



## Expanded HIV and AIDS Section of the 2015 USAID Health-Related Research and Development Progress Report

### AIDS-FREE GENERATION

USAID is a critical part of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), established in 2003. The U.S. Agency for International Development (USAID) has strong connections to the field and plays a leading role in the global network of donors. Since the beginning of the pandemic in the 1980s, USAID has been investing in HIV and AIDS research, funding developments that ensure we will achieve an AIDS-Free Generation.

USAID is investing in implementation science that will deliver results and translate them from research to practice for populations at risk. This model also allows researchers and program implementers to use research findings to examine the feasibility of integrating innovative ideas within existing programs and also to identify key linkages that will improve prevention programs, care and treatment options, and patient retention. Biomedical science is also integral to advancing HIV and AIDS prevention methods and technologies. More than two decades worth of investments with partners like the International AIDS Vaccine Initiative have helped strengthen clinical research capacity in regions most devastated by the epidemic. Several promising microbicide and ARV-based prevention products are in development that are less user-dependent and more potent than first-generation microbicide candidates. These enhanced products should better meet the needs of women and prove more acceptable, thus increasing adherence. In addition, research on Option B+, an approach for PMTCT treatment, is helping countries across sub-Saharan Africa roll out this promising model in cost-effective ways. *Read further to learn more about Bureau for Global Health efforts in behavioral, biomedical, and operations research in HIV and AIDS.*

### Research Goals

To improve treatment services and reduce rates of infection and transmission of HIV and AIDS, we are committed to:

- Develop, introduce, and scale the use of microbicides for women to reduce the risk of HIV infection.
- Accelerate the development of clinical testing of novel HIV vaccine candidates and build global capacity for vaccine research
- Strengthen the evidence base to improve HIV and AIDS prevention, care, and treatment programs to achieve epidemic control.

## **BACKGROUND**

With USAID's help, the fight against HIV and AIDS has made progress. Today there are 20 percent fewer infections than 10 years ago, and 115 million people are on antiretroviral therapy. However, an estimated 2 million people are newly infected with HIV every year. In sub-Saharan Africa, 1 in 20 adults is living with HIV, and in the Middle East and North Africa, new infections have increased by more than 35 percent in the last decade. Women and girls account for more than half of the 34 million people living with HIV worldwide.

While no single approach to HIV and AIDS prevention is likely to have a sufficient impact, integrated behavioral, biomedical, and structural interventions could yield the best results. Though several effective HIV prevention methods are available, the need to develop and evaluate novel technologies and evidence-based strategies is as urgent as ever if the course of the pandemic is to be reversed and an AIDS-free generation achieved.

USAID's research agenda contributes to the HIV and AIDS response and continues to harness USAID's extensive health and development expertise to maximize the reach of technically sound, cost-effective, and sustainable HIV and AIDS interventions. Through 2015, USAID will continue to collaborate with key partners dedicated to the development of an HIV vaccine and engage further to build capacity of researchers and institutions based in India and Africa. USAID supports the development of safe, effective, acceptable, and affordable microbicide candidates, including the advanced microbicide lead, the Dapivirine Ring, currently in a Phase III trial. USAID also funds novel microbicide delivery approaches and multipurpose microbicides in the hopes of bringing diverse options to market for women. The development and testing of novel HIV vaccine candidates for global use remains a high priority. HIV vaccine research and testing is supported by long-term epidemiological studies and research into access and policy issues. A key priority is strengthening clinical trial and laboratory capacity in developing countries.

Through implementation science, USAID is improving access to and quality and effectiveness of HIV and AIDS prevention, treatment, care, and support programs in developing countries to achieve epidemic control. Implementation research and program evaluations identify and address gaps in knowledge and increase the evidence base for scaling up and improving program effectiveness. Such investment in implementation science is critical to reaching UNAIDS' ambitious goal by 2020 – that 90 percent of all people living with HIV will know their HIV status; that 90 percent of all people with diagnosed HIV infection will receive sustained antiretroviral therapy; and that 90 percent of all people receiving antiretroviral therapy will have viral suppression.

### **I. Microbicides for Women to Reduce the Risk of HIV Infection**

Women make up almost 60 percent of new infections in sub-Saharan Africa. In many countries, women lack the power to negotiate the use of currently available prevention tools and approaches to protect themselves against HIV. There is a need for new HIV prevention methods that women can control on their own.

In 2010, the USAID-funded trial conducted by the Center for the AIDS Program of Research in South Africa (CAPRISA 004) found that 1 percent tenofovir gel provided 39 percent protection from HIV. A confirmatory trial, the Follow-on African Consortium for Tenofovir Studies (FACTS) 001 Trial, used the same application regimen as in CAPRISA 004 but was unable to confirm the efficacy of 1 percent tenofovir gel. Overall, consistent use in the study population may have been too low to determine whether or not tenofovir gel would be effective for the prevention of HIV acquisition in women.

To better meet the needs and lifestyles of women, promising new dosage forms that are less user-dependent are in development. A Phase III clinical trial, The Ring Study, is under way in South Africa and Uganda to test the monthly dapivirine vaginal ring with support from USAID and other donors. This trial is the first time a non-gel microbicide delivery system is being tested for effectiveness in women. Results of The Ring Study are expected in 2016. If these results are positive, along with those of ASPIRE, the confirmatory trial being conducted simultaneously, an open-label trial will follow and regulatory approval will be sought.

Other enhanced formulations, dosing regimens, and delivery systems are also being developed and tested. A new more-potent form of oral Pre-Exposure Prophylaxis (PrEP), tenofovir alafenamide fumarate (TAF), is in development that could prove to have fewer side-effects and be more acceptable to users than the currently available forms of PrEP. In addition, given the very low dosage required, TAF-containing oral PrEP is expected to cost much less to manufacture. Products with new mechanisms of action, including integrase inhibitors and entry blockers, are also being prioritized by USAID. In addition, USAID is supporting the development of longer-acting formulations, including a biodegradable implant, in order to help address adherence challenges associated with daily and user-dependent regimens.

Microbicide candidates that have multipurpose prevention activity are also in development and may prove attractive to potential users and providers. In addition to providing protection against HIV infection, these microbicide candidates may, for example, protect against other sexually transmitted infections and unwanted pregnancies. The first in-human study of a multipurpose prevention ring that combines both a contraceptive and anti-HIV activity is underway with study results expected in 2015.

USAID and its partners are working to prepare countries for the introduction and access programs that will be needed to deliver oral PrEP and new microbicide and ARV-based prevention products once they are approved. Introduction of oral PrEP is now of interest in many developing countries and normative guidance is expected to be issued by the World Health Organization in 2015 that will recommend PrEP for many populations at risk of HIV, including young women. The Agency has initiated introduction studies in order to:

- Develop a product delivery platform for current and future microbicide and ARV-based HIV prevention options
- Develop and evaluate effective, scalable strategies that are context-specific and gender responsive and address critical gaps in microbicide and PrEP delivery
- Focus on high-risk end users to identify individual, couple, and community-based motivations for and barriers to product use and to define and test product design changes accordingly

- Develop and pilot test an intervention designed to increase women’s agency to use microbicides consistently and safely, while simultaneously optimizing partner relationships and mitigating the risk of IPV
- Address policy and programmatic considerations related to the use of microbicides and the risk of resistance

USAID continues to collaborate with its partners and other donors to design and validate improved models for preclinical evaluation, clinical trials, and product introduction. These collaborations help USAID ensure that its resources are used as effectively as possible.

## **2. HIV Vaccine Candidates**

With support from USAID, the International Aids Vaccine Initiative’s (IAVI’s) Research & Development (R&D) and advocacy portfolios have deepened their engagement and partnerships with collaborators in Africa, India, and across the globe. These collaborations provide a strong and lasting foundation to strengthen and build leadership in HIV vaccine research design by establishing centers of scientific excellence, transferring HIV vaccine science capabilities to Africa and India and informing national policy makers on the importance of HIV research. These scientific efforts, coupled with in-country policy and advocacy work, contribute to nurturing country ownership and direct domestic investment toward HIV vaccine R&D.

In 2014, IAVI completed the Phase I clinical testing of the novel Sendai virus vector, the first study of a replicating viral vector HIV vaccine candidate to take place in Africa, at partner sites in Kenya (KAVI) and Rwanda (Projet San Francisco [PSF]). Although the candidate did not reach the criteria to be further advanced, data from the trial will inform and help refine the replicating vector strategy for IAVI and other researchers in the field. Importantly, the study resulted in significant capacity-building for both Kenyan and Rwandan Clinical Research Centers (CRC) partners and their regulatory systems.

IAVI continues to support the ongoing Phase I AAV-PG9 trial, the first-in-human study of a novel approach to HIV prevention that uses an adeno-associated virus (AAV) vector containing the gene for the PG9 broadly neutralizing antibody (bNAb). This trial, called A003, is a significant step toward obtaining proof-of-concept for a novel approach to HIV prevention. Its results may give researchers a preliminary indication of whether this technique can be used to produce bNAbs in humans that might then be able to prevent HIV infection. If the prototype strategy is successful, additional candidates could be developed to induce production of multiple bNAbs, which could provide more effective protection. Further testing of these candidates with African partners will require the development of enhanced local immunology capabilities and regulatory capacity.

IAVI and partners, with critical support from USAID, launched the Vaccine Immunology Science and Technology for Africa (VISTA) program, a collective effort that brings together research interests across collaborators, including partner CRCs in Africa, IAVI’s Human Immunology Lab (HIL), and Emory University to fill a scientific need for the field. VISTA enhances the capacity to perform immunogenicity and molecular virology in East and Southern Africa while enabling translational vaccine research to identify sites of viral vulnerability to inform the next generation T-cell based vaccine candidates while developing better tools to assess next generation vaccines. This program, a culmination of more than a

decade of collaboration between IAVI and CRC partners, builds on scientific research capacity established over the course of IAVI's partnership with USAID to engage and train the next generation of African scientific leaders in the field of HIV vaccine research.

IAVI and partners continue to explore genetic, viral, and immunological correlates associated with the development of powerful bNAbs that block the virus. Efforts continue to further characterize antibodies isolated from Protocol C, the largest longitudinal study of HIV infection among Africans, and Protocol G, the study that enabled the landmark discoveries of new bNAbs against HIV in 2009. With USAID support, IAVI has expanded its immunogen design work by establishing a collaborative research project between the HIV Vaccine Translational Research Laboratory in India, the HIL in London and African CRCs already engaged in Protocol C to study the immunology of the neutralizing antibody response. Additionally, IAVI has also launched a new partnership with Y R Gaitonde Center for AIDS Research and Education India (YRG Care) to expand Protocol G. Enrollment for this study has been completed at YRG Care and antibody isolation and characterization work is forthcoming. This work will lead to an improved understanding of envelope (Env) immunogens thought to be needed for an HIV vaccine, particularly during acute infection in African study volunteers while developing pathways for South-South collaboration between Africa and India on immunogen based research.

With USAID support, IAVI contributed to the development process for the [Kenya HIV Prevention Revolution Road Map](#) and was asked to join the technical team tasked with overseeing its implementation. The Road Map, officially launched in August 2014 by the Government of Kenya, provides guidance to the Government of Kenya to invest in targeted HIV interventions with the highest impact and contains important references to HIV prevention research and HIV vaccines. It utilizes a "Know your epidemic approach" to characterize sources of new HIV infections and service coverage while identifying interventions that are targeted to specific populations and geographic zones. The Global Fund to Fight AIDS, Tuberculosis and Malaria is currently supporting the road map pilot implementation in three regions of Kenya – Mombasa, Homa Bay, and Turkana. IAVI was also selected to chair the technical working group to develop a biomedical research component that ensures HIV vaccines and other new preventive technologies are identified as national priorities in the new Kenya AIDS Strategic Framework 2014–2019 document that contributes to Kenyan national health strategic planning processes.

### **3. Improving HIV and AIDS Prevention, Care, and Treatment Programs for Epidemic Control through Implementation Science**

USAID's HIV Implementation Science portfolio supports the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), which seeks to achieve sustainable epidemic control, and to reach the Joint United Nations Programme on HIV/AIDS' (UNAIDS) ambitious 90-90-90 global goals: 90 percent of people with HIV diagnosed; 90 percent of them on ART; and 90 percent of them virally suppressed by 2020. Adopting approaches that increase the impact of HIV and AIDS programs and make them more sustainable and cost-effective will ensure the continuation of long-standing, locally-owned HIV programs in the countries that are hardest hit by the epidemic. In order to achieve these outcomes, PEPFAR embraces an "implementation science" framework to improve the uptake, translation, and implementation of research into service delivery practices. USAID's own implementation science agenda

emphasizes methodological rigor, programmatic context, and sound scientific principles in support of HIV and AIDS prevention, care, and treatment research. Ongoing implementation science, operations research and evaluation aim to provide local implementing partners, donors, and national governments with the data and evidence needed to improve services and to inform policy, and ultimately achieve 90-90-90.

USAID is supporting research and evaluations to improve impact, quality, and cost-effectiveness of HIV and AIDS treatment and prevention programs. These include:

- In 2012 and 2013, USAID awarded more than \$20 million dollars to support 10 implementation science studies in 10 countries to answer critical questions across a range of program areas and populations to strengthen the integration of programs across the HIV prevention, care, and treatment continuum. The studies' findings will contribute to the evidence base for HIV programs and will maximize the impact of program investments around the world. Data gathered will help partner countries support their efforts to prevent new infections and save lives. A study in Swaziland evaluating Option B+ outcomes in the Kingdom of Swaziland concluded that the multitude and replication of maternal and infant documentation required for a single PMTCT visit burdens healthcare workers and increases risk for inconsistent, erroneous, and incomplete data. The study is developing recommendations for new approaches to Option B+ documentation to facilitate and accurately record maternal-child health service delivery and PMTCT outcomes. A multi-country study in Kenya and Uganda is evaluating whether providing pre-exposure prophylaxis (PrEP) to an HIV-negative partner as a "bridge" reduces HIV infection in the uninfected partner. As of early 2015, study results showed an estimated 96 percent reduction in HIV incidence among the discordant couple study population. These impressive findings will inform ongoing policy discussions about how to best incorporate PrEP and ART into HIV prevention strategies. Another study in South Africa will examine how to increase timely entry-into-care among people recently diagnosed as HIV-positive by examining four strategies that address key barriers to timely initiation of ART, including health perceptions, personal barriers, and structural barriers. The findings will strengthen care and treatment programs by identifying effective approaches to reducing late initiation of HIV treatment.
- The HIVCore Project supports research that seeks to improve the efficiency, effectiveness, scale, and quality of HIV and AIDS treatment, care and support, and PMTCT programs by conducting operations research and focused evaluations, and promoting the use of research findings. HIVCore will end in September 2016 and anticipates having over 20 different studies completed by this time. Results from a study on task-shifting in Uganda found that key tasks can be shifted for significant cost savings. Results from a nationally representative assessment of clinics in Cote d'Ivoire identified the causes for losses and delays throughout the PMTCT cascade. These findings will be used to help inform the country's Option B roll-out.
- The Gender-based Violence (GBV) Program Evaluation, "Tathmini GBV," identifies and addresses gaps in GBV prevention and service delivery through intensive monitoring and evaluation of GBV programs. It provides tools and methods to evaluate promising service delivery and community-based intervention models for GBV prevention and related HIV outcomes. The activity strengthens collaboration with local partners to bolster the evidence-

base for improving and scaling up effective GBV programs worldwide. This study was completed in 2015 and the findings are being widely shared among scientific forums and with stakeholders working on GBV programs.

- In late 2014, USAID awarded a \$70 million cooperative agreement called Project SOAR (Supporting Operational AIDS Research). This project conducts high-quality operational research studies that improve the impact and effectiveness of HIV program implementation. The project will focus on four, critical “how-to” evidence needs: (1) How do we optimize use of biomedical interventions?; (2) How do we leverage community platforms more effectively?; (3) How do we strengthen the continuum of care?; and (4) How do we address social and structural barriers to reach key populations and other groups at heightened risk? The project also seeks to build capacity among local institutions to conduct high-quality operational research, and to enable local researchers to conduct their own studies that are useful for improving HIV care and treatment services. SOAR promotes use of research findings for program and policy decision-making and translates study findings into action. In its first year, SOAR initiated 15 studies in Sub-Saharan Africa. This includes a rigorous evaluation of “Option B+” rollout in Lesotho, evaluating a multidisciplinary intervention to improve maternal and child outcomes and HIV service and antiretroviral therapy uptake and retention. Data generated from this study will support efforts to achieve sustained health outcomes for mothers living with HIV and elimination of pediatric HIV infections. Another effort under SOAR is to use program and cost data to mathematically model the impact of Voluntary Medical Male Circumcision (VMMC) in different programmatic contexts. These data have been used by program planners and government officials to make strategic decisions about how and where to invest limited HIV funding in VMMC, in order to gain maximum impact and cost-efficiency.

