

Report to Congress
U.S. Agency for International Development's
Microbicide and Vaccine Research Program

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Report to Congress
USAID's Support for Microbicide and Vaccine Research

I. BACKGROUND

In Report Number 107-663, Congress requested the State Department to provide a report on support for microbicide and vaccine research. This report is divided into two parts. The first part of this report describes U.S. Agency for International Development-funded microbicide research efforts, and complements the National Institutes for Health Office of AIDS Research's report on federally funded microbicide research as requested by Congress in the FY03 Appropriations bill for the Department of Health and Human Services and National Institutes for Health. The second part is an update to last year's report to Congress related to USAID's support of the vaccine research efforts by the International AIDS Vaccine Initiative.

II. MICROBICIDE RESEARCH

The U.S. Agency for International Development (USAID) has provided more funding for the fight against the global AIDS pandemic than any public or private organization in the world. This year USAID will assist more than 50 countries with HIV/AIDS programs, with 23 of these countries considered high priority. USAID has demonstrated a proven record of accomplishment in preventing new HIV infections, providing care and treatment, and addressing the needs of children and families affected by AIDS.

Ongoing biomedical and behavioral research to develop and test technologies for preventing HIV transmission is a hallmark of the USAID HIV/AIDS program. As a potentially valuable option for HIV prevention, microbicides have been one focus of USAID research into a prevention solution for women in developing countries. Microbicides are defined as antimicrobial products that can be applied topically for the prevention of sexually transmitted infections (STIs), including HIV. An ideal microbicide would be used by uninfected individuals to protect themselves from acquiring HIV, and by HIV-infected individuals to prevent transmission to their partners. Developing a safe, acceptable, and effective microbicide is a long and expensive process as it is for HIV vaccine development, but progress is being made.

The U.S. government is firmly committed to accelerating the development of safe and effective microbicides to prevent HIV and other STIs. To this end, there is cooperation and coordination of the microbicide-related activities of the federal agencies, including USAID and the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA) of the Department of Health and Human Services (DHHS).

Increased cooperation among federal agencies allows available resources to be used more efficiently and effectively. It is crucial to increase the momentum in microbicide research and development and to coordinate microbicide initiatives sponsored by the federal

government. The U.S. government supports a comprehensive program for the discovery, development, pre-clinical testing, and clinical evaluation of microbicides for the prevention of HIV and other STIs. This comprehensive program is built on a proven track record, established relationships, and a history of worldwide technical leadership by these U.S. agencies in the development of vaccine candidates, therapeutics, and prevention interventions addressing the HIV/AIDS pandemic.

NIH is the major federal government sponsor of microbicide research and development with approximately \$68 million in FY03. In FY 2001, Congress provided for USAID to establish a microbicide research and development program, and allocated a budget of \$12 million. Congress provided \$15 million to USAID in FY02 and approximately \$18 million in FY03. Other foreign governments and private donors (especially Gates Foundation) also provide funding to microbicide research.

As part of its comprehensive HIV/STI prevention strategy, USAID invests in research on the development, use, and appropriate introduction of existing and new technologies that may prevent transmission of HIV. The microbicide research and development activities that USAID supports are managed through the Bureau for Global Health. Management and funding decisions are based on the individual capacities of USAID-funded grantees and contractors and on the identification of other partners capable of using these funds in an effective and efficient manner.

USAID funded the following organizations in FY 2002 including several new partners, to work on microbicide research and development:

- Eastern Virginia Medical School, Arlington and Norfolk, VA
- Population Council – New York City, NY
- Program for Appropriate Technology in Health, Seattle, WA
- Global Campaign for Microbicides, Washington, DC
- Family Health International, Research Triangle Park, NC
- EngenderHealth - New York City, NY
- World Health Organization

While the enormous potential of microbicides is recognized, there is as yet no definitive clinical evidence establishing that any product applied topically in humans can prevent the transmission of HIV and other STI pathogens. Unique aspects of microbicide research and development provide challenges to progress in this area, including: the lack of a well-established correlation between *in vitro*, animal models, and clinical testing; insufficient knowledge about the biology of the sexual transmission of HIV and other STI pathogens; the lack of knowledge on optimal product formulations for delivery; and insufficient knowledge about cervico-vaginal and intercourse physiology.

While the challenges facing microbicide development are numerous, the scientific basis for developing the first generation of microbicides is continuing to progress rapidly. During the past decade, advances in basic research have identified many biological targets and agents, representing a variety of mechanisms of action. Several new compounds are now under development. In addition, several *in vitro* and animal models

are now available for use in pre-clinical studies. While the clinical relevance of these animal models has not yet been demonstrated, they will continue to be refined to more accurately reflect the biology of HIV transmission in humans. Significant progress also has been made in the process of bringing potential microbicide products to market. The FDA's requirements have been clarified for the pre-clinical testing of microbicide candidates, as well as for the appropriate design and conduct of clinical trials of these agents.

A. USAID Role in U.S. Government Strategic Plan for Microbicides

The U.S. Government Strategic Plan for Microbicides addresses the broad scope of needs in microbicide research from the basic to the behavioral sciences. It is built upon the framework of the NIH Strategic Plan for Microbicides, first issued in 2001, and an integral component of the annual NIH Plan for HIV-Related Research. The NIH has invited representatives from the CDC, FDA, and USAID, as well as other government and non-government experts to participate in the planning activity for it. The Plan is structured on six objectives that provide the sequential steps of the pathway for microbicide development. The following section is divided into the six objectives followed by recent significant efforts accomplished through USAID.

OBJECTIVE 1: Basic Biological and Physiological Research

USAID is not involved in basic biological and physiological research.

OBJECTIVE 2: Pre-clinical Development and Evaluation

Support the discovery, development, and pre-clinical evaluation of topical microbicides alone and/or in combination.

USAID, through its collaborating agencies, is implementing an extensive and long-term screening program to evaluate anti-HIV activity of agents that could be used as active agents in microbicides. The program evaluates both virus-killing activity and other antiviral activity that may neutralize HIV by preventing its attachment to target cells or by inhibiting a stage of the viral life cycle that is essential to establishing infection. Specific testing algorithms are used to ensure that each test agent is definitively and efficiently evaluated for anti-HIV activity. This screening program is co-funded by USAID and NIH's National Institute of Child Health and Human Development (NICHD) through an Inter-Agency Agreement.

An extensive and ongoing screening program is also being conducted to evaluate the anti-fertility effects of agents that could be used in microbicides. This USAID program (as mentioned above, co-funded by NICHD) evaluates the effects of specific agents on fertility parameters.

A network of investigators is using animal models to perform the pre-clinical evaluation of microbicide efficacy against HIV and other STIs. This network uses small rodent models as well as nonhuman primate models to evaluate efficacy against HIV and other STIs. Funds also are used to make technological improvements in these models, develop

useful alternatives where needed, and gain sufficient experience with current microbicide lead compounds so that animal model results can be validated as representative of similar protective activity in humans.

USAID is also supporting the development of identified promising new agents to bring them to the marketplace. This can include funding synthesis scale-up, developing sensitive analytical techniques, and completing the characterization of the biological activity and toxicology.

OBJECTIVE 3: Formulation and Delivery

Develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, and social sciences.

USAID supports quality control studies of microbicide candidates that have high buffering capacity and/or non-irritating gel basis, with *in vitro* and animal models, to demonstrate broad microbicidal activity without harming healthy vaginal microflora.

Some measure of acceptability is always included in USAID's studies. This usually entails administration of a questionnaire and occasionally includes focus group discussions. These questionnaires inquire about feel, appearance, and smell of new products and ask whether the participant would likely use the test product if it became available and he or she had a need for it.

USAID began a project in FY 2002 to assess the currently available microbicide applicators for vaginal and rectal use to identify and clarify preferences of potential users and then to translate those identified requirements into performance criteria and functional objectives if a new or improved device is recommended.

OBJECTIVE 4: Clinical Trials

Conduct clinical studies of candidate microbicides to assess safety, acceptance, and effectiveness in reducing the transmission of HIV and other STIs in diverse populations in domestic and international settings.

USAID is engaged in early clinical studies (Phase I and II) of several new potential microbicides that use different modes of actions, including cellulose sulfate, polys tyrene sulfonate, AcidForm, and PRO 2000. In collaboration with others, including federal agencies, USAID is also planning to support studies to test the effectiveness of promising microbicide candidates in large-scale studies (Phase III trials) - Carraguard™, C31G, and BufferGel.

USAID and the CDC will conduct a Phase I safety study with USAID funds in women at high risk for STI to test the efficacy of establishing vaginal colonization with exogenous *Lactobacillus* for HIV and STI prevention. Several laboratory and epidemiologic studies suggest that vaginal colonization with hydrogen peroxide producing *Lactobacillus* will lower risk of STIs including HIV. The normal vaginal flora in pre-menopausal women is

dominated by *Lactobacillus*, that produce a number of compounds which inhibit other bacteria.

An integral part of preparing for the Phase III trials of Carraguard™ involves determining the best method to inform and obtain consent from study participants and educate their communities. With support from USAID, a thorough evaluation will be conducted of informed consent procedures in the ongoing Phase II trial prior to designing the informed consent and educational materials for the Phase III study. As part of educating the community, a national consultation of researchers, government officials, activists, and advocates in South Africa will be held prior to the Phase III trial. In addition, community consultations will be held in the local communities with the aim of establishing community advisory groups that would meet regularly to review the protocol and informed consent procedures.

OBJECTIVE 5: Behavioral and Social Science

Conduct basic and applied behavioral and social science research to enhance microbicide development, testing, acceptability, and use domestically and internationally.

USAID is planning a study to identify and describe factors that enable individuals and couples to use microbicides consistently and long-term. The study will follow on a NIH study of vaginal microbicides and will be conducted in Pune, India.

With funding from USAID, a collaborative research project has been initiated to identify sociocultural and structural issues that are likely to be potential barriers or facilitating factors for the introduction of microbicides. Focusing particular attention on populations in low-resource settings, this initiative will identify the factors that might undermine access to and use of microbicides, and propose ways to overcome these barriers through introduction strategies, advocacy, and additional operations research. With USAID funds, CDC will mount preparatory studies in Phase III international sites to advance at least three areas which have come to the forefront of HIV/AIDS cervical research in the past several years: (1) improving and standardizing the process of informed consent, with emphasis on the informing process; (2) refining counseling protocols; and (3) testing alternative methods to improve measurement of self-reported behaviors.

USAID is supporting microbicide modeling that utilizes mathematical models to further explore the population-level impacts of potential migration from existing prevention methods with the introduction of a microbicide; to extend analysis by estimating the cost effectiveness of a microbicide intervention; and to produce user-friendly versions of the microbicide model to inform policymakers.

OBJECTIVE 6: Training and Infrastructure

Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide research domestically and internationally and to accelerate the access to microbicidal products to HIV and other STIs, in diverse populations.

In collaboration with the World Health Organization, USAID is conducting an expanded safety study on a new microbicide (cellulose sulfate) in three developing countries through CONRAD and Family Health International. This effort has required the strengthening of laboratory facilities, training at the clinical sites, and overall infrastructure development. It is anticipated that these sites will participate in Phase II and III effectiveness trials.

USAID, with the Global Campaign for Microbicides, is organizing this year a high-level consensus-building meeting in New Delhi among policy-makers, researchers, providers, private industry, and civil society groups to cultivate a positive policy environment for the testing, introduction, and widespread use of microbicides in India

USAID provides one-third of the operating budget of the International Working Group on Microbicides, which fosters information exchange and issue discussion among the key microbicide organizations. NIH and the World Health Organization also contribute to the budget.

III. VACCINE RESEARCH

With prevention efforts as the cornerstone of USAID's HIV/AIDS strategy, it is most logical that USAID be associated with the development of an intervention that can transform this global epidemic. USAID supports HIV vaccine research efforts through its grant with the International AIDS Vaccine Initiative (IAVI). Although USAID provided a small amount of funds to IAVI in fiscal years 1999 and 2000. USAID's formal relationship with IAVI began when a two-year, \$16 million grant was awarded to IAVI in September 2001. This has been extended, and IAVI is receiving \$10.5 million in FY03.

IAVI is an international, scientific non-governmental organization dedicated to ensuring the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. In addition to USAID, IAVI receives funding from a variety of public and private sources, including the governments of Canada, Sweden, Denmark, Ireland and Norway. IAVI is pursuing its mission through four complementary strategies:

- building worldwide demand for HIV vaccines by mobilizing growing public and government support for accelerated vaccine development;
- accelerating development of new and innovative HIV vaccine designs, and prioritizing the best candidate vaccines for large-scale efficacy testing where the epidemic is spreading fastest in the developing world;
- fostering an environment for successful vaccine development by expanding public/private collaboration and investment in global vaccine efforts; and
- confronting the challenges of making HIV vaccines available to all who need them as soon as feasible.

IAVI plans over the next five to seven years to accelerate HIV vaccine product development and testing to: develop new and innovative HIV vaccine designs applicable for use in the developing world, prioritize candidate HIV vaccines for accelerated

progression to large-scale efficacy trials through head-to-head comparisons, and shorten timelines in all facets of the HIV vaccine development process.

The goal of this accelerated scientific agenda would be for IAVI to advance three of its promising candidates into efficacy trials by 2007. IAVI's work is intended to be part of a larger effort in which they call upon the world to have six to eight of the most promising AIDS vaccines in large-scale efficacy trials in high incidence populations of the developing world where the epidemic is most severe within the next five to seven years. Efforts to decrease the time required for safety, immunogenicity, and efficacy testing of such candidates, without compromising the necessary high standards, would markedly increase the potential for successful AIDS vaccine development and utilization in the shortest time possible.

Several other U.S. governmental and commercial companies (e.g. NIH, CDC, and the VaxGen and Merck companies) are involved in HIV vaccine research and development. Therefore, it is important to note that IAVI itself does not propose to shoulder the entire workload for this global commitment. Rather, they aim to complement ongoing national, transnational, and industrial efforts. IAVI collaborates with these other federal agencies working toward the common goal of a safe and effective preventive vaccine for the developing world.

A. FY02 IAVI Accomplishments with USAID Funds

IAVI's efforts have focused on accelerating the development and introduction of new vaccines and technologies, specifically an HIV vaccine needed primarily in developing countries. Approximately 25% of IAVI's income last year came from USAID, and these funds are used to provide the majority of funding for specific projects. This section outlines the significant accomplishments they have achieved towards these goals on projects related to vaccine development partnerships and clinical and laboratory infrastructure that have been specifically funded by USAID.

1. Vaccine Development Partnerships

IAVI's Vaccine Development Partnerships (VDP) accelerate the development of safe and effective AIDS vaccines by linking vaccine designers with manufacturers (when necessary) and with developing country sites suitable for testing promising HIV vaccine candidates, in order to:

- expand the number of promising AIDS vaccine candidates being developed;
- ensure that new vaccines are designed to target strains of HIV circulating in developing countries hard hit by AIDS, and that these vaccines are stable, affordable and easy to administer in the developing world;
- accelerate the vaccine development activities to a period of 18-24 months from vaccine construction to Phase I Clinical Trials; and
- assure that vaccines approved for use are available and administered to the world's poor populations who are most at risk of infection.

PROJECT NO. 1: Recombinant Adeno-Associated Viral (rAAV) Vectors to Deliver Genes Aimed at Protecting Against HIV

Partners: This project is a collaborative activity between Children's Research Institute (Columbus, Ohio), Targeted Genetics Corporation (Seattle, Washington), and researchers in South Africa.

This vaccine concept has several attractive features for use in the developing world including the possibility of long-lasting immunity following a single vaccination and a long shelf life at controlled room temperature. Advances made with this vaccine candidate over the past year positions IAVI well for the initial clinical trials of this promising candidate in 2003. USAID funding has made possible the key pre-clinical studies that are important prerequisites for regulatory approval, and studies were initiated to determine the effectiveness of a single administration of the candidate HIV vaccine in macaque monkeys. Documentation for the regulatory dossiers, clinical site preparation and clinical trial protocol development all have begun. IAVI's goal is to develop the infrastructure needed at the Chris Hani Baragwanath Hospital in South Africa to become an AIDS vaccine clinical trials unit, and to conduct the Phase I trials at this unit.

PROJECT NO. 2: Salmonella as a DNA Vaccine Delivery System

Partners: This project is based at the Institute of Human Virology, University of Maryland and is working closely with researchers in Uganda and with the MRC Human Immunology Group, University of Oxford. This VDP includes a linkage with the Uganda Virus Research Institute in Entebbe for the eventual development and testing of preventive AIDS vaccines applicable for use in East Africa.

This VDP is focused on evaluating administration orally of weakened bacterial vectors as HIV vaccine candidates. Such bacterial vaccine would also be easily administered and thus particularly attractive for use in developing countries. Two different bacterial strains—Salmonella and Shigella—are being evaluated as candidate vectors in pre-clinical studies and in manufacturing. A contract was signed with Berna Biotech Ltd., a Swiss vaccine manufacturer that commercializes a live attenuated Salmonella vaccine against typhoid fever. Recently, an agreement was signed with the Walter Reed Army Institute of Research, which has recognized expertise in the evaluation, development and production of Shigella vaccine candidates.

2. Strengthening Clinical and Laboratory Infrastructure by IAVI's in-country VDPs.

In preparation for clinical trials in developing countries, it is essential to build a strong team that includes both laboratory and clinical staff, and to strengthen existing laboratory capacity. The projects have critical needs that must be addressed to ensure that all tests are performed in conjunction with accepted international regulatory standards. Grant funds are being used for (i) upgrading and improving existing technology; (ii) purchasing new lab equipment; (iii) instituting established and accepted standards of Good Laboratory Practices for specimen collection, transport, processing, and analysis; and (iv)

providing enhanced training for clinical investigators in a variety of virology techniques. Additional clinical infrastructure is also generally needed to ensure that trials adhere to the highest international research standards, including training for research staff in clinical trial design and implementation, epidemiological research, data collection methods and analysis, informed consent processes and ethical review boards, quality control measures, HIV risk-reduction interventions and services, participant retention, and clinical care referrals.

IAVI's Uganda project is based at the Uganda Virus Research Institute (UVRI) in Entebbe. This site was selected by IAVI as being well-suited to conduct a series of Phase 1 clinical trials of candidate HIV vaccines based on several factors that included UVRI's reputation for conducting quality research, and an excellent collaborative, local environment that includes the CDC, the Medical Research Council, and Johns Hopkins School of Public Health.

The vaccine candidate has now been approved by the government of Uganda's national committees, following a positive review from the WHO Vaccine Advisory Committee. Clinical trials have begun and were made possible in part through the efforts in equipment procurement and training. Specifically, USAID funding was utilized to transfer technology to Uganda including the purchase of state-of-the-art laboratory equipment used to perform a variety of sophisticated tests to measure immune responses to vaccines. Comprehensive, ongoing training has been and continues to be provided in the use, maintenance and quality control of both this machine, and other lab equipment. Additionally, IAVI provides specific training for clinical investigators and laboratory scientists in a variety of virology techniques, thus ensuring adherence to established international standards in areas such as specimen collection, transport, processing, and analysis according to Good Laboratory Practices. This has involved both on site instruction, as well as bringing research scientists from Uganda to IAVI's Core Lab in London for training. A course on Good Clinical Practices was conducted in Kampala and was attended by members of several projects in addition to the IAVI staff.

B. Other IAVI Accomplishments in 2002

This section highlights some of the other IAVI accomplishments in its three broad areas of effort not federally funded:

1. Vaccine Research & Development

- Made a strategic decision to fast track the first-generation DNA+MVA prime-boost HIV vaccine candidate into efficacy trials in Africa by 2005, pending continued achievement of safety and immunogenicity milestones, and made considerable progress in the development and clinical testing of this vaccine's components
- Conducted assessments of 16 sites in eastern and southern Africa to evaluate capacity and readiness for participation in future efficacy trials.
- Commenced full operation of IAVI's Human Core Immunology Lab in London; validated assays and began testing samples from clinical trial sites in the UK and Kenya.

- Established the non-human primate studies core lab to assist with IAVI's vaccine design and development decisions; developed protocols and standardized immunoassays; and began studies to generate supporting data for two IAVI-sponsored candidate vaccines.
- In collaboration with the NIH Vaccine Research Center, formed a consortium of scientists from leading laboratories to accelerate the development of candidate vaccines that induce effective neutralizing antibodies against HIV.

2. Preparing Communities for HIV Vaccine Trials

Vaccine Preparedness efforts include activities at the national, community and trial site levels. The program's goal is to work with countries to prepare for trials of any preventive candidate HIV vaccine. Successful and ethical HIV vaccine trials require the informed and active participation of local communities and broad understanding and support from within the countries in which they take place. During 2002, the primary focus has been creating a supportive political, social and media environment for the successful conduct of Phase I and Phase II HIV vaccine trials, specifically IAVI:

- Created and worked with a 12-member Community Advisory Board in Uganda.
- Developed an extensive array of country-specific educational materials.
- Conducted three media trainings in Kenya, attended by journalists from Kenya, Uganda and Tanzania.
- Provided fellowships and training for eight journalists from Kenya and Uganda to attend the XIVth International AIDS Conference in Barcelona, Spain.

3. Public and Advocacy Efforts

IAVI strengthened its policy and advocacy efforts in 2002 by creating a Policy Research and Development Unit and establishing a 15-member Policy Advisory Committee of prominent experts from fields related to HIV vaccines. Priority areas for public policy efforts were also identified, including accelerating HIV vaccine Research & Development, demand forecasting and regulatory issues.

- IAVI held briefings with permanent representatives from IAVI Vaccine Development Partnership countries at the United Nations and established a comprehensive framework for policy and research and development collaboration with the European Union.
- IAVI continued outreach to the Japanese Diet, Aktionsbündnis gegen AIDS in Germany, the Spanish and Catalan governments, and the Swiss Ministry of Health. IAVI continued to build relationships with and gain support from governments: the Canadian government pledged CAN\$45 million over a three-year period; Sweden committed to provide SEK 4.5 million over three-years; Denmark made a first grant of DKK 15 million; an additional grant from Ireland of €2 million; and continued support from Norway of NOK 10 million.

Finally to demonstrate the similar challenges faced in the development of HIV vaccines and microbicides and the collaborative nature in these fields, IAVI has worked closely with the microbicides community to share experiences and identify areas for future collaboration. These include:

- IAVI and the Global Alliance for Microbicides jointly hosted a meeting on issues relating to standards of care in HIV vaccine and microbicide trials. The meeting provided an opportunity for trial sponsors to share information and perspectives on how best to approach the standard of care issue, as part of a wider effort to ensure that trials in developing countries are conducted in an ethical manner. The meeting drew experts from the leading product developers from both fields, including the NIH.
- IAVI served on the planning committee and participated in a meeting held in Botswana sponsored by the WHO aimed at identifying common issues that should be of concern to regulatory authorities across the vaccine and microbicide fields.
- IAVI took the lead in organizing an ad-hoc group of public-private partnerships — including microbicides, HIV, TB and malaria vaccines, and others — to address issues common to each group. These include: incentives to increase private sector investment in Research & Development, mechanisms to ensure swift regulatory approval of products in developing countries, creative financing mechanisms, and access and delivery issues. The Global Alliance, the International Programme for Microbicides, and the Alliance for Microbicide Development have been active participants in the group, which has produced a briefing paper identifying actions that the US could take at the federal level to accelerate the development of these products.
- IAVI is planning a meeting with the International Programme for Microbicides for policy makers to look at the policy synergies and divergences between the vaccine and microbicide fields to enable effective and appropriate collaboration and planning.

IV. CONCLUSION

Clearly, USAID has leveraged effectively U.S. funds by partnering with other U.S. government agencies and by partnering with key scientific institutes. U.S. government leadership in this area may also have played a role in increased contributions from other foreign governments. Thus, these USAID efforts have resulted in a major contribution toward the global effort of accelerating the development and introduction of vaccines and microbicides to prevent HIV infection. USAID is strategically positioned to advance further the development and eventual fielding of a HIV vaccine and/or microbicide especially for their introduction into developing countries.