1. The name of activity, development challenge addressed, alignment with overall development strategy, target group/beneficiaries, budget?

**Name of activity:** Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women (CAPRISA 004)

**Development challenge addressed:** The HIV/AIDS pandemic continues to impose a severe global burden, especially in developing countries. Worldwide, an estimated 33 million people are living with HIV/AIDS, and 2.7 million new infections occur annually. Women and girls account for more than half of all global cases of HIV/AIDS and for more than 60 percent of new infections in sub-Saharan Africa. Current strategies for preventing HIV infection, such as delay of sexual debut, partner reduction, and use of condoms, are often not possible for many women in developing countries. There is an acute need for HIV prevention methods that women can use to protect themselves.

**Alignment with overall development strategy:** This activity has contributed substantially to promoting research and innovation, implementing a woman- and girl-centered approach, strengthening and leveraging global health partnerships and private sector engagement, and encouraging country ownership and leadership.

**Target group/beneficiaries:** This activity is benefitting women in developing countries who want to protect themselves from HIV infection, as well as their families and local communities.

**Budget:** Over a period of three years, USAID provided $16.5 million of the total cost of $18 million. The South African Department of Science and Technology provided the balance of funds. Gilead Sciences donated the tenofovir used to make the test gels.

2. What was the science and technology response to the development challenge? Why was science and technology deemed the best response?

It has long been apparent that many women need alternative methods to protect themselves against HIV infection since many cannot negotiate or successfully use existing approaches and consequently have no prevention options at all. Advocates for women’s health have been intensely interested in safe and acceptable technological approaches to remedy this situation. Testing in laboratory and animal models, supported extensively as part of the USAID microbicide research and development program, provided evidence that tenofovir, an antiretroviral drug already used for treatment, might be safe and effective in preventing HIV infection when used as a topically applied vaginal gel formulation. Building on USAID’s history of successfully developing other reproductive health products, pioneering individuals took the initiative in 2007 to design, fund, and implement a clinical trial that demonstrated the clinical efficacy of this approach. This scientific breakthrough provided the first-ever proof of concept that the microbicide approach, using active agents applied in the vagina for protection, was feasible and offers the promise of great impact for women in Africa and developing countries worldwide.
This activity implemented a clinical trial (CAPRISA 004) to assess effectiveness and safety of a 1% vaginal gel formulation of tenofovir, a nucleotide reverse transcriptase inhibitor, for the prevention of HIV acquisition in women. A double-blind, randomized controlled trial was conducted comparing tenofovir gel (n=445) with placebo gel (n=444) in sexually active, HIV-uninfected 18 to 40 year-old women in urban and rural KwaZulu-Natal, South Africa. HIV serostatus, safety, sexual behavior, and gel and condom use were assessed at monthly follow-up visits for 30 months. HIV incidence in the tenofovir gel arm was 5.6 per 100 women-years (38/680.6 women-years), compared to 9.1 per 100 women-years (60/660.7 women years) in the placebo gel arm (incidence rate ratio = 0.61; P=0.017). In high adherers (gel adherence > 80%), HIV incidence was 54% lower (P=0.025) in the tenofovir gel arm. In intermediate adherers (gel adherence 50 to 89%) and low adherers (gel adherence < 50%) the HIV incidence reduction was 38% and 28% respectively. Tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence. No increase in the overall adverse event rates was observed. There were no changes in viral load and no tenofovir resistance in HIV seroconvertors.

This activity demonstrates that tenofovir gel and similar microbicide products could potentially fill an important HIV prevention gap, especially for women unable to successfully negotiate mutual monogamy or condom use.

3. What individuals at USAID, partners, etc, were most responsible for the design and implementation of the science and technology solution, and what were their individual responsibilities?

**USAID:** Jeff Spieler (Senior Technical Advisor), Judy Manning (Project Manager and Agreement Officer Representative), Lee Claypool (Microbicide Team Leader)

**FHI:** Laneta Dorflinger, Amanda Troxler, Doug Taylor, Ward Cates (Design and management of activity as a subaward)

**CONRAD:** Henry Gabelnick, David Friend, Gustavo Doncel (Product license holder and provider of manufactured and packaged test products)

**CAPRISA:** Quarraisha Abdool Karim, Salim Abdool Karim, Janet Frohlich, Anneke Grobler, Cheryl Baxter, Leila Mansoor, Ayesha Kharsany, Sengeziwe Sibeko, Koleka Mlisama, Zaheen Omar, Tenuja Gengiah, Silvia Maarschalk, Natasha Arulappan, Mukelisiwe Mlotshwa, Lynn Morris, CAPRISA 004 Trial Group (Implementers of clinical trial at sites in South Africa)

Vulindlela Community: Gethwana Makhaye (Community engagement manager)

University of Cape Town: Carolyn Williamson (Analysis of HIV gene sequences)

University of North Carolina: Angela Kashuba (Analysis of tenofovir drug levels)

**Department of Science and Technology, South Africa:** Glaudina Loots (Program Director at donor agency)

**LIFElab / Technology Innovation Agency:** Blessed Okole, Carl Montague (License recipient and technology transfer in South Africa)
Gilead Sciences: James Rooney (Private sector partner providing tenofovir as active ingredient, license to use tenofovir for this indication, as well as technical and regulatory support)

4. How was the activity monitored and evaluated? Was there a systematic effort to evaluate the extent to which the activity was successful as a result of science and technology?

Programmatic and financial monitoring of this activity was conducted by USAID staff (above) as part of managing USAID cooperative agreements with FHI and CONRAD.

Compliance with USAID regulations (for the protection of human subjects) and with regulations of the FDA and Medicines Control Committee of South Africa (for clinical testing of new products to be submitted for product approval and licensure) was monitored by FHI staff (above plus others).

Quality assurance of all active ingredients, formulated products, and packaging was conducted by CONRAD staff (above).

As a clinical study to demonstrate proof of concept for this entirely new class of HIV prevention products, this activity was implemented entirely as an application of the science and technology approach to solve an important health and development problem.

5. To what extent were science and technology innovations shared across USAID, partners, et al, and what feedback loops or consultative processes have been planned or undertaken?

The results of this activity have been presented at international HIV and public health conferences, published in SCIENCE and other professional journals, reviewed and discussed with key stakeholders in the US and South Africa (including a meeting hosted by the USAID Administrator with high-level US and South African stakeholders), and continue to be a fundamental platform for ongoing work with next-generation product designs and preparations for microbicide scale-up and introduction programs. USAID/South Africa has been fully engaged in follow-up activities and other USAID missions in Africa have participated as well, and will be further integrated in the future.

6. To what extent were other partner organizations directly involved in the design, funding, or implementation of the science and technology response? Did the science and technology response achieve any leverage (financial or non-financial) from partners?

The partners involved and their contributions to the design, funding, and implementation of this activity are briefly described above. These contributions demonstrate extensively leveraged collaborations from the beginning of this activity. Since the success of this activity, substantial additional resources (financial and other) have been committed to support follow-up activities to support regulatory approval, scale-up, and distribution. These additional resources have been provided by USAID/Washington, the USAID/South Africa mission, the Bill & Melinda Gates Foundation, and the Department of Science and Technology of South Africa, among others. A joint venture named Propreven has been established with both public and private-sector partners to pursue product licensure, scale-up, and introduction.

7. To what extent was this intervention replicable in other communities within the country? Would it likely be effective in other development contexts?
The safety, efficacy, and acceptability of this new technology, which was demonstrated in this activity, are now being confirmed in new studies ongoing at nine sites in South Africa. With the completion of these replications and regulatory licensure, this new technology will be effective in many contexts throughout sub-Saharan Africa and other developing countries.

8. Were the science and technology benefits accessible and affordable (if applicable) for target groups?

During implementation of the activity, extensively enhanced HIV prevention counseling and medical services were provided to participants and their communities. With scale-up and introduction of this new product, e.g., through public sector and social marketing programs, it is anticipated that the benefits of this science and technology approach will become accessible to large numbers of women who most need a new method of HIV prevention that they can use.

9. Provide statement on how a prize in the form of programmatic support would benefit the activity and the overall program strategy.

This particular activity, in which tenofovir gel was shown to reduce the risk of HIV infection in women, and the overall program strategy, to support the development and introduction of new HIV prevention technologies such as the tenofovir gel or alternative agents and formulations, would both be well-served by the unique opportunity to investigate why, or under what circumstances, some women may become HIV infected, even if using a product that is protective under other conditions. By maintaining the cohort of participants who were in the completed CAPRISA 004 clinical trial with tenofovir gel, investigators at CAPRISA and CONRAD could continue important studies with these women to understand the mechanisms of protection of tenofovir gel and the factors that can sometimes circumvent this protection, as well as the consequences of using tenofovir gel on the viruses which do establish break-through infections and the associated host immune responses. In particular, understanding the role of genital and systemic inflammation in predisposing some individuals to HIV infection and reducing the effectiveness of new prevention technologies would be a great contribution to our product development efforts and the entire field of HIV prevention.

4 Sept 2013