Preventive HIV Vaccine Research and Routine HIV Testing: The Challenge of Vaccine-Induced Seropositivity (VISP)

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Background

Trial participants are instructed to only have HIV testing done by their research site, where more specific tests can distinguish between a response to the vaccine or a true infection. Because of the new CDC guidelines for HIV testing, individuals may be tested for HIV in situations they have not previously encountered, such as an emergency room or their health care provider's office. They may not realize that they can opt out of being tested. This could cause social impact for the individual, and it creates a potential for errors in reporting new HIV infections (surveillance).

Vaccine-induced seropositivity has been a concern since HIV vaccine trials began. Some participants from trials as long ago as the early 1990s continue to test HIV antibody positive. Vaccine-induced seropositivity can be distinguished from true infection using more specific laboratory tests such as nucleic acid testing, also known as PCR.

We expect the problem to increase as study vaccines become more complex, as trials enroll larger groups of people, and as more trials are conducted around the world.

The HVTN has always attempted to provide resources to help participants address any issues that arise, and is increasing our proactive efforts in light of these concerns.

Language regarding vaccine trials from the CDC Testing Guidelines issued September 22, 2006:

Additional Considerations for HIV Screening Test Results

Participants in HIV vaccine trials. Recipients of preventive HIV vaccines might have vaccine-induced antibodies that are detectable by HIV antibody tests. Persons whose test results are HIV positive and who are identified as vaccine trial participants might not be infected with HIV and should be encouraged to contact or return to their trial site or an associated trial site for the confirmatory testing necessary to determine their HIV status.

The Ways the HVTN Deals with Vaccine-Induced Seropositivity

Informed Consent

The HVTN's informed consent process and consent forms have been revised to provide more information about this issue to potential study participants for their consideration as they decide whether or not to join a trial.

All of the following excerpts are from the HVTN Informed Consent template which address VISP.

EXPLAINING VISP

"*Risk of a Positive HIV antibody test caused by the vaccine:*
The study vaccines may cause you to have a positive antibody test result on some types of HIV tests. This means that the test says you have HIV, even when you don't. The antibody test result may be positive because your immune system is reacting by making antibodies to the study vaccine."

CDC GUIDELINES

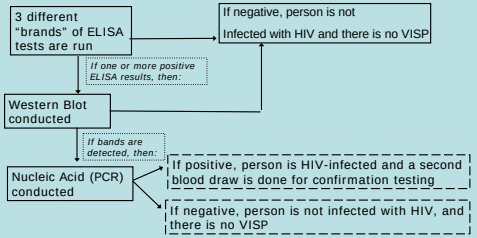
"The US Centers for Disease Control (CDC) now recommends that HIV testing become a part of routine healthcare. It is very likely that you will be asked to have an HIV test outside of this study. You can refuse to have this test and explain that you are in a research study that could affect the results of the test. You can contact us for help if you are asked to be tested for HIV outside of this study site. With your permission, we can confirm that you are in this study and explain this situation to those who want to test you for HIV."

TESTING AT THE SITE

"At the end of the study, we will test you using several common antibody tests for HIV. If you test negative at this time, you will go elsewhere for future HIV testing. It is unlikely, but if you receive a study vaccine you might test negative at the end of the study and later receive a positive test result caused by the vaccine. This change could happen because more sensitive HIV antibody tests are available. You can talk to the study staff before you get an HIV antibody test outside of this study site if you are concerned."

HIV testing algorithm used at the end of HVTN's HIV vaccine trials

At the conclusion of each trial, participants who received the study vaccine are tested using a variety of HIV tests, hoping to imitate what they might experience if tested for HIV outside the research setting. Participants who are identified as having VISP can receive their HIV testing at the research clinic free of charge for as long as the VISP response continues.



US Participant ID Card

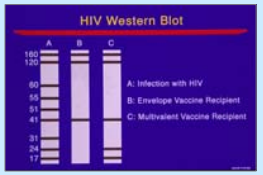
Once participants enroll in a trial, they are reminded throughout their study participation about the importance of being tested for HIV only at the research site. They are also provided with a study ID card to confirm their participation in a trial. This card contains a toll-free phone number for the NIAID Division of AIDS assistance line.

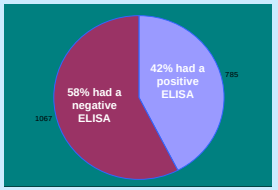
Overview: The challenge of vaccine trials and routine HIV testing

The Challenge: **People who participate in a preventive HIV vaccine clinical trial may have antibodies to HIV which are caused by an immune response to the vaccine, and not due to actual HIV infection. Given the new CDC HIV testing guidelines, individuals could be at greater risk of being incorrectly identified as HIV-infected if they are tested outside the research setting. Researchers and testing providers must work together to best serve the needs of every individual.**

The Data:

HIV-1 Western Blot testing may be used to help distinguish actual HIV infection from a VISP response. The figure (right) depicts the banding patterns of blots demonstrating actual HIV infection and vaccination with 2 types of study vaccines.





End-of-study HIV test results among vaccine participants in HVTN Phase I or II trials that began enrolling 12/1/2000 through 9/30/2007:

- **2942 participants were enrolled during this time**
- **Among them, 1852 had an end-of-study HIV test completed by the 9/30/2007 cut-off (229 still in study follow-up; remainder reflect early terminations, or lab tests for trials not yet complete). Among the 1852 participants:**
  - **57.6% male**
  - **66.4% < 35 years of age**
  - **59.1% white**
- **The VISP rate was 785/1852 = 42.4%.**

Our Concern: **Vaccine trial participants are counseled to undergo HIV testing only at the research clinic. However, now people may be tested in situations they have not previously encountered, or they may not realize the need to opt out of testing. HIV test results could be easily misinterpreted if the provider is unaware of the individual's participation in a vaccine trial. This can cause social impact for the individual, and potential for errors in reporting new HIV cases. Additionally, it can unblind both the participant and the researchers, potentially compromising the study data.**

Solutions – *what are we doing?*

- **There is a need to educate testing providers about VISP. Presentations are being made at conferences such as the 2008 National Summit on HIV Diagnosis, Prevention and Access to Care, and local research sites are also working in their own communities to educate health care professionals in private practice, hospital departments through Grand Rounds, health departments and CBOs that provide HIV testing services, etc.**
- **Researchers must continue to work collaboratively with HIV testing providers to ensure minimal social impact to trial participants**
- **Research staff must educate trial participants about their rights regarding HIV testing, including the right to refuse testing (opt out).**
- **The HVTN's informed consent process and consent forms have been revised to provide more information about this issue to potential study participants for their consideration as they decide whether or not to join a trial.**
- **In the event that off-study testing happens and VISP occurs, research staff work with the participant to mitigate the situation. This can include, but is not limited to, providing confirmatory testing to rule out HIV infection and explaining test results to others (such as insurance companies or healthcare providers) with the participant's permission. There is additional assistance available through the National Institute of Allergy and Infectious Disease's Division of AIDS (the HVTN's sponsor) that can be accessed as well.**
- **Once participants enroll in a trial, they are reminded throughout their study participation about the importance of being tested for HIV only at the research site. They are also provided with a study ID card to confirm their participation in a trial. This card contains a toll-free phone number for the NIAID Division of AIDS assistance line.**
- **If a participant relocates away from the research site, or if the research site closes, we can continue to provide HIV testing through mailed test kits or by setting up testing services for an individual in their new location.**

Concern about Negative Social Impact

The HVTN fully supports the CDC's recommendations for routine HIV testing so that more people will have the opportunity to know their HIV status, protect themselves and their partners, and seek appropriate medical care and treatment. However, we recognize that trial participants may be at risk for increased social impact events due to the likelihood of being tested for HIV outside the research setting. Examples of social impacts related to VISP that may occur include:

- Obtaining disability or life insurance
- Employment or pre-employment physical examination
- Routine medical or dental care
- Interaction with government agencies relating to foreign travel or citizenship
- Enlistment into the military

Case Studies: Negative Social Impact Events

Negative Social Impact Events Related to Off-study HIV Testing in Phase I/II trials

Major Impact

- Obstetrician's office refused to provide care unless participant had HIV testing done by them. Site offered to provide HIV testing results to provider, but participant decided to have no further contact with provider.

Moderate Impact

- Participant attempted to enroll in a medical research study at another institution and was refused due to a positive HIV antibody test. That institution referred the participant's name to the State Dept of Health. Site staff provided HIV testing documentation to the other institution and DOH to clarify that the participant was not HIV positive.
- Participant was denied life insurance and suspected that this was related to study participation. Site staff planned to provide HIV testing results to company.
- Participant wanted to participate in another HIV research study that required HIV testing but decided not to because of vaccine trial requirement of no off study testing .

Minimal Impact

- Participant had an off-study HIV test performed as part of screening for another research study.
- Participant wanted to be a liver donor and liver clinic wanted to perform HIV test. For other reasons, participant was not considered a suitable donor.
- Participant disclosed participation in the vaccine study to his Army reserve officer so he would not be tested for HIV by the military.
- HIV testing required for taking a job in Canada. Site provided study HIV test results to Canadian officials.

Negative Social Impact Events Related to Off-study HIV Testing in an efficacy trial from one US site enrolling female Commercial Sex Workers (in a state where written consent was required by law at the time the event was reported)

Birth Control

- 22 year old African American woman saw her regular health care provider at a community clinic to receive Depo Provera. Physician refused to provide birth control unless she agreed to HIV testing, and disregarded the woman when she explained that she was in a vaccine trial. The woman ultimately consented to testing in order to receive her birth control. Physician later told her that he thought she was HIV infected and wanted to do confirmatory testing. Woman then contacted the research site for assistance in resolving the situation. Our testing found VISP. The site has helped the woman to follow up with her provider, and she has successfully sued the clinic for violating her right to consent to testing.

Prenatal Care

- 22 year old African American woman was seen by her OB-GYN. An HIV test was done without her consent as part of routine prenatal care. When the positive result was given to her, she explained her trial participation and asked her doctor to contact the research site. He did, and the site investigator reevaluated the Western Blot results. Woman was subsequently seen at the research site for confirmatory PCR testing, which found VISP. These results were provided to her OB-GYN at the woman's request.
- 19 year old African American woman was seen at the University Hospital for routine prenatal care. She was HIV tested without her permission. The indeterminate Western Blot was given to her at the same time they requested another blood draw for confirmatory testing, and told her that monthly HIV testing of pregnant women was part of their routine care. After a second indeterminate result, a family member reminded her about the possibility of VISP so she contacted the research site. The site conducted testing the same day, found VISP, and provided the results to the Hospital at the woman's request.

Emergency Care

- 24 year old African American woman, 7 weeks pregnant, was seen in the emergency room for moderate bleeding, with a provisional diagnosis of "threatened spontaneous abortion". Hospital records show an order for perinatal rapid HIV test, but consent was not obtained. She was discharged with orders to follow-up at a community clinic. Subsequently, the community clinic contacted the research site to ask for information about the trial, explaining that they had a patient who insisted she was a participant and that her indeterminate Western Blot result was due to a study vaccine. The site was able to reevaluate the WB result, found VISP, and conducted confirmatory PCR which found VISP. Participant feels that the medical personnel at the hospital and clinic were more concerned about the possibility of her being HIV-infected than they were with the bleeding that caused her to seek care. She reports that a resident tried to comfort her and told her that she was in denial about her HIV status.
- 27 year old African American woman was hospitalized for a tubal ovarian abcess related to pelvic inflammatory disease. She reports that she was told she was HIV infected at the same time as they requested consent for confirmatory testing, and the hospital staff referred her to a community clinic for HIV treatment. She refused to consent and asked them to contact the research site. Hospital notes show that she stated her trial participation several times, and that staff concluded it was possible she was telling the truth. She kept the appointment with the treatment clinic, and a physician there contacted the research site for more information. He complimented the site on the thoroughness of the education that had been provided to the participant. The site conducted confirmatory testing which found VISP.