Hamilton Richardson to serve as interim Global CAB co-chair

Gail Broder, Domestic Project Manager, Community Engagement Unit

In April 2013, Kate Miller had to step down from her role as the US co-chair of the Global CAB leaving a term that was not due to expire until July 2014. Because sites may change for the upcoming DAIDS award cycle, holding an interim election seemed strange. The staff of the Community Engagement Unit at HVTN Core suggested that the Global CAB could consider appointing someone to serve as an interim co-chair for the remainder of the term. This would ensure continuity of leadership from someone familiar with the Global CAB, and also allow for a fair and representative election to occur as planned in 2014, when the Network sites for the new award cycle were known. The Global CAB approved, and in June, 2014 Hamilton Richardson stepped into his new role as interim co-chair.

Hamilton was also recognized at the May HVTN Full Group Meeting with the Octavio Valente, Jr. Volunteer Service Award. It was noted that Hamilton stands out for the longevity of his involvement, and his willingness to step up whenever he is asked, including serving as an at-large member ever since his site left the network with the last DAIDS award cycle more than 6 years ago. In his time with the network Ham has held almost every HVTN CAB leadership position, including Global CAB co-chair, Global CAB representative to the Scientific Governance Committee, as well as serving as an HVTN representative to the cross-network Community Partners group and serving on the Legacy Project Advisory Committee.

The HVTN thanks him profusely for all that he has done and will continue to do.
The year 2004 brought great hope to the high HIV/AIDS–prevalent areas around Nyanga and Cross Roads. The Desmond Tutu HIV Foundation’s Emavundleni Research Centre established a CAB in preparation for HIV vaccine research starting there. The HVTN was the first network that the CAB worked with. HVTN Community Education Unit staff came to the site to assist in building the capacity of the CAB. Workshops were conducted on the role of CAbS and the HVTN. For continued training, CAB members are also given opportunities to travel outside of South Africa to attend HVTN conferences and workshops leading them to feel greatly empowered through the opportunity to work with researchers and CAbS from other sites and countries.

The Emavundeni CAB is a vibrant and diverse group that includes self-identified males, females, MSM, and previous trial participants from different ethnic and age groups. This diversity in age, religious background, culture, and education results in frequent heated debates and rich discussions on issues such as provision of medical male circumcision in areas where cultural circumcision is practiced.

The CAB is structured with an executive committee and general members, with about 20 members in all. The executive committee chairperson leads meetings and acts as the leader. The vice-chairperson stands in with the same powers in the chairperson’s absence. The secretary and vice-secretary keep minutes of meetings and write letters on behalf of the CAB when necessary, and the treasurer is able to talk about budgets and money for CAB activities. The executive committee has 5 additional members who form task teams to help with site or CAB community activities. The site also does other HIV prevention research with the HIV Prevention Trials Network (HPTN), Microbicide Trials Network (MTN), The South African AIDS Vaccine Initiative (SAAVI) and The International Aids Vaccine Initiative (IAVI). The CAB uses each meeting to discuss the work of each of these different networks.

One historic challenge our CAB faced was when the Phambili study was stopped and we needed to inform the community. We are grateful for the excellent way the site and HVTN worked with us in dealing with the issue. They informed the CAB as quickly as possible of the stoppage and why. They also helped with tips for developing messages, staying on message, and dealing with difficult questions. This resulted in the community not losing faith in the research team and future research activities. Some recent challenges include member retention, electing a new executive committee, and budget constraints. These challenges actually resulted in the members bonding and working harder together to resolve these issues.

During a recent Cross Roads stakeholder meeting the importance of CAB capacity building and information updates was highlighted. Our CAB works in an area where misconceptions and negative rumors about HIV/AIDS and HIV research practices are rife. We regularly help with rumor control and clarifying misconceptions. This is done through one-on-one talks, presentations, workshops and awareness events.

Memorable highlights for our CAB are visits by the HVTN staff and US CAB member Hamilton Richardson in October 2008. The CAB was in high spirits during and after these visits. Our CAB was also eager to participate in the HVTN Conference that took place in Cape Town this October. This… continues on page 6
Phase 1 studies - filling the HIV vaccine toolbox

Cristine Cooper-Trenbeath, Associate Director of Vaccine Evaluation and Senior Staff Scientist, SCHARP; Genevieve Meyer, International Project Manager, Community Engagement Unit, HVTN

“HVTN 505, the Step Study, Phambili, HVTN expansion in southern Africa” — lately it seems that the only HVTN studies to get a lot of attention are the big phase 2B efficacy studies. Phase 2B studies can be exciting, because they enroll thousands of volunteers and are designed to see if the vaccines can stop or slow an HIV infection. But the work to create a successful vaccine doesn’t just start there.

Before any product can make it to a phase 2B study, it has to be tested in smaller studies called phase 1 studies. However, not all phase 1 studies lead to phase 2 studies. The investment in HIV vaccine research has given the HVTN many tools for finding better HIV vaccines. One of the challenges is knowing how best to put these vaccines together to create diverse and long-lasting immune responses. Phase 1 studies play an essential role in assessing safety and figuring out the best dose and order to give the vaccines. In 2013 alone, the HVTN was running and conducting analyses on nearly 30 studies. A recent article in the HVTNews (“Probing scientific questions to advance HIV vaccine development”) sheds light on recent data from the phase 1 studies summarized below. For the full article, visit hvtn.org/science/hvtnews.html.

HVTN 083 and 085: Testing combinations of vectors and inserts. HVTN 083 and 085 looked at how to increase the T-cell responses to HIV. T-cells are thought to play a key role in controlling the amount of virus in the blood of people who are HIV infected. HIV is diverse in how it appears and evolves, so one goal of HIV vaccines is to create diverse anti-HIV T-cell responses ready to fight a variety of HIV strains. Both HVTN 083 and HVTN 085 were designed to try to figure out the best ways to give vaccinations to increase the variety of these T-cell responses. The boost vaccinations were either matched to the priming vaccination or mismatched for the insert and/or the vector.

The study showed that prime/boost regimens containing mismatched inserts and vectors increased the variety of T-cell responses. Even better, the parts of HIV that the T cells seem to target are thought to be more difficult for HIV to avoid.

HVTN 085 used only the Ad5 vector, but the products had 4 different HIV inserts. What made this study unique was that it compared different strengths of the vaccine in several combinations. One group got the whole vaccine at once in the arm. Another group got the whole vaccine at 4 body locations (1 injection in each arm and each leg). In the final group, the vaccine was separated into its 4 parts, each given in a different limb.

The results showed that the T-cell response was greatest when the whole vaccine was given in 4 different body parts (1 in each arm and 1 in each leg).

Both studies combined indicate that mixing up vectors, inserts, and even injection location increases the diversity of the T-cell response.

HVTN 073E and 088: Testing protein boosts. In October 2009, exciting news came that a vaccine regimen tested in Thailand actually prevented HIV infections. While the products weren’t effective enough to become licensed, the study opened new doors for vaccine regimens and study designs. That regimen was based on a vaccine made with a canarypox vector prime and envelope protein boost. Further analysis of the results showed that the antibodies created in response to the Env boost were important in providing protection against HIV. To learn more about these protein boosts, the HVTN launched HVTN 073E and HVTN 088.

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Different time zones, different hemisphere, different languages being spoken in the hallways: many things were different about the October HVTN Conference this year. For starters, it took place in beautiful Cape Town, South Africa instead of rainy and cold Seattle. Instead of an audience of site staff and CAB members from all of our current sites, the HVTN audience was much smaller yet peppered with staff members from all of the potential sites we are exploring for southern Africa site expansion, including Botswana, Malawi, Mozambique, Namibia and Zimbabwe.

The conference flow was also a bit different. Normally the HVTN conferences include a handful of plenary sessions, then many time slots for smaller groups like protocol teams to meet. This time, there were numerous plenary sessions focusing almost exclusively on issues relevant to site expansion—from ethical and regulatory considerations, the role of community involvement through Good Participatory Practice, and the science behind the clade C HIV vaccines to be used in the region, to considerations for vulnerable populations such as adolescents, sex workers, and men who have sex with men.

Yet some things stayed the same: the enthusiasm for the science, the sense of togetherness necessary to be able to conduct large studies across multiple sites, and the role community plays in ensuring sound and relevant research. The community program was smaller than at other conferences but rich in discussion. Drs. Glenda Gray and Jim Kublin joined the first community session to talk about the recent data from the Phambili study. The second community session continued with this theme and moved toward what sites are feeling and needing in terms of future recruitment and community awareness.

The final plenary, chaired by Dr. Glenda Gray, laid a foundation for the research path and challenges ahead including presentations about SAAVI’s (South African AIDS Vaccine Initiative) vaccine developments, the HIV research perspective from the Medical Research Council of South Africa, and funding considerations from the Bill and Melinda Gates Foundation.

After nearly 4 days of intense meetings and detailed presentations, attendees left with a greater understanding of the HVTN’s programs, enthusiasm for the journey ahead, and a greater desire to work together to ultimately stop HIV.

Most of the conference presentations are posted on the new members’ website, but you may need to ask one of your 4 CAB leaders or a staff member to help you access them.

members.hvtn.org/hvtn-conference/SitePages/Oct2013-HVTN-Conference.aspx
If you have ever taken children on a long car ride then you have probably heard the cry, “Are we there yet?” When the journey is long it’s easy to get impatient, but if the destination is important to you, it’s worth the time and energy to get there.

Since HIV was first identified as the cause of AIDS in the early 1980s, we—a community of scientists and advocates—have been searching for a safe and effective vaccine. The journey so far has been a long and challenging one. Some scientists began to wonder if it would ever be possible to find a vaccine. In 2009, that question was answered by RV144, the Thai vaccine trial that enrolled more than 16,400 volunteers. The results showed that 2 years after receiving injections, participants who got the vaccine had 31.2% fewer HIV infections than those who got the placebo. One year after vaccination the difference was as high as 60%. We now knew that if we could just build upon the success of RV144, we could create a vaccine that could stop HIV infection once and for all. We are now on that path.

The HVTN, as part of a group called the Pox-Protein Public-Private Partnership (P5), will be...
SUMMARY OF THE MAIN “UHAMBO” TRIALS:

HVTN 100 (followed by 702), also called the “licensure” track or phase 3 program will use the Thai trial regimen (RV144) but adapted for South Africa, which means using clade C HIV pieces in the vaccines instead of B/E which were in the Thai vaccines. All of the HIV pieces are made in a laboratory and are not real, so they cannot cause HIV infection. The other changes are adding a product called an adjuvant to help the vaccine work better in the body. The adjuvant is called MF 59. First there will be a small phase 1 trial (HVTN 100) to look for safety and how the vaccines work in the body. If these results are favorable, there will be a bigger trial, HVTN 702, that will enroll many more people and begin to see if the vaccine regimen is actually protecting against HIV.

HVTN 701, also called the correlates program, will test several newer vaccine regimens and adjuvants. This study will be at multiple sites in southern Africa and is designed to learn more about how the immune system may develop ways to protect against or defeat HIV if is exposed.
Phase 1 studies - filling the HIV vaccine toolbox

HVTN 073E was a follow-on to the study HVTN 073/SAAVI 102, which had given a DNA vaccine with an MVA boost. These were different vaccines than in the Thai trial, but both used a poxvirus vectored vaccine. In 073E, 27 participants came back and received 2 boost vaccines that contained the Env protein. Early data showed giving these boosts, even 2 years after the initial vaccines, led to strong, high-quality antibody responses.

HVTN 088 was also designed to provide a boost vaccine to participants who had been vaccinated in a previous study, up to 7 years earlier. This study looked at whether an Env boost from a different HIV strain than in the original vaccination would diversify the immune response. Remarkably, anti-HIV antibodies were detected in blood samples from some of the participants even before the boost, showing that the immune response to the original vaccination could last as long as 7 years. However, the boost with an Env from a different strain of HIV did not seem to increase the diversity of antibody immune responses. More research is needed to better understand these results and to see if a third boost might be needed.

While each of these studies looked to address different scientific questions, collectively they play a crucial role for vaccine researchers to be able to explore new concepts and build off previous studies. These particular studies were designed to learn how to get the best types of responses overall. This knowledge can now be applied to a wide variety of vaccine products and allow future study regimens to generate more optimal responses.

HVTN 077 and HVTN 078: Mixing it up with different doses and combinations of vaccines. Using viral vectors in vaccines is often helpful, because they can lead to strong immune responses. Two recent studies, HVTN 077 and HVTN 078, looked at the effects of vaccine regimens that use a different vector in the prime than in the boost.

HVTN 078 explored whether the order and the dose of the vaccines had any impact on immune responses. Because both antibodies and T cells are helpful in preventing and controlling HIV infection, vaccines that create both responses may work best. But it can be challenging to stimulate both T-cell and antibody responses, and what is helpful for one type of immune response can end up suppressing another. HVTN 078 provided some clues for how to get the best of both worlds. The study showed that a high-dose rAd5 prime followed by a NYVAC boost, rather than the other way around, led to strong antibody immune responses and good T-cell responses. This finding shows that that the order that products are given is very important. It also shows that using a high dose of a potent vaccine for the first vaccination results in better antibody responses than when a lower dose is used.

HVTN 077 used an Ad35 vector, given in combination with rAd5 or DNA vaccine. Antibodies to Ad5 are known to be very common in the general community but antibodies to Ad35 are relatively rare. This trial tested whether immunization using an Ad35 vectored vaccine led to similar responses to Ad5-vectored vaccines, and how Ad35 compared to DNA when used as primes. Results showed that strong immune responses were created by all the vaccine combinations. This means that overall, Ad35 can create responses as favorable as those to Ad5, even among participants who already had exposure and immunity to Ad5.

We know that creating diverse and long-lasting responses is complex. Because these studies showed some unexpected responses, it means that more research is needed to understand protein boosts with these vaccines.
New HVTN members’ website launches

Gail Broder, Domestic Project Manager, Community Engagement Unit

The members’ website, a password-protected part of www.hvtn.org, has existed since the Network began. However, technology has rapidly evolved and the website has not. One update in particular was a need for individual logins to improve security, rather than group passwords shared by an entire site. Personal logins would also allow for different kinds of staff and CAB members to have access to different information on the website.

In August 2013, the HVTN launched a new members’ website and distributed personal login information. For CAB members, this represents a big change! Instead of sharing a site login, the CAB chair and co-chair (if applicable) and the Global CAB representative and Global CAB alternate (if applicable) of each local CAB would have their own login, for a total of up to 4 CAB member logins per site.

These 4 individuals will need to work with their local CABs to help other CAB members if they are interested in finding some information. This is a big change, but the planning group felt it was a reasonable starting point, and would give everyone a chance to get used to the change and see if it works.

Those who now have a login to the members’ website are encouraged to log in and explore the information that is available and share updates with the rest of their CAB! If there is other information you would like to see there, send your suggestions to the staff at HVTN Core. We will also be looking for your feedback about whether this new system of having up to 4 CAB member logins per site is working.

Also in the works are plans to revise the HVTN’s public website. This is still in the early planning stages, but we will provide updates as the project moves forward. Stay tuned!

Glossary from Phase 1 studies - Filling the HIV vaccine toolbox

**INSERT**: The pieces of HIV used in the vaccine. Different inserts come from different parts of the virus particle.

**VECTOR**: A product made from a virus or bacteria that has been changed so it cannot cause disease in humans. Vectors are used in vaccines as vehicles to transport HIV pieces into the body in order to create a strong immune response.

**VACCINE REGIMEN**: A regimen is a combination of products given on a particular schedule. For example, a vaccine regimen may include getting 4 injections several weeks apart. The Hepatitis B vaccine regimen includes 3 doses of the vaccine given over a period of 6 months.

**PRIME-BOOST REGIMEN**: A vaccine regimen that uses at least 2 different products. The priming injection makes the body more ready to receive the boost, which may be given at the same time or at a later date. The idea of combining different products is that they work together and make a better response than if one was used alone.