Building on the Success of RV144

In 2009, the RV144 Thai vaccine trial provided the first evidence in humans that a safe and effective preventive HIV vaccine is possible. Although efficacy was 31.2% at the end of the study, there was a higher early effect (60%) at 12 months.

The Pox-Protein Public-Private Partnership (P5) is a diverse group of organizations committed to building on the success of the RV144 HIV vaccine trial and evaluating potentially improved pox-protein vaccines to determine if they might provide significant public health benefit.

Follow-up clinical studies using modified vaccine regimens and extra boosts are set to begin in Southern Africa in 2015. Results from an initial study to ensure that the RV144 vaccine regimen is safe and well-tolerated in South African volunteers will be reported at the 2014 HIV Research for Prevention (R4P) conference.

Clinical Studies

In planning and launching clinical studies, P5 members are working with government and communities within host countries to develop collaborative clinical development plans as well as initiate regulatory and access planning.

The planned studies are sequential (or rolled out in phases), and therefore the plans for large-scale clinical trials may evolve as researchers gather information from smaller studies regarding product safety and immune responses. A unique aspect of the large-scale studies is that new go/no-go criteria have been developed to help determine if those studies should move ahead. These decisions will be based on many factors such as vaccine potency and the ability to further test the hypotheses generated by the RV144 trials.

Clinical trial implementation in Southern Africa is led by the HIV Vaccine Trials Network (HVTN) and studies in Thailand are led by the U.S. Military HIV Research Program (MHRP), in collaboration with the host country governments and ministries.

Improving the Vaccine Regimen

Researchers have discovered important clues about the immune responses that may have played a role in protecting some volunteers in RV144. The data from extensive laboratory studies on correlates of risk of HIV infection will be used in one aspect of the clinical trial design.

In parallel, scientists with the P5 have been developing, analyzing and selecting protein components of the vaccine candidates for use in planned studies. They seek to improve and prolong the level of protection seen in RV144 by using an extra vaccine boost and different adjuvants that may increase and prolong antibody responses.

Southern Africa Clinical Trials

Development Track

The HIV Vaccine Trial Network (HVTN) plans to conduct clinical trials in heterosexual adults that will evaluate a prime-boost vaccine regimen similar to that used in RV144 adjusted to target the most common subtype of HIV in the region (subtype C). The development track will begin with a Phase I trial to test the vaccine regimen’s safety and immunogenicity and, depending on those study results, a larger efficacy study will follow.

A modified version (subtype C) of ALVAC, the pox vector vaccine used in RV144, will be used as the prime or first vaccination received by study participants. That prime will be followed by the boost vaccinations with the vector and Bivalent GP120, a protein product adjusted for subtype C.

Current estimates are for the Phase I trial to start enrolling 252 participants early in 2015. The efficacy trial, HVTN 702, should start enrolling 5,400 volunteers during the second half of 2016 provided all products are ready, agreements are in place, study sites are ready and “go” criteria are met.

A small Phase I trial to evaluate the RV144 vaccine regimen in 100 volunteers in South Africa began in June 2013. This trial, HVTN 097, aimed to ensure that the vaccine regimen tested in Thailand, targeting subtypes B and E, is safe and well-tolerated in this population. Results, which will be presented at R4P 2014, show that the regimen was safe and elicited a robust immune response in South Africans. Studies are ongoing to compare these results to those seen in Thailand in the RV144 trial.
**Research Track**

The HVTN also plans to test other HIV vaccine regimens in Southern Africa in a parallel research track using multiple vaccine candidates. These studies may provide additional clues on important immune responses to prevent HIV infection if the regimens prove effective. The study design allows for flexibility to accelerate progress and potentially identify new correlates.

The research track includes several Phase I studies looking at different priming regimens in combination with a new pox vaccine vector and unique adjuvants. Results from these studies, which are planned to begin in mid-2015, will inform the follow-on Phase IIb study, HVTN 701, which is planned to begin in early 2018.

Upcoming development and research studies will be conducted in Mozambique, Tanzania, Zambia, Zimbabwe, Malawi and South Africa.

**Thailand Clinical Trials**

**Development Track**

MHRP, in collaboration with the P5, is planning an efficacy trial in a high-risk population of men who have sex with men (MSM) to hopefully improve upon the RV144 result and extend its relevance to at-risk populations to achieve the greatest public health impact.

A private-public partnership called the AIDS Vaccine Efficacy Consortium (AVEC) was formed in 2012 to accelerate the development and testing of a pox-protein HIV vaccine prime-boost regimen in Thailand.

In 2014, the Government of Thailand signed an agreement with MHRP to build on the success of the RV144 trial. The Thai Government committed to supporting future HIV vaccine efficacy studies and establishing a flexible biologics manufacturing capability that could support HIV vaccine production in Thailand. AVEC hopes to finalize plans for the protein development in 2014, so plans for an initial efficacy study can proceed and potentially begin in 2017.

**Immunogenicity Studies**

MHRP, which led the RV144 trial with the Thai Ministry of Public Health, initiated follow-on clinical studies to conduct intensive immunogenicity research.

One study, RV305, began in 2012 in Thailand to evaluate re-boosting volunteers who participated in the RV144 study. Through this study, MHRP researchers have determined that the most effective boost is when both ALVAC (Sanofi Pasteur) and AIDSVAX (GSID) are given together, or when AIDSVAX is given alone.

Researchers have also found that the late boosts in this study, given six to eight years after initial vaccination, are producing some surprising and promising immune responses. Studies are ongoing to characterize these responses, along with analysis of host genetic factors that may play a role.

Another clinical study, RV306, began in September 2013 using the RV144 vaccine regimen to compare additional vaccine boosts and gather more immunogenicity data in 360 new volunteers. This study will explore how timing of the boosts may impact immune responses.

These studies are informing ongoing vaccine research and are helping lay the groundwork for future vaccine studies in Thailand.

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**About the Pox-Protein Public-Private Partnership (P5)**

Established in 2010 to build on the RV144 results, the Pox-Protein Public-Private Partnership (P5) seeks to advance and potentially license HIV pox-protein vaccine candidates that have the potential to achieve a broad public health impact. The P5 has assembled a collaborative team across four continents to accelerate progress towards an effective and durable HIV vaccine. The studies are sponsored by NIAID, and core funding is being provided by NIAID/NIH and the Bill & Melinda Gates Foundation, with additional contributions from South Africa and the P5 private sector partners.

- Bill & Melinda Gates Foundation
- Centre Hospitalier Universitaire Vaudois (CHUV)
- GlaxoSmithKline (GSK)
- HIV Vaccine Trials Network (HVTN)
- Novartis Vaccines and Diagnostics
- Sanofi Pasteur, the vaccines division of Sanofi
- South African Medical Research Council
- U.S. Military HIV Research Program (MHRP)
- U.S. National Institute of Allergy and Infectious Diseases/Division of AIDS (NIAID)