologies applicable to VISP/R testing. CHAI does not fund product development, but helps companies enter the marketplace more rapidly and implement validated products into routine test algorithms in different countries. As an example, CHAI currently receives support from USAID to procure HIV POC technologies in selected countries on a trial basis for operational studies. Dr. Ware reviewed several emerging assays and devices for projected market entrants for 2013 through 2016, as well as expected later entrants. The trend for assays is to move away from the serological responses and focus

directly upon detection of biomarkers of the virus itself such as viral proteins, e.g., the viral capsid p24 antigen, or viral RNA or DNA revealed through nucleic acid amplification-based tests. Some investigators feel that the availability of a low-cost, FDA approved NAAT would greatly simplify the strategy for in-study testing for the increasing proportion of participants developing VISP/R; ultimately, the cost of implementing a multistep algorithm may exceed the cost of running NAAT on all vaccine recipients during a trial. However, even in this context post-study testing will, for some time to come, rely on serology-based tests being used in the community. Evidence-based studies are needed to determine the validity of RNA-based NAATs as primary screen, as well as DNA tests to detect suppressed infections in people on anti-retroviral therapy or who have innate control of viral load. Chosen NAATs will also have to be robust enough to detect new genetic variants and multiple viral genome targets.

Assay reagents are not the only technology necessary for implementation of wide VISP/R testing. Platforms to capture and process samples, and analyze results need to evolve in parallel. Dr. Ware also reviewed the trends in devices currently in the pipeline.

Devices

When it comes to emerging testing devices, Dr. Ware identified the following trends:

- Smaller and more portable POC platforms
- Easier to use with little training of personnel required
- Capable of providing more rapid results
- More stable and reliable at various temperatures
- Able to process whole blood samples for NAATs
- Integrated NAAT sample processing, amplification and signal detection cartridges to avoid contamination with amplicon products
- Capable of both qualitative and quantitative analysis
- Capable of digital connectivity

Helen Lee of Diagnostics for the Real World described the Simple Amplification Based Assay system (SAMBA) as an example of market entrant devices. She explained that this NAAT-based HIV diagnosis system provides both qualitative and semi-quantitative detection of viral nucleic acid sequences with approaches for both RNA and DNA detections; one specifically developed for Infant Infection Diagnosis. SAMBA reduces the complexity of NAATs by converting a complicated detection system into a visual signal reference and by a simplified front-end automated sample preparation. Temperature-stable reagents have been developed to avoid the need for cold-chain transport. The system requires minimal staff training and can be implemented in lower healthcare levels such as district hospitals or health centers with a basic laboratory and could be used as POC technology.

Support to Trial Volunteers

The challenges raised by the emergence of VISP/R are not limited to technical feasibility and implementation. Individuals who volunteer to participate in HIV vaccine trials need to be accurately, but sensibly informed about VISP/R and social impact as a possible outcome. Some vaccine trialists are concerned that this may be an impediment to trial enrollment because participants with long-term vaccine-induced antibodies to HIV may face related difficulties in their everyday life. It is necessary to provide as much support as possible to volunteers and to mitigate risks of social harm whenever possible.

Mary Allen from NIH-NIAID, reported on the results of a 14-question survey about VISP/R practices that had been completed by nine organizations involved in HIV vaccine trial studies (namely: HVTN, China CDC, EDCTP, ANRS, Harvard, US MHRP, UK HVC, US VRC, and IAVI). The study revealed that some services were at least partly in place in all nine sites; these are:

- VISP/R explained in Informed Consent
- Collection of VISP/R data
- End of Study testing for VISP/R
- Post-study testing
- Assisting participants with long-term issues
- Participant registry, kept locally

Other services were lacking; the identified current and future needs include:

- Establishing centralized database registries for trial participants
- Working with the insurance industry on HIV testing procedures for trial volunteers applying for insurance; this is already happening in South Africa and the US, but needs to be expanded to other countries
- Informing volunteers about the impact of trial participation and VISP/R on military careers, especially in the US, where VISP/R responses in HIV vaccine trial volunteers will preclude accession into the U.S military
- Providing sustained services for relocated volunteers post-study, especially for people moving across state lines or across international borders
- Improving volunteer identification and provision of rapid NAAT during pregnancy, labor and delivery

Enrollment and in-study support

Pat Fast from the International AIDS Vaccine Initiative (IAVI) moderated a discussion about best VISP/R practices for vaccine trial enrollment and study conduct. It is important, but sometimes difficult to convey to volunteers that making antibodies to HIV is desirable, but may not provide adequate protection from the virus. Disclosure to volunteers should state that specialized testing may be needed and that the volunteer may need to reveal study participation to others such as a health care provider. Volunteers will need to be tested for their understanding of the information provided in the informed

consent (e.g., through the narrative interactive approach used at IAVI sites). The VISP/R issue should be discussed with volunteers by trialists during all study follow-up visits.

Dr. Fast identified the potential social harms for volunteers who develop VISP/R:

- Volunteers or their loved ones may have concerns regarding infection status; this may strain personal relationships
- They may experience community stigma due to misunderstanding of their HIV infection status
- The requirement for specialized testing at designated sites may create practical inconveniences
- Inability to travel or immigrate into countries that require HIV testing and may discriminate against people perceived to be HIV-infected
- Complications of application for employment in cases where HIV-testing is required by the employer or is conducted without consent
- Ineligibility to accession into military service in the U.S. for HIV vaccine trial volunteers with VISP/R response to the HIV vaccine; inability to deploy outside the continental U.S. if suspected of being HIV infected
- Potential for misdiagnosis, notably during pregnancy, labor or delivery and, as a result, unnecessary medical treatment
- Complications when obtaining medical, life, or disability insurance
- Inability to donate blood, stem cells, organs
- Ineligibility to participate in other HIV clinical studies or other clinical trials

The discussion group on ‘Social Impact and Informed Consent’ (*) reiterated and stressed the ethical obligation to provide HIV vaccine trial participants with accurate testing and mitigation of social harms. Investigators at sites where vaccine trials are conducted need to have a specialized testing plan in place and state in advance how VISP/R will be handled during short and long term scenarios. The testing plan needs to be easy to explain and must be perceived as beneficial by volunteers. An example of how a testing plan could be expressed was: “Special Category of Test for Trial Participants” with the acronym ‘SCOTT’. The testing design should aim to follow standardized approaches, yet must remain flexible to allow incorporation of new testing platforms as they become available and to adapt to locally available platforms.

Other important concerns were raised during the discussions, such as:

- The increased availability of self-testing (in-home testing), which has the potential for misunderstanding the results without proper counseling
- The unknown effect that un-blinding may have on the clinical trial’s outcome
 - Un-blinding will occur if the VISP/R status of volunteers, and therefore their participation on the vaccine arm of the study, is revealed during the conduct of a double blinded study. The proportion of vaccinees developing VISP/R is expected to be very high in upcoming trials, therefore un-blinding during the course of the study may be extensive.

Post-study support

Carissa Karg of HVTN reported on the HVTN post study testing services where HVTN algorithms are used to determine the participants VISP/R status over time after their participation in a vaccine trial. The testing is currently performed upon request, free of charge at clinical research sites (CRSs). The services are intended for participants who have received an investigational HIV vaccine product in DAIDS-funded HIV preventive vaccine trials and include local phlebotomy, centralized diagnostic labs for analysis, and specimen storage. In addition, post study testing services are offered, to US participants who have moved away from their original clinical trial site since August 2010; discussions are underway for expanding this feature to Southern Africa.

Carissa delineated several challenges to long-term post-study follow-up:

- Volunteers may relocate, potentially across state lines or internationally, and may not have further access to adequate testing
- Counseling, testing, and reporting are adapted to different state guidelines
- Confirming that a particular person participated in a vaccine trial may not be simple, especially for closed study sites, because the records may not be easily accessible
- Recurrent testing and counseling needs increase the workloads on various personnel, while no FTE has been allocated to this particular issue
- There is no definite budget allocated to cover the growing cost of extensive testing and storage of numerous specimens post-study

Participants who develop vaccine-induced antibodies by the end of their HVTN study may enroll in a long term follow-up observational clinical trial (HVTN 910) designed to better characterize the persistence of VISP/R by routinely testing former trial participants and to record any social harm caused to participants as a consequence of VISP/R.

Exclusion of altruistic participants with VISP/R from donating blood, stem cells, or organs was recurrently mentioned during the workshop discussions as a potential social harm. Carissa Karg noted that the HVTN is considering providing ad-hoc testing at clinical research sites for people who plan to donate blood, stem cells, or organs.

Participant registries

Dr. Karg also presented the HVTN registry for VISP/R-tested participants. The database registry serves to confirm participation in a specific study, to accelerate further testing, and to mitigate harm. Following enrollment, all participants may elect to have their name added to the registry. As mentioned, access to specimens collected under HVTN-approved protocols and recorded in the HVTN 910 registry can be a valuable resource for assay and algorithm development. The implementation and maintenance of national registries for trial participants raise great concern about cyber-security for sensitive data and electronic medical records. Legal considerations and cyber-capabilities will vary country to country, but

precedents exist: a registry in South Africa was rolled out as part of a protocol and could be a model for implementation in other countries. In the U.S., the HVTN registry is housed in a secure and un-exportable web-based system. The U.S Army Medical and Materiel Command (Ft Detrick, MD) as well as the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Thailand employ a Volunteer Registry database that is used to contact participants long-term should issues arise that require follow-up. Pat Fast of IAVI mentioned that HIPAA compliance will be an issue only if patient identifiers are entered in the database registries. This may become the case if volunteers need to be identified for insurance purposes or mitigation of social harms.

Participant identification could also be implemented through biometrics, ID cards, medical bracelets, and providing a contact phone number to get information on trial status. Access to data registry for volunteers who relocate to a different country is an added difficulty.

Messaging

Messaging and communication about VISP/R was a recurrent theme throughout the meeting. The discussion group on 'Logistical Issues of Trial Follow-Up' (*) recommended the use of standardized messaging to participants in order to normalize HIV vaccine trial participation and understanding of VISP/R. Such "Volunteers' Bill of Right" would help shift the onus from the participants onto trial sponsors and public health agencies. Voluntary Testing and Counseling (VTC) should also be standardized to include questions about participation in HIV vaccine trials. But communication should not be limited to trialists and volunteers; there is a need to increase public awareness of VISP/R via social media and engaging science writers to provide updates on the issue. Furthermore, the field needs to engage regulatory bodies and other groups (such as WHO and developers of National HIV Vaccine Plans, Blood Banks, Embassies, Manufacturer's package inserts) to coordinate messaging and policies.

One of the challenges in outreach and overall communication is the lack of a standardized terminology for both the scientific and the general communities. This is why some stakeholders consider settling on a standard term for VISP/R a priority. **Hélène Zinszner** of the Global HIV Vaccine Enterprise, working with partner organizations, conducted consultations with community members about appropriate names for VISP/R. The discussion groups were two CABs and one MSM Advisory Mechanism group (MAC) in Nairobi, Kenya, and CABs in New York and Seattle, U.S. The same presentation material was used at each site and was designed to ensure that all participants understood the issues around VISP/R. Less than 40 percent of discussants in Kenya were aware of VISP/R, whereas, about 70 percent of those in the United States were. Participants from Africa almost unanimously made the point that the words "positivity" and "positive" should be avoided because of their association with the stigma of being HIV-positive.

Discussants in general advised against using the words "sero-", deemed too obscure for lay people. The majority of participants thought that neither VISP nor VISR was the best denomination and that terms to be considered should be simpler and emphasize that having vaccine-induced antibodies is desirable. Some of the suggested alternate terminologies were:

- Vaccine Induced Antibodies
- Vaccine Antibody Response
- Vaccine Associated Reactivity

Global Health Policy and Regulatory Issues

Globally, post-study participants with durable VISP/R can challenge the healthcare systems, especially in resource-limited regions, because of the need for long-term specialized testing and follow up. Workshop participants acknowledged the essential role of the World Health Organization (WHO) and other national and international organizations in establishing guideline recommendations and assisting with country-specific approaches to deal with VISP/R. Post-study testing requires local, national, and international policymaker engagement to include: Blood banks, Transplantation organizations, Vaccine Clinics, US CDC, and other countries' disease control equivalents. There is also a global need for enhanced education of clinical staff and physicians about the existence and impact of VISP/R. An informed primary care physician could play the role of gatekeeper and main point of contact for post-study participants who need to confirm HIV infection status as well as engagement with other parties, but educating primary care physicians is a major challenge in itself.

The discussion group on 'Financial Issues of Trial Follow-Up' (*) pointed out that the financial and logistical management of VISP/R is intimately linked to regulatory and policy issues. The guidelines to define minimum ethical obligations for VISP/R assistance will inform budgets, which will still depend on many factors including sponsors and countries. An electronic in-country registry, for example, could significantly reduce the time and effort required to support volunteers beyond the trial study period, although establishing such registry requires approval by Ethics Committees and compliance with local healthcare privacy laws.

As previously mentioned, the availability of low-cost accurate testing will be key for managing VISP/R-associated costs. However, since vaccine products and diagnosis will evolve over time, there is a need for regulatory fast-track approvals for new products to adapt testing to the outcome of new trial studies in a timely manner.

Licensure of Vaccines and Diagnostic Tests

Hana Golding of the Food and Drug Administration presented the FDA's regulations and stages of reviews as applied to the development of HIV vaccines and HIV diagnostic tests. She noted that the FDA considers HIV tests to be Class 3 high-risk medical devices. She emphasized that an algorithm capable of rapidly confirming infection versus vaccine-elicited immune responses during a Phase 3 Trial needs to be

in place as breakthrough infections are certain to occur in large trials with high-risk populations. VISP/R will have to be addressed continuously during the pre- and post-licensure phases for a preventive vaccine. It is possible that the HIV diagnostic tools used after licensure may differ from those used during HIV vaccine licensure studies.

During the discussion, Dr. Golding explained that even though there is currently no approved DNA-based assay for the detection of HIV, a sponsor could negotiate with the FDA to conduct a Phase 3 HIV vaccine trial using an approved RNA-based test along with a non-approved DNA-test. She emphasized that US investigators will want to have an algorithm in place that only includes FDA validated assays at the time they engage in the licensure trial, and noted that such assays are likely to be approved by the time the HIV vaccine trial goes into Phase 4.

Joseph Mulenga of the Zambia National Blood Transfusion Services discussed international vaccine development and licensing, national regulatory authorities (NRAs), national immunization technical advisory groups (NITAGs), and the collaborative efforts of these groups with WHO, SIVAC (Supporting Immunization and Vaccine Advisory Committees) and the DCVRN (Developing Countries Vaccine Regulators Network). He explained that NITAGs provide recommendations to NRAs based on evidence and unbiased scientific review. He delineated the differences between in-country and out-of-country processes for international vaccine development and licensing. He emphasized that oversight of clinical trials depends on each country's NRA as well as on each country's ministry of health (MOH). The time between the NRA approval and the MOH approval may be lengthy. However, a special license may be given to expedite introduction of the first batch of vaccines.

Dr. Mulenga described the numerous challenges faced by NITAGs and NRAs and explained that the WHO supports these organizations by helping to establish regulatory mechanisms for licensing new vaccines and obtaining vaccines made in Europe for use in developing countries.

The point was made during the discussion that much of the responsibility for building the capacity to implement vaccine trials is borne by the manufacturers and the sponsors. Moreover, regulatory authorities in resource-limited countries may not be able to seek advice from regulatory experts in the developed world due to the confidentiality of the application. Trial sponsors need to establish confidentiality agreements or memoranda of understanding that would allow such interaction to happen. Lack of standardized approaches for in-country level approvals and the inability to share regulatory expertise globally are noted as major impediments to moving the field forward. Dr. Ware indicated that CHAI has been involved in global discussions to include the African community on harmonization of regulatory approval processes. For example, the WHO pre-qualification program is streamlining the process for multi-country approval for small POC manufacturers of CD4 and viral load diagnostic assays. This program, however, is not the final step in some countries. Vendors may have to go through local approval processes to register their products.

Conclusion and Next Steps

Vaccine induced antibodies interfering with diagnosis in participants of HIV vaccine trials is an emergent, growing issue, which will culminate with the deployment of a universal prophylactic vaccine to HIV.

Individuals seeking to enroll in an HIV vaccine trial should be informed in advance of the potential for and implications of developing VISP/R. Messaging about this impactful issue must be scientifically accurate, yet clear and concise enough to be unequivocally understood by all volunteers. At the same time, it should be expressed in such a way that altruistic individuals would continue to consider participating in HIV vaccine trials.

While test platforms and algorithms for effective differentiation of VISP/R from viral infection currently pose technical challenges, they must be in place for the conduct of clinical trials and for use of licensed vaccines. Technologies must be affordable and adaptable to communities where trials are being conducted. As such, some current POC technology trends seem to be moving toward meeting these goals. As new candidate vaccines emerge, novel assays and devices will need to be validated and eventually approved to be commercially available in a timely manner and this may require coordination of regulatory expertise.

HIV vaccine recipients need to be provided with follow-up clinical test services and/or other services as long as needed. This requires logistical planning and financial support from trial sponsors and public health agencies in many countries. The HIV diagnostic test field, national health authorities and regulators also should start to consider how the diagnosis of true infections within large populations would be handled once an effective vaccine is licensed and deployed.

The Global HIV Vaccine Enterprise is taking steps to further engage the HIV vaccine field regarding the challenges of VISP/R. As part of a communication strategy, the writing committee assembled during the meeting will draft a manuscript inclusive of an executive summary with recommendations, emphasizing the importance of the issue to the field and outline a roadmap to address VISP/R milestones over the next five years. The outcomes of the meeting were presented at the Chinese AIDS Vaccine Initiative (CAVI) and the WHO-UNAIDS HIV Vaccine Advisory Committee (VAC) joint meeting in Beijing in June 2013. The Enterprise is also engaged in a process to incite the field to adopt a common terminology, which would greatly simplify standardized messaging for HIV vaccine trial participants and the entire field.

It is clear that addressing all the issues related to vaccine induced antibodies in HIV vaccine recipients requires commitment and concerted action from the field as a whole in collaboration with local and global agencies such as the WHO.

Appendix

Plenary Speakers

The meeting agenda and the speakers' presentations can be found on the Enterprise website:

www.vaccineenterprise.org/content/timely-topic-VISP-presentations

- **Barney Graham**, NIAID, Vaccine Research Center (VRC) - *Vaccine Candidates Pipeline*.
- **Sheila Peel**, US Military HIV Research Program - *HIV Diagnostic Algorithms in the Clinic*.
- **John Hural** and **Carissa Karg**, HIV Vaccine Trials Network- *HVTN VISP/R program*.
- **Mary Allen**, NIH- Division of AIDS - *Current VISP/R Practices Overview*.
- **Pat Fast**, International AIDS Vaccine Initiative - *Best Practices Discussion*.
- **Mark Ware**, Clinton Health Access Initiative (CHIA) – *Pipeline of Diagnostic Tests*.
- **Andrew Levin**, Immunetics, Inc. (Boston, US) - *Developing a Commercial VISP Test: Selectest*.
- **Christopher Bentsen**, Bio-Rad. Laboratories (US) - *The Challenges in Developing and Commercializing HIV Tests that are Useful in Differentiating VISP*.
- **Helen Lee**, Diagnostics for the Real World (UK) - *Molecular POC Diagnostics: SAMBA*.
- **Helene Zinszner**, Global HIV Enterprise - *The VISP-VISR terminology- Community Focus Groups perspective*.
- **Hana Golding**, US Food and Drug Administration - *Preparing for Vaccine Licensure – US perspective*.
- **Joseph Mulenga**, National Blood Transfusion Service, Zambia - *Preparing for Vaccine Licensure – African perspective*.
- **Robert Coombs**, University of Washington - *Meeting Summary*.

* Composition of the discussion panel and discussion groups

- The discussion panel about the technology needed to address VISP/R in trial participants was moderated by **Bob Coombs** (U. Washington) and included **Helene Lee** (DFRW), **Michele Owen** (CDC), **Marco Schito** (HMJF), and **Mark Ware** (CHAI).
- The discussion Group concentrating on 'Technical Feasibility at Trial and Public Health Levels', was chaired by **Michael Busch** (Blood Systems Research Institute, US) and co-chaired by **John Hural** (HVTN).

- The discussion group on 'Social Impact and Informed Consent' was chaired by **Pat Fast** and co-chaired by **Nomampondo Barnabas** (Perinatal HIV Research Unit, SA).
The discussion group on 'Logistical Issues of Trial Follow-Up' was chaired by **Carissa Karg** (HVTN) and co-chaired by **Glenda Gray** (PHRU, SA).
- The discussion group on Financial Issues of Trial Follow-Up was chaired by **Margaret McCluskey** (USAID) and co-chaired by **Mary Allen** (NIAID, US).
- Members of the writing committee chaired by **Robert Coombs** (U. Washington) are: **Renee Holt** (HVTN), **Sheila Peel** (MHRP), **Robert O'Connell** (MHRP), and **Katie Brooks** (HVTN), **Carissa Karg** (HVTN).

Resources

- A Webinar about VISP/R was organized by the Enterprise and presented by Pat Fast and Mary Allen on May 2nd, 2013. A recording is available at: www.vaccineenterprise.org/content/timely-topic-VISP
- Additional resources about VISP/R are available at: www.vaccineenterprise.org/VISP-resources