

**Report to Congress by the U.S. Global AIDS Coordinator on the
Development of Safe and Effective Microbicides and an HIV
Vaccine**



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The Office of the Global AIDS Coordinator at the Department of State provides this Report on Strategies to Support the Introduction, Distribution, and Use of a Safe and Effective HIV Vaccine and Microbicide pursuant to P.L. 110-293, the Tom Lantos and Henry J. Hyde United States Global Leadership Against HIV/AIDS, Tuberculosis, and Malaria Reauthorization Act of 2008.

Nearly three decades after the discovery of HIV/AIDS, the pandemic continues to spread and threaten the prosperity, stability, and development of nations around the world. Under the leadership of the President's Global Health Initiative (GHI) and PEPFAR's programs in prevention, care, and treatment, the Office of the Global AIDS Coordinator (OGAC) and USAID play a critical role in the strategic development and future introduction of an HIV vaccine and microbicide appropriate for the specific disease and population characteristics of developing countries, especially in Sub-Saharan Africa. Multiple prevention approaches, including new technologies, are needed for the greatest impact in protecting against HIV/AIDS and mitigating its spread.

U.S. Expertise Has Helped Bring Safe and Effective New Health Products to Developing Countries

Health research is integral to the ability of PEPFAR to achieve its development objectives worldwide. Through targeted research and public health evaluations, OGAC and USAID support the development and introduction of health products, policies, and practices that effectively improve global health. OGAC, in collaboration with USAID and other key public and private sector agencies and nongovernmental organizations (NGOs), has applied cycles of assessments, development, testing, and introduction of products and interventions to tackle high-priority disease and health issues in developing countries. Past USAID research investments led to products that today reach millions, saving lives throughout the developing world, such as oral rehydration salts, vitamin A to prevent blindness, auto-disable syringes, and vaccine vial monitors. Most recently PEPFAR, through USAID, has funded a promising proof of concept through microbicide trials. The U.S. has decades of field experience and presence in over 70 countries, combined with in-house technical expertise and recognized strengths in private sector engagement. The U.S. is uniquely positioned to strategically catalyze the development and introduction of novel health products for the developing world.

Status and Promise of HIV Vaccine Research

Vaccines provide powerful and efficient tools to prevent infectious diseases. An effective HIV vaccine would significantly advance a comprehensive prevention strategy, and the search for this promising HIV prevention tool must be intensified.

Many of the activities the U.S. supports lay lasting groundwork for the eventuality of presenting such a product to the public. The current focus of efforts is scientific

design, preclinical and human trials; should these come to fruition, it will be important to plan the specifics around introduction, distribution and use of a vaccine. Even now, significant interim benefits of HIV vaccine research are emerging. Scientists are making notable progress in understanding how the human immune system resists HIV in people known as “elite controllers,” which may lead to defining the correlates of protection, and inform how a vaccine may induce antibody responses. In addition to remarkable ongoing discoveries of broadly neutralizing antibodies capable of blocking the virus, multiple vaccine candidates are in the pipeline for clinical testing throughout 2010-13, by the International AIDS Vaccine Initiative (IAVI), the NIH’s Vaccine Research Center, the HIV Vaccine Trials Network (HVTN), and others throughout the world.

USAID support for IAVI, a nonprofit organization that acts as a virtual pharmaceutical company, began with Congressional directives in 2001. The goal of the support is to accelerate the development and clinical testing of HIV vaccine candidates. IAVI facilitates collaborations among university, government, and private sector groups to ensure that the appropriate resources are available for each phase of product development.

As human trials are conducted in developing countries, USAID’s technical expertise, international perspective and field presence is fundamental to the success of HIV vaccine development and eventual roll-out. IAVI also provides critical analyses of important issues affecting the HIV vaccine field. Examples are new strategies to engage biopharmaceutical companies in HIV vaccine development, regulatory and licensing issues, and preparations for the manufacture and distribution of vaccines once they are proven effective.

In addition to the basic discovery and clinical programs, a \$28 million per year cooperative agreement with IAVI supports critical policy and implementation issues of concern to the HIV vaccine field. Planning is under way for the introduction of safe and effective HIV vaccines in developing-country settings when available, including engaging partner country governments to register the new products, managing supply chain and logistics of vaccine delivery, developing protocols, and training health care workers to integrate this new technology into the ever-changing landscape of HIV prevention.

Status and Promise of Microbicide Research

In sub-Saharan Africa almost 60 percent of HIV-infected persons are women. Current behavioral strategies for preventing HIV infection, including delay of sexual debut, partner reduction, and use of condoms, are not negotiable for many

of these women. The development of an effective microbicide would help fill the need for a new prevention option for women and complement other approaches. The U.S. plays a critical role in shaping the strategic and technical direction of microbicide development to meet this need.

The U.S. microbicide strategy focuses on testing the most promising candidates available. Since 2004, USAID has moved five candidates -- Carraguard™, Ushercell™ (cellulose sulfate), Savvy™ (C31G), Tenofovir 1% Vaginal Gel, and Oral Truvada -- into the advanced (Phase IIb and III) stages of clinical testing in international trials for their safety, effectiveness, and acceptability. For reasons related to feasibility and safety, which only became apparent at this advanced stage, the Savvy and Ushercell trials were ended.

With PEPFAR funding in 2007-2010, USAID supported two trials with specific antiviral agents and unique delivery regimens which might increase user acceptability and compliance as well as product effectiveness. The CAPRISA 004 trial used 1% Tenofovir as a vaginal gel and the FemPrEP trial is using oral Truvada in women. **In July 2010, the landmark results of the CAPRISA 004 Phase IIb trial of 1% Tenofovir Vaginal Gel, were announced, providing the first-ever proof of concept that a microbicide can significantly reduce the risk of HIV infection in women.** Volunteers using 1% Tenofovir Gel had an overall reduction in HIV infection of 39% at 30 months compared to those using a placebo gel (p=0.017). In volunteers who were most compliant in using the gel, the reduction was even higher, at 54%.

USAID is proactively collaborating with other partners, agencies, and donors to confirm these results, pursue the regulatory requirements for product approval, and introduce this new technology where it is needed most. USAID will continue to advance this specific ARV-based approach (including in the FemPrEP trial), as well as additional microbicide research on:

- Novel delivery methods (such as vaginal rings, tablets, or films)
- Combination products including multi-mechanism and multi-purpose agents (to also prevent pregnancy or other STIs)
- Understanding and preventing the risk of viral resistance
- Novel non-ARV leads
- Optimized trial design and coordination; and
- Ensuring post-trial availability of new prevention products.

Supporting Introduction, Distribution, and Use of HIV Vaccines and Microbicides

As preclinical and clinical research on HIV vaccines and microbicides continues, the U.S. is simultaneously supporting appropriate preparations for the future introduction, distribution, and use of these new technologies in developing countries. Multiple social, cultural, economic, and political factors will influence the acceptance and use of these new products at the individual and community levels. The U.S. is already addressing many of these factors through the activities described below.

Vaccines: Initiatives for Introduction, Distribution, and Use

Important work in planning for wide access to first-generation HIV vaccines is being conducted through IAVI's salient policy and country-level activities with U.S. support. Once discovered, an AIDS vaccine would have a central role in reversing the HIV pandemic, sparing millions of lives, immeasurable suffering and the resources necessary to provide care and treatment for those infected. For a vaccine to have such an impact it must be widely available and deemed acceptable to the countries that could most benefit from a rapid roll-out. USAID, with IAVI, seeks to identify the key determinants of vaccine demand, model global adoption and uptake dynamics, and forecast potential demand and revenues associated with vaccines.

Microbicides: Initiatives for Introduction, Distribution, and Use

For microbicides, activities which support each of the following initiatives are completed or under way. Many of these activities contribute to the success of preclinical and clinical activities as well as expediting access to these products once they are approved and available.

- **Understanding behavior that determines microbicide acceptability and use:** Behavioral research is examining the circumstances in which a microbicide would be useful and the reasons why it would or would not be used.
- **Involving local communities in clinical research and future introduction:** Community consultation and education are used to ensure that the value of the product being tested, and hopefully introduced, is understood and supported.
- **Modeling the use and impact of microbicides for HIV prevention:** Modeling is instrumental to understand what prevention may work in various circumstances, plan investments, leverage donors, and motivate introduction.
- **Developing regulatory policies needed for product approval and distribution:** International workshops engaging national regulatory officials have addressed how a microbicide will be evaluated, approved, and introduced.

- **Learning lessons from the introduction of other health products:** Given U.S. experience in introducing health products in developing countries, key lessons learned are being identified and applied to microbicide introduction.
- **Facilitating communication between stakeholders in microbicide introduction and access:** An annual Microbicides Access Forum was established to plan for successful introduction and scale-up of microbicide use.
- **Assessing and developing capacity for future manufacturing and distribution:** Worldwide capabilities to produce active agents and products are being assessed to expedite scale-up and high-quality manufacturing when needed.
- **Focusing on the process and costs of future procurement and distribution:** The U.S. engages multilateral and bilateral donors and NGOs, to address how a future microbicide will be bought and distributed in developing countries.

Future Activities to Prepare for Distribution of Vaccines and Microbicides

During the next three years, the costs of ongoing or new multi-site clinical trials, possibly including confirmation of the CAPRISA 004 results with 1% Tenofovir Gel, will increase, especially to ensure that HIV incidence rates at each site are adequately evaluated before studies begin. It is also likely that testing of next-generation leads and formulations will be warranted for both a vaccine and microbicide.

During and beyond the next three years, an increased investment will also be needed to prepare for vaccine and microbicide manufacturing, distribution, and introduction in developing countries. U.S. and partner activities will focus on policies, procurement, financing, logistics, and distribution in the public and private sectors. Assistance will be needed to meet the information needs of diverse audiences. Procedures to license safe and effective vaccine and microbicide products need to be developed at national and global levels. The recent proof of concept for microbicides provides a focus and rationale to move forward.

With the approval of the first effective vaccine or microbicide, resources will be needed for the programs that provide these products to the people who need them the most. Long-term studies on the impact of a vaccine or microbicide on reducing HIV incidence and prevalence will also be needed, and will require substantial resources to enable the success of these HIV prevention options.