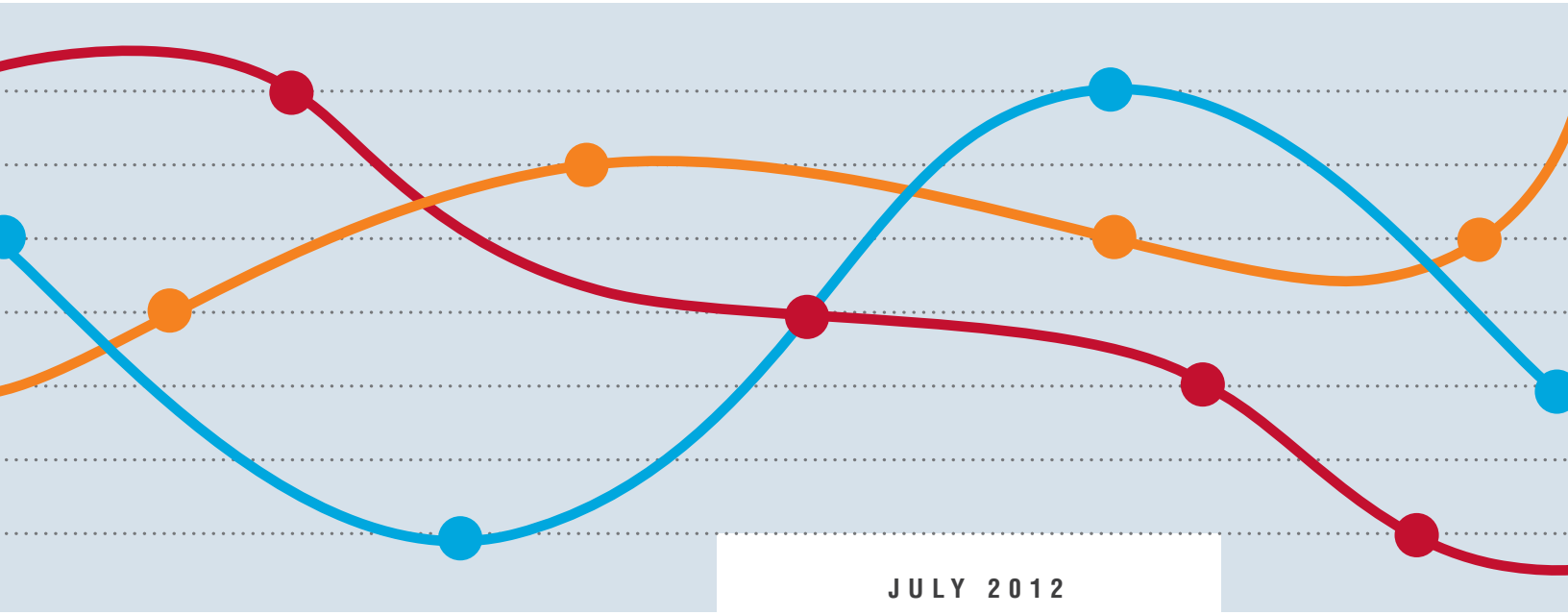
Investing to End the AIDS Epidemic:

A New Era for HIV Prevention Research & Development



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HIV VACCINES & MICROBICIDES RESOURCE TRACKING WORKING GROUP

HIV Vaccines and Microbicides Resource Tracking Working Group

www.hivresourcetracking.org

AVAC	Global Advocacy for HIV Prevention
IAVI	International AIDS Vaccine Initiative
IPM	International Partnership for Microbicides
UNAIDS	Joint United Nations Programme on HIV/AIDS

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Introduction 1.0

In June 2011, thirty years after the start of the AIDS epidemic, heads of state and other high-level government officials gathered in New York for the United Nations General Assembly High-Level Meeting on AIDS. At that landmark meeting, UNAIDS Executive Director Michel Sidibé called on leaders to end the epidemic by agreeing on a common agenda—an agenda that would allow us to achieve the goal of "zero new HIV infections, zero discrimination and zero AIDS-related deaths."

At the 2011 High-Level Meeting, UN member states were also called on to reaffirm their commitment to the Declaration of Commitment on HIV/AIDS, adopted by member states in 2001, and to make new commitments, both financially and through action, to sustain the global AIDS response.

The 2001 Declaration had specified a set of global and national indicators to be monitored annually, the second of which was the "amount of public funds available for research and development (R&D) of vaccines and microbicides."[1] The HIV Vaccine & Microbicides Resource Tracking Working Group (the "Working Group") took on that task and has for 10 years collected and analyzed public, philanthropic and other private-sector funding for HIV vaccine and microbicide R&D. As research evolved, the Working Group extended its monitoring reach to include R&D investments in other HIV prevention options. The Working Group acts as collectors and analysts of funding information for use by Working Group members and other advocates and partners, and not as policy-makers or spokespeople for the HIV prevention research field.

Since publication of the first Working Group report,[2] HIV prevention research has progressed, and its priorities have moved beyond biomedical research to embrace implementation research and combination prevention. In the past year, a flood of research results showing proof of concept, or effectiveness, of new prevention options has both expanded the research agenda and moved public discourse to an evidence-based understanding that HIV prevention and treatment could end the AIDS epidemic.[3]

Yet, just as 2011 was yielding significant new HIV/AIDS prevention opportunities, the realities of the global economic climate created constraints for global health financing in general. A scarcity of funding led to increased pressure to provide evidence of impact and to deliver immediate value for money invested. Despite scientific successes, some development agencies have pulled back from funding long-term research. Additionally, emphasis has shifted away from single-disease-specific projects to other priorities, such as health systems strengthening[4] and broader efforts to address non-communicable diseases.

To navigate the tensions between increased fiscal austerity, competing priorities and the enduring need to sustain and advance research, HIV prevention R&D has had to adapt. The global HIV prevention research field has sought to become more efficient, results-driven and coordinated. Efficiencies in the conduct of clinical trials and collaborations by product development partnerships (PDPs) and other product developers are allowing for greater progress with fewer resources.[5] Implementation initiatives blending prevention and treatment are underway, as are joint explorations by researchers and implementers to integrate HIV prevention R&D and research on tuberculosis, malaria, other neglected diseases and family planning—addressing improving overall health.

1.1 EXECUTIVE SUMMARY

Global Investments

Since 2001, global preventive HIV vaccine R&D investment has totaled US$8 billion, with an average yearly investment of US$824 million. The 2011 investment was US$845 million, US$14 million lower than in 2010. The public sector provided the majority of funding in 2011, at US$702 million (83 percent). The philanthropic sector provided US$113 million (13 percent), and the commercial sector contributed an estimated US$30 million (4 percent). Investment by European governments was US$48.5 million in 2011, a decrease of over US$12 million (21 percent) from the previous year and a 40 percent decrease from their US$82 million peak in 2006. Philanthropic investments in HIV vaccine R&D increased in 2011 by US$10 million (10 percent).

Global investment in microbicide R&D has reached nearly US$2 billion over the past 10 years, with an average yearly investment of US$196 million—US$10 million more than the investment of US$186 million in 2011. The public sector provided the majority of the funding in 2011, at US$176 million (95 percent). The philanthropic sector provided US$9 million (5 percent), and the commercial sector contributed a little over US$1 million (<1 percent). Several large European donors reduced their contributions in 2011, resulting in a US$24.3 million decline in European contributions from 2010. Additionally, the United States (US) government decreased its total funding by US$39 million from 2010, with the largest decline coming from the National Institutes of Health (NIH) at US$36 million (24 percent) less funding. However, South Africa more than doubled its funding in 2011, investing US$10 million.

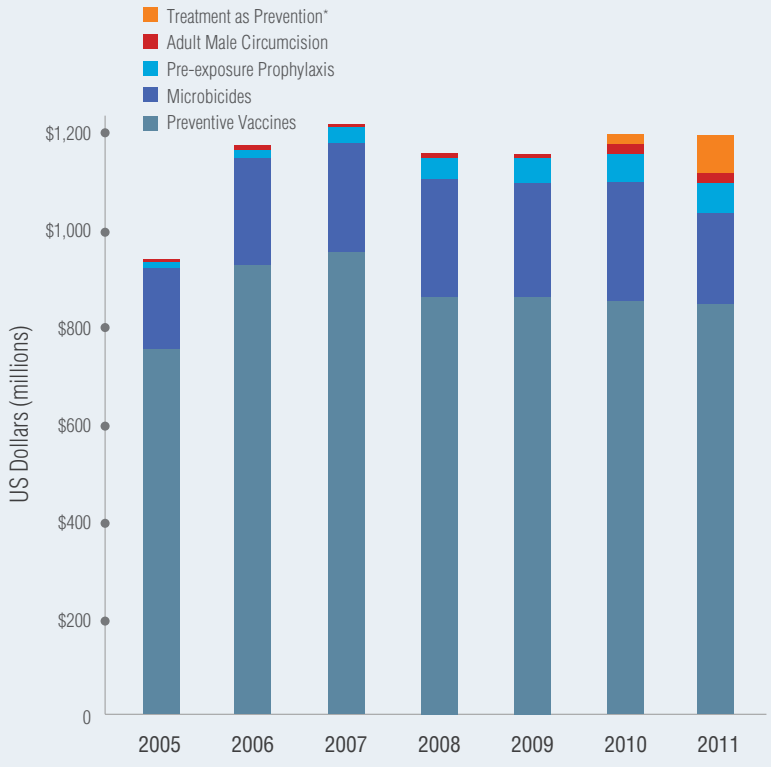
Table 1 **HIV Prevention R&D Investments Over Time**

HIV Prevention Option	10-year Total	10-year Average	10-year Growth Rate*	2011 milestones
Vaccines	US$ 8 bn	US$ 824 mn	9 percent	The field moved forward with the RV144 findings of two antibodies whose presence either increases or decreases the risk of HIV infection. With follow-on trials underway, new neutralizing antibodies being identified, and the HVTN 505 efficacy trial scheduled to release results in the coming years, HIV vaccine science is evolving rapidly.
Microbicides	US$ 2 bn	US$ 196 mn	11 percent	Efficacy studies continue on 1% vaginal tenofovir gel. New microbicide candidates advanced to clinical trials, with a rich pipeline that includes a vaginal ring and a rectal gel. The field is gearing up for large-scale, later-stage trials set to begin in 2012 and 2013.
HIV Prevention Option	**5-year Total**	**5-year Average**	**5-year Growth Rate***	**2011 milestones**
Pre-Exposure Prophylaxis	US$ 251 mn	US$ 50.2 mn	30 percent	Clinical trials showing the efficacy of PrEP for men and women moved the field into implementation research, with a marketable PrEP product on the horizon.
Adult Male Circumcision	US$ 69.4 mn	US$ 13.9 mn	14 percent	Implementation research expanded and transitioned to rollout. With a global focus on the protection from HIV gained from male circumcision, many countries in sub-Saharan Africa look to significantly scale up their efforts.
HIV Prevention Option	**2-year Total**	**2-year Average**	**2-year Growth Rate***	**2011 milestones**
Treatment as Prevention[6]	US$ 100 mn	US$ 50 mn	305 percent	With the results of HPTN 052, treatment as prevention research shifted to implementation and large-scale rollout in many countries worldwide.

* Compounded annual growth rate (CAGR).

Global investments in other prevention technologies totaled US$203 million in 2011. Investments directed toward male circumcision, reducing vertical transmission at birth and during breastfeeding, treatment as prevention, pre-exposure prophylaxis (PrEP), and female condom R&D increased overall from 2010 by US$41 million (25 percent). In 2011, public-sector sources provided US$152 million (75 percent) and the philanthropic sector provided US$51 million (25 percent). The commercial sector provided in-kind assistance in the form of antiretroviral (ARV) drugs and assays to be tested and used in preclinical and clinical research, and in R&D directed at the next-generation female condom.

Figure 1 **Global HIV Prevention R&D Investments from 2005–2011** (US$ millions)



* The Working Group began tracking funding for treatment as prevention in 2010.

Scientific Advances

While total funding for all HIV prevention R&D decreased by US$30 million from 2010 to 2011,[7] HIV prevention science had one of its most successful years in 2011.[8] The world is further than ever before along the scientific pathway to the end of the AIDS epidemic. In 2011, as in 2010, advances were made both across the full spectrum of R&D for HIV prevention options and in the translation of R&D into on-the-ground realities.

The first of these advances came in May 2011, with the results from the HPTN 052 study, honored by *Science* magazine as the "Breakthrough of the Year". The study showed that initiating antiretroviral therapy (ART) in HIV-positive people at an early stage and maintaining adherence to that treatment regimen reduced the risk of transmission of HIV to an HIV-negative partner by 96 percent. HPTN 052 became the first randomized clinical trial to show what many had long suspected: treatment is also prevention.[9]

The results of two studies released at the International AIDS Society conference in Rome, Italy, in July of 2011 showed the effectiveness of taking daily oral ARV drugs to reduce HIV acquisition among HIV-negative individuals in heterosexual serodiscordant couples. The TDF2[10] and Partners PrEP[11] studies built on the iPrEx study results released in 2010[12] by showing that PrEP reduces HIV transmission in heterosexuals as well as gay men and men who have sex with men (MSM). Based on these findings, the US Food and Drug Administration (FDA) is reviewing Gilead Science's application for an indication for tenofovir/emtricitabine (TDF/FTC) as PrEP for all adults and has set a deadline of September 2012 for its decision.

Additional follow-up analysis of the RV144 Thai vaccine trial revealed another significant discovery in September at the AIDS Vaccine 2011 Conference in Bangkok, Thailand.[13] Aiming to better understand how RV144 protects against HIV infection, the study team found two important molecular clues—two antibodies correlated with the risk of HIV infections. This highly-anticipated post hoc analysis, along with an

Table 2 **Investment Snapshot for 2011**

HIV Prevention Option	Amount 2011	Amount 2010	Change from 2010	Headlines
Preventive vaccines	US$ 845 mn	US$ 859 mn	-US$14 mn (-2 %)	The year saw lower US public-sector investment and the end of the US stimulus package, along with lower European investment overall.
Microbicides	US$ 186 mn	US$ 247 mn	-US$61 mn (-25 %)	The year was one of preparation for clinical trials and decreased investment, due in part to the cyclical nature of clinical trials, with many follow-on and large-scale trials set to begin in 2012 and beyond.
Pre-Exposure Prophylaxis	US$ 62.3 mn	US$ 58.3 mn	+US$4 mn (+7 %)	PrEP funding in 2011 saw increased funding as a result of the large-scale trials that took place in 2011, with next-generation and follow-on trials getting ready to begin in the following years.
Adult Male Circumcision	US$ 20.3 mn	US$ 21.7 mn	-US$1.4 mn (-6 %)	While funding for R&D and operations research may have decreased slightly in 2011, this is due to an increase in implementation, rollout and scale-up of adult male circumcision as a proven HIV prevention technology.
Treatment as Prevention	US$ 79.4 mn	US$ 19.6 mn	+US$59.8 mn (+305 %)	Funding increased substantially due to improved data collection and a post–HPTN 052 focus on scale-up of treatment as prevention trials worldwide.
All HIV prevention R&D	**$US 1.24 bn**	**$US 1.27 bn**	**$US 30 mn (-2%)**	Budget constraints and competing priorities led to an overall flatlining of global HIV prevention R&D spending in 2011.

array of new insights into the mechanics of broadly neutralizing antibodies against HIV brought the vaccine field closer than ever before to finding a strategy for an effective HIV vaccine.

In October, the FACTS 001 trial started, testing the safety and effectiveness of 1% tenofovir gel in preventing HIV and herpes simplex virus type 2 (HSV-2) in women. The results of FACTS 001 will enable the field to understand the effectiveness of 1% tenofovir gel, particularly important in light of the discontinuation of the 1% tenofovir arm of the VOICE trial in November.

Public- and private-sector funders sustained investments in HIV prevention research in 2011. Yet, the need for long-term support to ensure success in these endeavors was confronted by escalating budget constraints in an increasingly volatile global economy and shifts in research focus. These challenges underscore the need for a strategic revitalization of public- and private-sector investments–one that is essential to completing ongoing trials efficiently, supporting confirmatory trials and transforming recent discoveries into new, diverse and more effective HIV prevention options.

Key Conclusions

In line with global health research and development trends overall,[14] this year's resource tracking analysis found that funding had decreased slightly–an effective flatlining of investment in HIV prevention R&D. Yet, in an age of economic challenges, continued investment without significant cuts can be considered a sign that the top funders understand the importance of continuing to invest in HIV prevention R&D. Overall, investments in vaccine and microbicide R&D decreased. Yet, the decreases for microbicide R&D can be attributed to funding disbursement cycles and do not represent declines as compared with past investments. Funders increased their investments for PrEP and treatment as prevention research, supporting clinical trials that in turn have yielded groundbreaking results.

In 2011, the field began to see the effects of a challenging global economic environment, with reductions in public-sector funding in many donor countries. While some public-sector donors reduced their funding levels in 2011, the Bill & Melinda

Gates Foundation (BMGF) and a number of other philanthropic donors filled some of the funding gap, increasing their investments for vaccines and other prevention options by nearly US$20 million. Across both the public and philanthropic sectors in 2011, shifting investment strategies led new funders to invest in HIV prevention R&D and long-time donors to adjust their funding.

With advances in research come the expenses associated with the later stages of R&D. It is critical that donors continue to explore ways in which HIV prevention trials can be funded in order to plan for and complete the large-scale, late-stage trials needed to apply for regulatory approval. In the short term, funding will need to meet the requirements of research institutions and entities preparing to launch these studies in 2012 and beyond.

The Structure of Funding

Funder concentration. Funding for HIV prevention remains highly concentrated among relatively few funders. Although nearly all public-sector donors decreased their funding in 2011, decreases in US and European investment have been the most profoundly felt. Research agencies are fighting for funding, as budgets are cut and fewer grants disbursed. Development agencies are, in some cases, increasingly focused on implementation of global health technologies that have quick, measurable outcomes rather than on long-term R&D projects for which the results are uncertain.

Thus, the sustained and increased investments by some lower- and upper-middle-income countries—including India, China, South Africa and Thailand—as well as their participation in R&D projects, are now proving critical both to broadening the prevention research funding base and to expanding research globally. China has continued to invest in HIV prevention research. While China is currently between funding cycles for its HIV vaccine R&D program, investments from the country continue to prove invaluable to moving R&D forward across a variety of prevention options. India's Department of Biotechnology (DBT) and the Indian Council of Medical Research (ICMR) collaborative program on "HIV/AIDS and Microbicides" is soliciting proposals for HIV vaccine and microbicide research for 2012. In 2011, the International AIDS Vaccine Initiative (IAVI) and the Translational Health Sciences and Technology Institute (THSTI), an institute of the Indian government's Department of Biotechnology, launched a program, known as the HIV Vaccine Design Program. In 2012 the program will open a new center on the campus of THSTI in New Delhi. South Africa has hosted numerous clinical trials of different prevention technologies, and Thailand is hosting vaccine and PrEP trials. Local production is also on the rise. For example, in 2011, CONRAD and the South African government's Technology Innovation Agency (TIA) signed a license agreement that grants TIA the right to manufacture and distribute tenofovir 1% gel in Africa as soon as it has confirmatory results and regulatory approval. The expansion of the funding base with new contributors is making a critical difference in advancing research—which is especially important as traditional funders decrease their investments.

Philanthropic funding was relatively concentrated among a few top funders. Some philanthropies decreased their funding in 2011; however, new funders entered the HIV prevention R&D field, making substantial contributions to a variety of R&D efforts.

Emerging efficiencies. As the field of HIV prevention evolves, so do the organizations and research institutions undertaking R&D projects. Members of the HIV prevention field have increasingly come together to form partnerships and joint endeavors in order to become more efficient and streamlined in conducting R&D. Partnerships and collaborations are vital to the success of the field, and they require the participation of the public, private and philanthropic sectors. Further efficiencies can be achieved as researchers across prevention approaches share and develop crosscutting research.

Funding allocations. It has been challenging to obtain data on funding allocations for categories of R&D expenditure (e.g., basic research, clinical trials, etc.).[15] Yet, reporting shows that the majority of funding for both microbicides and vaccines over the past five years has been allocated to preclinical research and clinical trials.

Figure 2 **Investing in HIV Prevention R&D to End the Epidemic: 2011 Investments and Progress**

DEVELOP	**Developing new HIV prevention options through research and development**	Vaccines **US$ 845 million**	The field is closer than ever before to an effective HIV vaccine with the discovery from RV144 researchers of two antibodies whose presence either increases or decreases the risk of HIV. The only large scale efficacy trial, HVTN 505, is scheduled to release results in 2013, moving the field even closer to the reality of a vaccine.
DEMONSTRATE	**Demonstrating new HIV Prevention options in implementation studies**	Microbicides **US$ 186 million**	The results of CAPRISA 004 are being built upon by trials underway. New technologies – a ring, long-acting injectable and rectal formulation – are being tested. A marketable product is within reach and the field has moved to form partnerships and collaborations furthering its efficiencies.
		Pre-Exposure Prophylaxis **US$ 62.3 million**	PrEP has been proven effective for heterosexual couples and men who have sex with men. It is at the beginning of the roll-out stage as the FDA reviews Gilead's application for Truvada as PrEP for adults.
DELIVER	**Delivering proven HIV prevention tools**	Treatment as Prevention **US$ 79.4 million**	HPTN 052 proved that treatment as prevention works. Roll out of treatment as prevention is occurring worldwide.
		Male circumcision **US$ 20.3 million**	Rollout of voluntary adult male circumcision is on the rise.
Total of US$ 1.24 billion			Combined, these new options could get the field closer to ending the epidemic. Investing in these tools is crucial to avert new infections.

Aside from vaccines and microbicide R&D expenditures, the Working Group is not able to track allocations of R&D funding for prevention options. The lack of information on allocations for other prevention options is a critical gap in resource tracking as the fundamental issue of uptake and adherence across all new options is paramount to the success of any new tool. As products advance through clinical trials and the reality of new, marketable prevention options is imminent, it is imperative that investment in behavioral and social science research becomes a priority. In 2011, only three percent of all funding for microbicide R&D was allocated to behavioral and social science research. Increased investment in behavioral and social science research is in accord with the view expressed in recent international and US domestic guidance documents[16] on the necessity of social science research within and beyond the context of clinical trials.[17] As clinical data shows the importance of adherence to regimens, additional social science research is increasingly vital to the success of new technologies.

2.0 HIV Prevention R&D

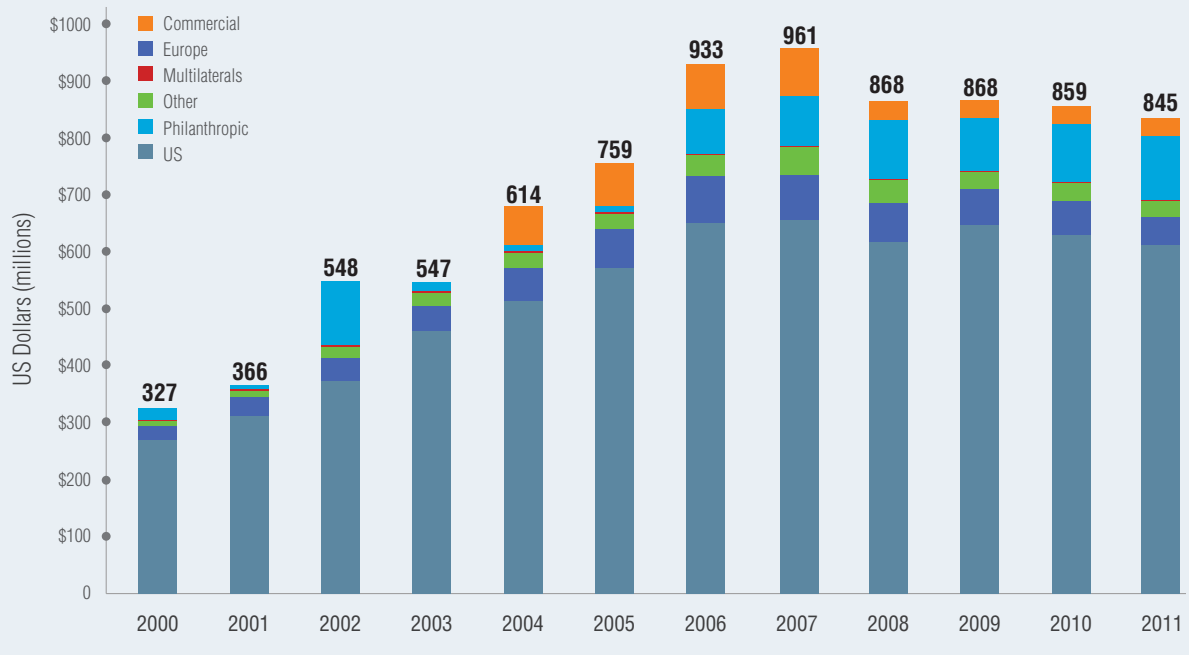
2.1 GLOBAL INVESTMENTS IN HIV VACCINE R&D

Since 2001, global preventive HIV vaccine R&D investment has totaled US$8 billion, with an average yearly investment of US$824 million. The 2011 total investment was US$845 million, a decrease of US$14 million from 2010. As in past years, public-sector funders provided the largest part of the investment, followed by the philanthropic sector and the commercial sector.[18] *In 2011, the public sector provided US$702 million (83 percent), the philanthropic sector provided US$113 million (13 percent) and the commercial sector contributed US$30 million (4 percent). Investment by European governments was US$48.5 million, a decrease of over US$12 million (21 percent) from 2010, and a 40 percent decrease from the US$82 million peak in 2006. Philanthropic investments in HIV vaccine R&D increased in 2011 by US$10 million (10 percent).*

In 2011, RV144 researchers revealed new findings, identifying two correlates of immunity that have the potential to move the field closer to an effective vaccine. In addition, over 30 other HIV vaccine trials were underway. Most ongoing trials are supported primarily through public-sector funding and are collaborative efforts among a range of public and private-sector entities.

RV144 researchers presented results at the AIDS Vaccine 2011 conference in Bangkok, Thailand,

Figure 3 **HIV Vaccine Funding from 2000 - 2011** (US$ millions)



of a two-year effort to identify an immunological explanation for the modest 31 percent efficacy afforded by the prime-boost vaccine regimen tested in the RV144 trial. Two immune responses were found to correlate significantly with HIV infection rates in RV144 vaccine recipients: The first, involving immunoglobulin IgG antibodies that bind to the V1/V2 variable loops in the HIV envelope, correlated with a 43 percent reduction in HIV infection rate. The second involved plasma IgA antibodies that bind to the HIV envelope and correlated with a 54 percent increase in the HIV infection rate. Follow-up trials are now underway. RV305, a small immunogenicity study that aims to evaluate extended boosting regimens using the same vaccine components as RV144, began in Thailand in April 2012. RV305 is the first of two planned follow-up trials to RV144, with the second study, RV306, expected to begin later in 2012.

Additional studies evaluating a prime-boost mechanism similar to that used in RV144 are being planned for initiation in 2013 and 2014 in Thailand, Uganda and South Africa.

Broadly neutralizing antibody research is a large focus of R&D efforts and collaboration within the HIV vaccine field. The Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID) has been focused on designing vaccines to stimulate broadly neutralizing antibodies against HIV. The VRC has completed novel research using computational biology to design immunogens capable of eliciting antibodies in animal models.

Additionally, in 2009, IAVI established the Neutralizing Antibody Center at the Scripps Research Institute dedicated to studying neutralizing antibodies. The Center is the hub for IAVI's Neutralizing Antibody Consortium, which has isolated more than two-dozen antibodies from volunteers worldwide, deciphered some of the structures of the most potent antibodies and applied their discoveries to the design of novel vaccine candidates.

Larger pharmaceutical companies are entering into antibody research and several biotechnology companies are also engaged in R&D that has yielded promising results.

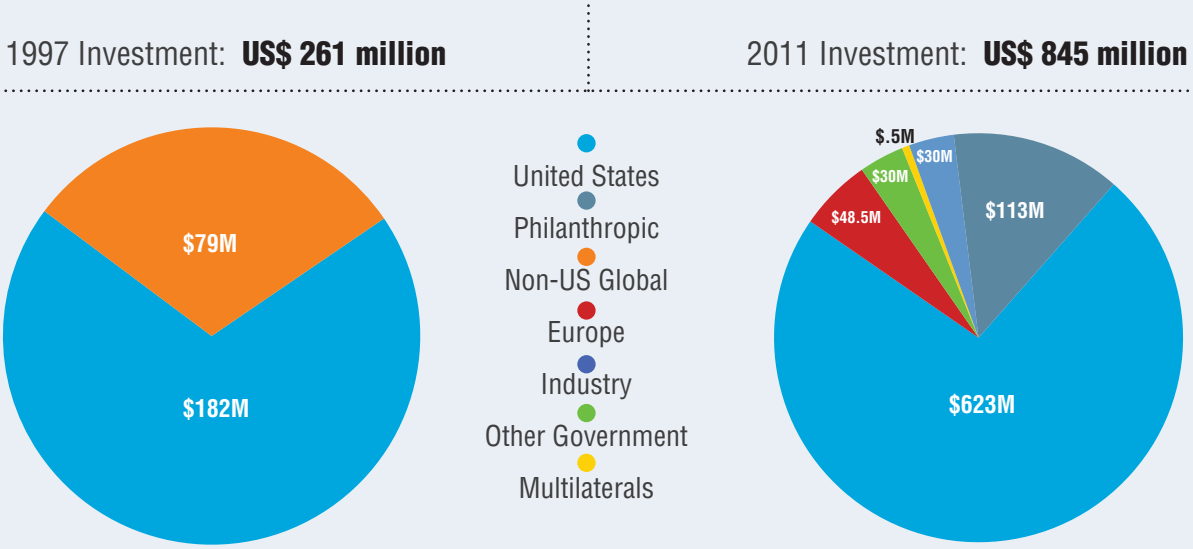
The year 2011 saw more than just the identification of new broadly neutralizing antibodies. Additional

Table 3 **Annual Investments in HIV Vaccine R&D from 2006 – 2011 (US$ millions)***

	2006	2007	2008	2009	2010	2011
PUBLIC SECTOR						
US	654	659	620	649	632	623
Europe	82	79	69	65	61	48.5
Other public sector	38	49	41	31	32	30
Multilaterals	2	2	1	1	1	0.5
Total public	**776**	**789**	**731**	**746**	**726**	**702**
PHILANTHROPIC SECTOR						
Total philanthropic	**78**	**88**	**104**	**92**	**103**	**113**
NON-COMMERCIAL SECTOR						
Total non-commercial	**854**	**877**	**835**	**838**	**829**	**815**
COMMERCIAL SECTOR						
Total commercial	**79**	**84**	**33**	**30**	**30**	**30**
Total global investment	**933**	**961**	**868**	**868**	**859**	**845**

* Numbers may be rounded, including total.

Figure 4 **Total Global Investment in HIV Vaccine R&D Breakdown 1997 vs. 2011** (Valued in 2011 US$ millions)



advances have been made in identifying the structures of antibodies, how they evolve and how they are produced by the immune system. These discoveries help researchers in identifying new targets, understanding how and where antibodies interact with HIV and how they are able to block the virus from infecting cells. Furthermore, VRC was able to map the way in which broadly neutralizing antibodies evolve. Collectively, these discoveries provide clues to design and evaluate vaccine candidates that can elicit such antibodies.

EuroNeut-41, funded under the European Union's (EU) Seventh Framework Programme (FP7), aims to develop new vaccines capable of eliciting neutralizing antibodies. The EuroNeut-41 project involves 17 partners, including Sanofi Pasteur, the University of Granada in Spain, Polymun Scientific, Clinical Research Centre at the University of Surrey and PX'Therapeutics.

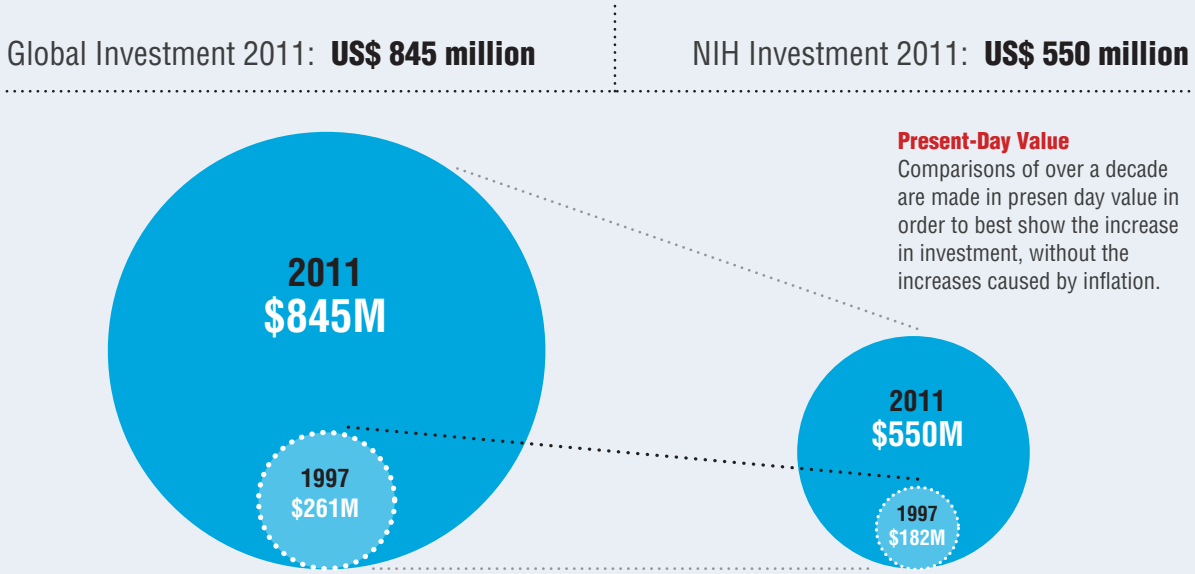
Among other trials moving forward is HVTN 505, currently the only active vaccine efficacy trial. HVTN 505 is a Phase IIb trial evaluating a DNA prime and adenovector vaccine boost to assess whether it prevents infection or lowers the viral load of individuals who seroconvert during the trial. The regimen is being tested in over 2,000 gay men, MSM and transgender women in the US. In 2011, the trial changed its protocol to add HIV infection as an end point for analysis.[19] HVTN 505 is expected to release results in early 2013.

2.1.1 PUBLIC INVESTMENTS IN HIV VACCINE R&D

Public-sector funding has accounted for the majority of funding for HIV vaccine research since research began. National research agencies, through investigator-initiated programs, have been successful in supporting basic, preclinical and clinical research. Public agencies and institutions accounted for 83 percent of all investments in 2011. Agencies in the US alone accounted for 74 percent of HIV vaccine R&D funding. The United Kingdom (UK) and Canada were the second- and third-largest contributors, investing US$18.0 million and US$13.0 million, respectively.[20] Public agencies in eight additional countries invested more than US$1 million each. Ten public agencies increased their investment from 2010 to 2011.

The final disbursement of stimulus funding from the American Recovery and Reinvestment Act (ARRA) came in 2010, providing US$26.7 million in NIH funding for HIV vaccine R&D. While there was only a two percent drop in overall funding for HIV vaccine R&D in 2011, and a three percent drop in US funding, the current budget debates could influence funding

Figure 5 **Total Global and NIH Investment in HIV Vaccine R&D 1997 vs. 2011** (Valued in 2011 US$ millions)



for the NIH, the US Agency for International Development (USAID) and the US Department of Defense's Military HIV Research Program (MHRP) in 2012 and 2013. Pressure on the US Congress to cut spending grew in 2011 and early 2012. Under the sequestration provisions of the Budget Control Act of 2011, significant cuts on the order of eight percent are proposed for the NIH starting in January 2013.

Most members of the G8[21] and 11 members of the G20[22] supported HIV vaccine research in

Table 4 **Top HIV Vaccine Funders for 2010 and 2011 (US $millions)**[23]

2010 Rank	Funder	Amount	2011 Rank	Funder	Amount
1	NIH	561.6	**1**	**NIH**	**550.4**
2	BMGF	80.9	**2**	**BMGF**	**78.5**
3	MHRP	41.6	**3**	**MHRP**	**43.3**
4	USAID	28.7	**4**	**USAID**	**28.7**
5	EC	19.9	**5**	**DFID**	**11.8**
6	Chinese Government	18.3	**6**	**Ragon Foundation**	**10.0**
7	DFID	16.6	**7**	**EC**	**10.3**
8	Ragon Foundation	10.0	**8**	**ANRS**	**7.3**
9	ANRS	6.6	**9**	**Chinese Government**	**6.9**
10	Wellcome Trust	5.1	**10**	**Wellcome Trust**	**6.5**
11	UK MRC	5.0	**11**	**UK MRC**	**6.2**
12	EDCTP	4.5	**12**	**CHVI**	**5.8**
13	CIDA	3.8	**13**	**CIDA**	**4.9**
14	AECID	3.6	**14**	**NMHRC**	**3.9**
15	NORAD (Norway)	2.5	**15**	**Government of the Netherlands**	**3.8**

2011, with China, Canada, the EU, France, the UK and the US contributing more than US$5 million. Support from Canada, France and Japan increased in 2011. Canada significantly increased its R&D investment through the Canadian Institutes of Health Research (CIHR) and is a top funder of HIV vaccine research. The CIHR HIV/AIDS Research Initiative oversees the Federal Initiative to Address HIV/AIDS in Canada and the Canadian HIV Vaccine Initiative. These initiatives provide US$22.5 million annually to support research.

Funding from the European Commission (EC) in 2011 declined dramatically from the previous year. In 2010, the EC invested US$20 million in HIV vaccine R&D. However, in 2011, EC funding decreased by approximately 50 percent to US$10 million. This is on par with the larger trend of decreased funding from European countries, with Italy, the Netherlands, the UK and Spain all reporting lower funding in 2011.

Public-sector funding has also been the backbone of many large PDP efforts and supports collaborations with other sectors, such as the commercial sector. Many commercial-sector efforts are incentivized through grants offered by the public sector. For instance, the US government supports the work of the HIV Vaccine Trials Network (HVTN), testing commercial available vaccines, through NIAID. The US NIH-supported HVTN 505 is the only vaccine efficacy trial currently underway that is testing a DNA/

Figure 6 **Public Sector Donors Who Increased Funding for HIV Vaccine R&D in 2011**
How much did donor funding increase?

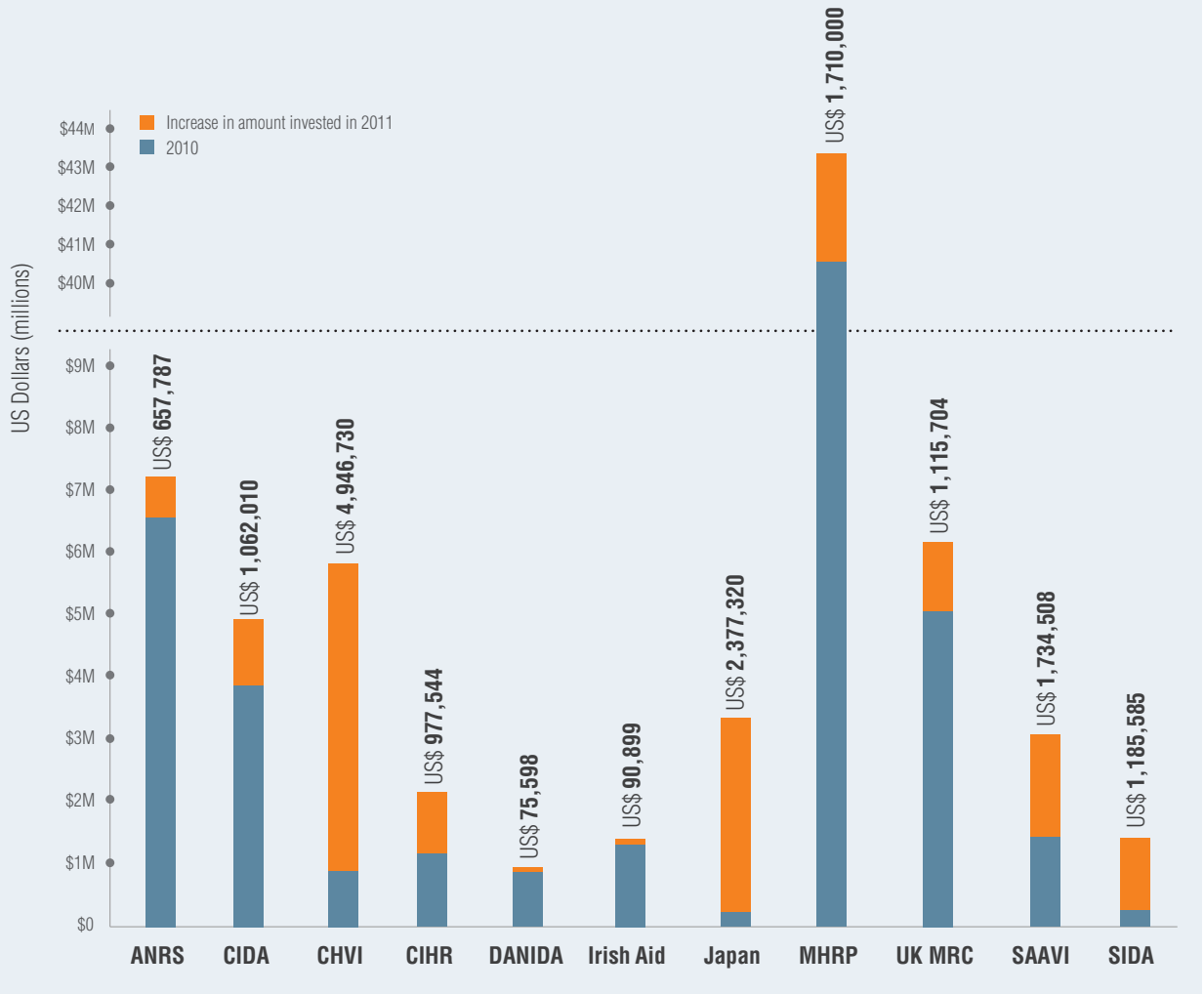


Table 5	**Philanthropic Investment in HIV Vaccine R&D by Foundations and Commercial Philanthropy in 2011 (US$)**
US$ 78.5 million	BMGF
US$ 5 million to US$ 10 million	Ragon Foundation, Wellcome Trust
US$ 1 million to US $ 5 million	OFID, Starr Foundation
US$ 500,000 to US$ 1 million	Doris Duke Charitable Foundation, Fundació la Caixa, NYC Economic Development Corporation
US$ 250,000 to US$ 500,000	Foundation for the National Institutes of Health, GlaxoSmithKline, Google
<US$ 250,000	amfAR, BMS Foundation, Broadway Cares/Equity Fights AIDS, Carlsberg Foundation, Continental Airlines, EMMES Corporation, Hearst Foundation, Institut Mèrieux, John D. Evans Foundation, John M. Lloyd Foundation, The Louis & Rachel Rudin Foundation, Inc., UNIT4 Business Software, Inc., VWR Charitable Foundation, White & Case LLP, William and Mae Salcone Charitable Trust, Ziff Brothers Investments

Ad5 vaccine. The US NIH is supporting 20 of the 33 clinical trials that are currently underway. Additionally, the US Military HIV Research Program (MHRP) and the Walter Reed Army Institute of Research (WRAIR) are supporting additional studies on pox protein vaccines, following up on the results of the MHRP-led RV144.

France's National Agency for Research on AIDS and Viral Hepatitis (ANRS) is also supporting a late-stage clinical trial, set to begin in September 2012, testing a DNA vaccine. Additionally, the public sectors in China, Italy, Spain, Sweden and the UK are all supporting ongoing clinical trials underway in their respective countries.

2.1.2 PHILANTHROPIC INVESTMENTS IN HIV VACCINE R&D

The philanthropic sector accounted for US$113 million (13 percent) of the total funds disbursed for HIV vaccine R&D in 2011, with the BMGF contributing US$81 million (72 percent) of that total. Overall, philanthropic contributions increased in 2011. The UK's Wellcome Trust and the Spanish Fundació la Caixa increased their contributions in 2011.

Increases in philanthropic-sector funding offset cuts to public-sector funding in 2011. While the BMGF decreased its funding in 2011, it remains the second-largest funder and provides invaluable investments in research for HIV vaccines. The Ragon Institute, established in 2009 at Massachusetts General Hospital (MGH), Massachusetts Institute of Technology (MIT) and Harvard University, was founded with a five-year commitment of US$100 million from the Ragon Institute Foundation. Since its founding, the Institute has diversified its funding portfolio, bringing in funding from a variety of other sources. In 2011, funders contributed an additional US$10 million on top of the Ragon Foundation's investment.

2.1.3 COMMERCIAL INVESTMENTS IN HIV VACCINE R&D

In 1997, there were 17 multinational pharmaceutical companies and biotechnology firms engaging in HIV vaccine R&D. While the level of company engagement has fluctuated over the past 15 years, the number of companies conducting HIV vaccine R&D remains relatively stable, with 16 private sector companies engaged during 2011.

While many biotechnology companies invest in HIV vaccine R&D, the majority of private-sector investments in vaccine R&D come from large, multinational pharmaceutical companies.[24] Five multinationals currently have HIV vaccine programs: GlaxoSmithKline (GSK), Johnson &

Johnson (through its subsidiary Crucell), Merck & Co., Novartis Vaccines and Sanofi Pasteur.

In 2011, Johnson & Johnson acquired the Dutch biotechnology company, Crucell, which has been working in collaboration to evaluate its Ad26 adenovirus vector. With the Beth Israel Deaconess Medical Center (BIDMC) and the Ragon Institute, both in Boston, Massachusetts, and the Walter Reed Army Institute of Research, in Silver Spring, Maryland, Crucell has looked at several prime-boost vaccine combinations of Ad26. In addition, Crucell, BIDMC, Ragon and the HVTN also have a collaboration with IAVI to conduct a clinical study of a Ad26/Ad35 prime boost regimen. GSK has a long history of HIV vaccine R&D, beginning with the initiation of its vaccine program in 1986. The company currently has three areas of focus in the preventive HIV vaccine field. The company is investigating an HIV-1 vaccine candidate containing a recombinant fusion protein along with their proprietary adjuvant, AS01, in collaboration with IAVI. Additionally, with the Institut Pasteur, funded in part by the EC Sixth Framework Programme, GSK is investigating a vaccine approach based on the measles vaccine.

Table 6 Estimated Commercial Engagement in HIV Vaccine R&D by Company in 2011

US$5mn to US$10mn	GSK, Merck & Co., Novartis International AG, Sanofi Pasteur
US$1mn to US$5mn	Crucell, ESTEVE, GeoVax, Mymetics
US$100K to US$1mn	Advanced BioScience, Argos Therapeutics, Bionor Immuno, FIT-Biotech, Genvec, Ichor, Inovio Pharmaceuticals, Vical

The third area of investigation of GSK's program is early-discovery R&D to identify new envelope antigen candidates in partnership with several academic institutions.

Merck, along with various partners, is working on an R&D program that aims to identify an HIV envelope–based protein vaccine capable of producing broadly neutralizing antibodies against HIV infection. The company continues to analyze the results of the STEP trial, which tested its adenovirus-5 vaccine, and to explore its implications for vaccine design, as well as

Box 1 HIVACAT Collaboration in Action

The Spanish HIVACAT program is a collaboration of two academic research centers, a philanthropic foundation, a private pharmaceutical company and regional government departments, working to design, develop and test potential preventive and therapeutic vaccines for HIV for further development and regulatory approval. This public-private partnership is made up of two research institutions in Barcelona, Spain, the AIDS and Infectious Diseases Service at Barcelona's Hospital Clinic, (affiliated with the University of Barcelona),, and the IrsiCaixa Institute for AIDS Research, (affiliated with the Autonomous University of Barcelona), the Fundació la Caixa, the pharmaceutical company ESTEVE, and two departments of the government of the Generalitat de Catalunya, the Department of Health and the Department of Economy and Knowledge.

HIVACAT's collaborations include global partnerships with institutions, agencies, universities and organizations in Australia, Canada, France, Germany, Italy, Japan, Mexico, Peru, Netherlands, South Africa, Switzerland, the UK and the US.

The collaboration's success is due to local patient cohorts with data and sample base of 15 years, a high-acceptance of HIV vaccine trials in the population and a team of scientists from institutions and universities worldwide. The pharmaceutical firm ESTEVE has been involved from the initiation of this program in 2008, providing financial support for the research phase, as well as intellectual property, preclinical and clinical development, regulatory affairs and good manufacturing practices expertise—totaling over US$7.6 million in four years.

The program's eight lines of investigation tackle some of the challenges in both preventive and therapeutic HIV vaccine design, including cellular and humoral immunity to HIV and how they affect viral control, the impact of viral sequence diversity and host genetics on vaccine immunogen design, neutralizing antibodies and the function of dendritic cells. In recent years, HIVACAT researchers have had active therapeutic vaccine candidates, with a number of candidates moving to Phase I and II clinical trials.

Box 2 Local Production

The Italian Institute of Health (ISS) is set to fund a new United Nations Industrial Development Organization (UNIDO) project in South Africa that aims to strengthen the local production of essential medicines and other health commodities. The project supports development of a network of clinical sites and good manufacturing practice (GMP) compliance in the production of vaccines in South Africa, and it includes a therapeutic HIV vaccine clinical trial developed by ISS. The US$1.25 million project will be implemented with the South African government and the Directorate General Development Cooperation of the Italian Foreign Ministry. The work in South Africa will be coordinated with UNIDO's ongoing global project, which focuses on strengthening the local production of essential medicines in developing and least-developed countries.[26]

the development of antigens to elicit protective antibodies to HIV. Despite the disappointing results of the STEP trial, the data has continued to yield important findings. In February 2011, scientists from University of Washington, who were not affiliated with the STEP trial, analyzed the genome sequences in HIV-1 isolated from newly infected STEP trial participants and found that the Step vaccine had exerted pressure on the genetic evolution of the virus.

Novartis Vaccines continues to research its alphavirus vector, and is developing different envelope proteins as well as adjuvants for use as a boost to ALVAC prime in the follow-up trials to the Thai RV144 trial or with other candidates. The company has supplied the envelope proteins for the first phase of clinical testing of a preventive HIV vaccine study launched in June by the National Center of the Istituto Superiore di Sanità (ISS) in Italy, part of a collaboration of the AIDS Vaccine Integrated Project (AIVP).[25]

Sanofi Pasteur, the vaccines division of the Sanofi-Aventis Group, is engaging in follow-up studies to RV144 with multiple partners in Thailand and South Africa. In 2011, Sanofi Pasteur signed an agreement with Novartis Vaccines to collaborate on an HIV vaccine prime-boost regimen to build and improve on the efficacy level obtained in the RV144 study in Thailand. The focus will be on the development and clinical evaluation of the HIV prime-boost approach in South Africa and Thailand. Novartis Vaccines and Sanofi Pasteur are working in partnership with the Pox-Protein

Figure 7 HIV Vaccine Expenditures from 2001–2011 (US$ millions)

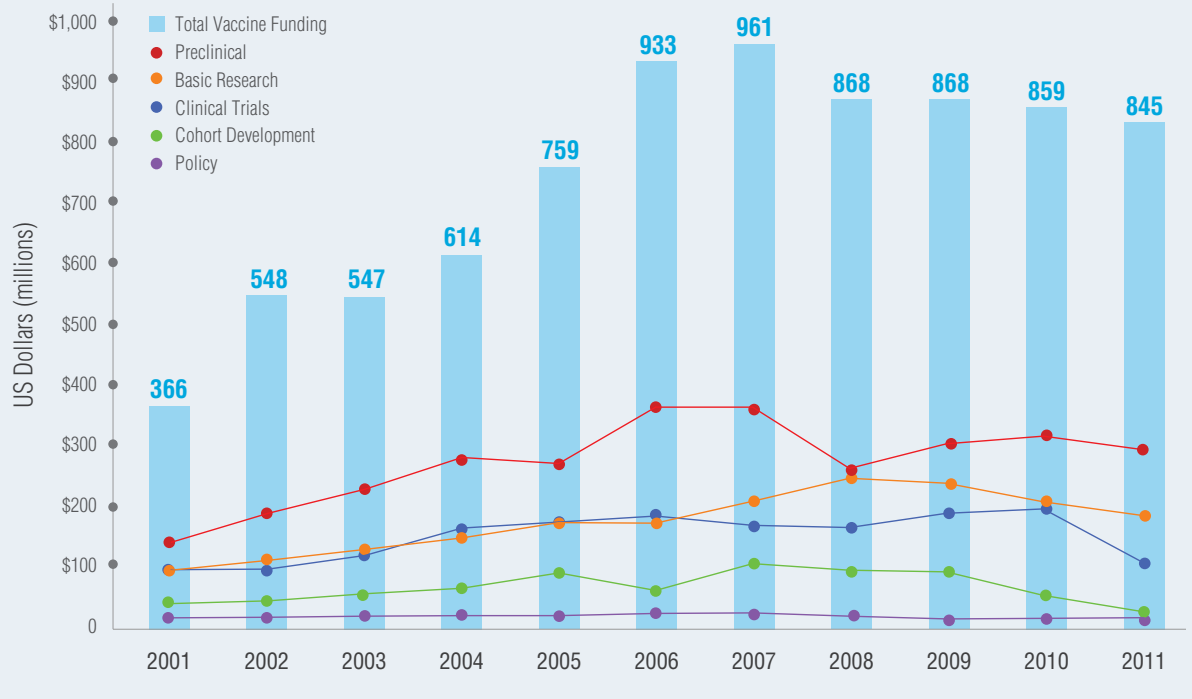
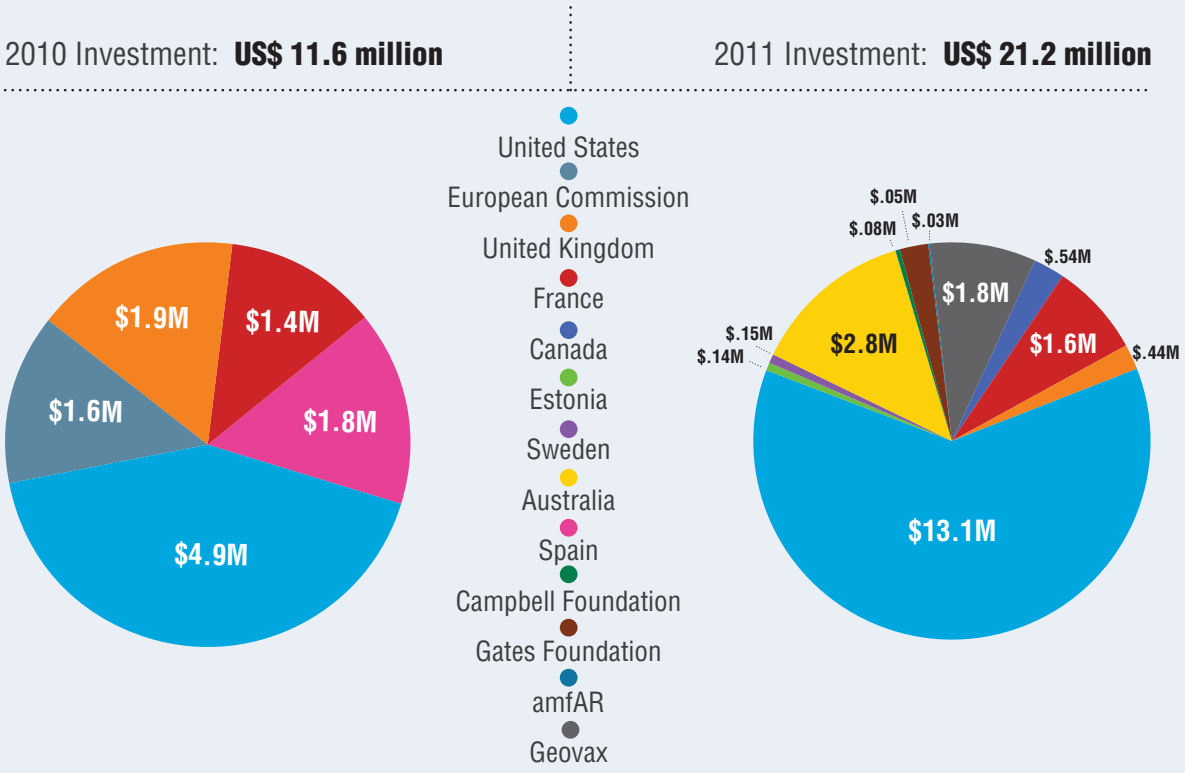


Figure 8 **Investment in Therapeutic HIV Vaccines in 2010 and 2011** (US$ millions)



Public-Private Partnership (P5), which includes the US NIAID, the BMGF, the HIV Vaccine Trials Network (HVTN) and the US MHRP.

Sanofi Pasteur also contributed expertise and funding to the BMGF's Collaboration for AIDS Vaccine Discovery (CAVD) project, which contributes funds, expertise and products to the EuroVacc Foundation, and is a member of EuroNeut-41, the European consortium on neutralizing antibodies.

2.1.4 FUNDING ALLOCATIONS FOR HIV VACCINE R&D

In 2011, spending by public and philanthropic sectors on preventive HIV vaccine R&D was allocated to five categories: basic research (27 percent), preclinical research (39 percent), clinical trials (28 percent), cohort and site development (5 percent), and advocacy and policy (1 percent). The percentage distribution of investment among the five categories in 2011 was similar to that of 2010, with a small decrease in preclinical research and an increase in clinical research. Further information about the categories used to define R&D can be found in the Appendix.[27]

2.1.5 GLOBAL INVESTMENTS IN THERAPEUTIC HIV VACCINE R&D

Therapeutic vaccines enhance immune responses for HIV-positive individuals to help them better control infection. Investment toward research for therapeutic HIV vaccines for HIV-positive individuals increased in 2011 to US$21.2 million, a change of US$9.6 million from 2010.[28]

Investment from public-sector sources increased. Investors included the US NIH (62 percent), France's Institut Pasteur (8 percent), Australia's National Health and Medical Research Council (NHMRC) (7 percent), the Australian Research Council (ARC) (6 percent), the UK Medical Research Council (2 percent), the Canadian Institutes for Health Research (CIHR) (1.4

percent), the Canadian HIV Vaccine Initiative (1.2 percent) and the Swedish Research Council (SRC) and Estonia Research Council (less than one percent each).

Philanthropic sources began funding therapeutic vaccine research, with funding from the BMGF, the Campbell Foundation and amfAR (3 percent).

Funding from pharmaceutical and biotechnology companies is likely underrepresented, since only a few biotechnology firms reported their investment in 2011.[29] Companies involved in R&D for therapeutic vaccines in 2011 include Argos Therapeutics, Bionor Immuno, FIT Biotech, Genetic Immunity, GeoVax, GSK, Invio Pharmaceuticals, Profectus Biosciences and VIRxSYS.

2.2 GLOBAL INVESTMENTS IN CURE RESEARCH

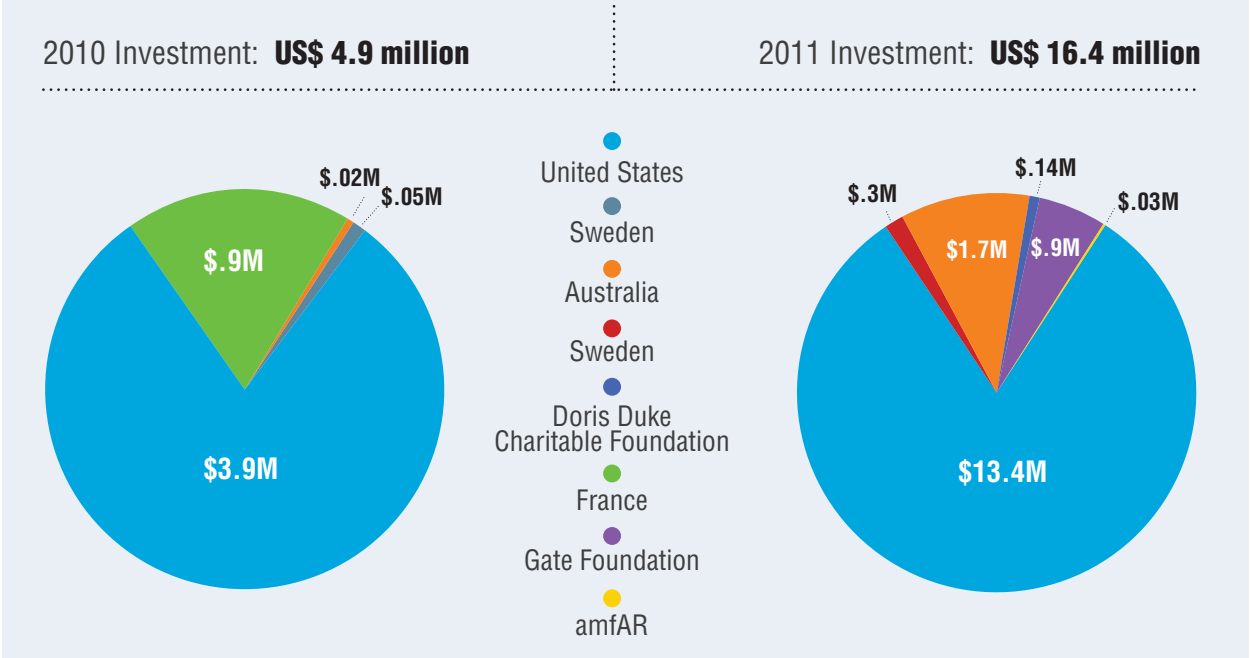
HIV cure research has been galvanized in recent years. Two approaches are being studied: a sterilizing cure that would eradicate HIV from the body, and a functional cure that would keep the patient healthy without drugs but not eliminate the virus from the body.

In 2007 and 2008, Timothy Brown, the "Berlin patient", received two bone marrow transplants to treat his leukemia. The donor was among the one percent of Northern Europeans lacking the CCR5 protein on the surface of CD4 cells, without which the virus is unable to enter the cells. With an immune system resistant to HIV infection, the Berlin patient has been off of ARVs for almost five years. However, finding a donor with mutations in the CCR5 gene who's also a good immunological match for the patient is very difficult.

Another approach is to treat CD4 cells removed from an HIV-positive individual with gene therapy in order to remove the CCR5 protein and to then infuse the treated cells back into the individual. In the case of the "Trenton patient," one month after treated cells were put back into his body, the man was able to stop taking ART for a short period. Other approaches include interventions to activate latent HIV virus in CD4 cells and other locations that have proven resistant to ART. Complementary strategies, such as therapeutic vaccines, that would attack latent HIV once it becomes active, are being developed.

Pharmaceutical and biotechnology companies have invested in cure research. Multinational

Figure 9 **Investment in Cure Research in 2010 and 2011** (US$ millions)



companies like Gilead, Tibotec and Merck, as well as biotechnology firms like Calimmune and Sangamo BioSciences, have started to increase their efforts. Merck's vorinostat, used to treat a rare cancer, is being tested in an early-stage clinical trial. Another Merck candidate in preclinical trials is an antibody that blocks a protein called PD-1, associated with HIV latency.

NIAID awarded grants under the Martin Delaney Collaboratory totaling nearly US$70 million over five years to three research teams in pursuit of cure research. The California Institute for Regenerative Medicine has committed a total of over US$40 million to projects related to finding a cure.

Investments in HIV cure research increased by US$11.5 million from 2010 to 2011. The total amount in 2011 was US$16.4 million. Public-sector funding came from the US NIH, the ARC, Australia's NHMRC and the SRC. Funding from philanthropic sources came from the BMGF, the Doris Duke Charitable Foundation and amfAR. Private-sector sources provided an unknown amount of funding in 2011.

2.3 GLOBAL INVESTMENTS IN MICROBICIDE R&D

Over the past 10 years, global investment in microbicide R&D has reached a total of nearly US$2 billion, with an average yearly investment of US$196 million. Total global investment in microbicide R&D was US$186 million in 2011. Of the 2011 total, the public sector provided US$176 million (95 percent); the philanthropic sector, US$9 million (5 percent); and the commercial sector, US$1 million (<1%).

Several large European donors reduced their contributions in 2011, resulting in a US$24.3 million decline in European contributions from 2010. In addition, the US government decreased its total funding by US$39 million, with the largest decline coming from the NIH at US$36 million less (24 percent). South Africa more than doubled its funding in 2011, investing US$10 million, a 54 percent increase over 2010.

The philanthropic sector decreased its funding, with the BMGF reducing its contribution by US$6.7 million (42 percent). New philanthropic

Table 7 **Annual Investments in Microbicide R&D from 2006–2011 (US$ millions)***

	2006	2007	2008	2009	2010	2011
PUBLIC SECTOR						
US	129.7	139.8	154.4	172.6	181.7	148
Europe	56.3	59.6	39.9	44.4	40.3	16
Other public sector	4.7	3.4	12.1	5.7	8.3	12
Multilaterals	1.4	0.2	0.2	0.2	0.1	0.1
Total public	**192.1**	**203**	**206.6**	**222.9**	**230.4**	**176**
PHILANTHROPIC SECTOR						
Total philanthropic	**26.2**	**19**	**34.6**	**11.8**	**15.9**	**9**
NON-COMMERCIAL SECTOR						
Total non-commercial	**218.3**	**222**	**241.2**	**234.7**	**246.3**	**185**
COMMERCIAL SECTOR						
Total commercial	**4.5**	**4.5**	**2.5**	**1**	**1**	**1**
Total global investment	**222.8**	**226.5**	**243.7**	**235.7**	**247.3**	**186**

* Numbers may be rounded, including totals.

Figure 10 **Microbicide Funding from 2000–2011** (US$ millions)

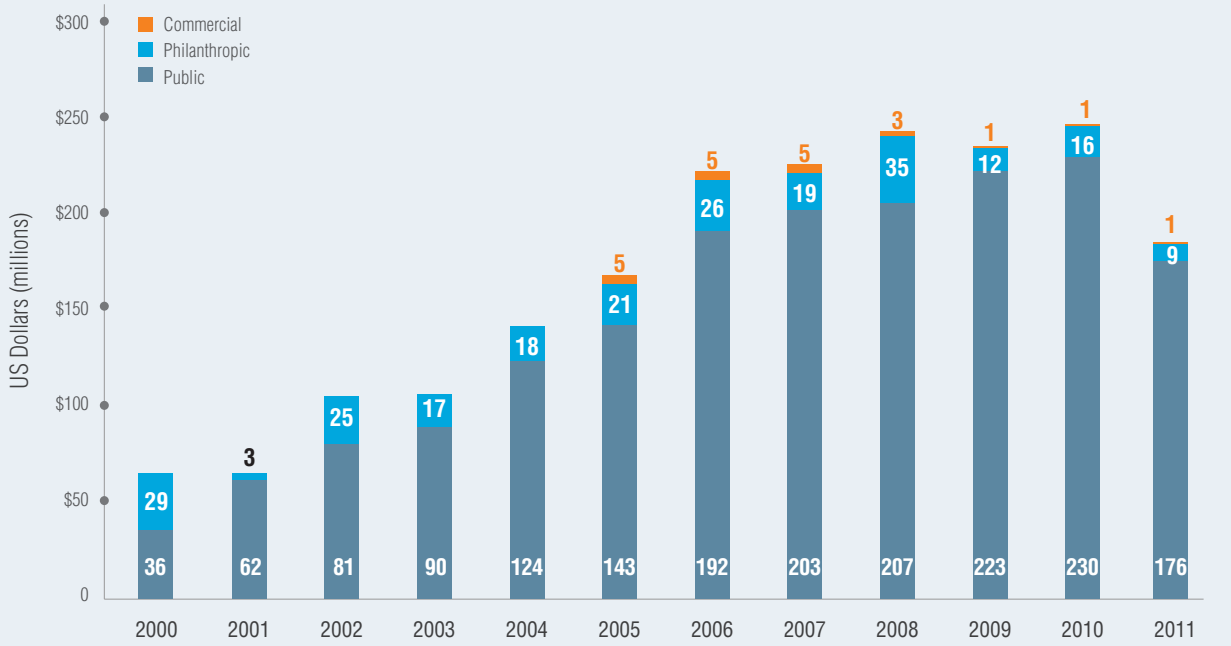


Table 8 **Top Microbicide Funders for 2010 and 2011 (US $millions)**[30]

2010 Rank	Funder	Amount	2011 Rank	Funder	Amount
1	NIH	147.0	**1**	**NIH**	**111.8**
2	USAID	38.0	**2**	**USAID**	**36.0**
3	DFID	16.5	**3**	**South African DST/DOH**	**10.0**
4	BMGF	15.7	**4**	**BMGF**	**7.0**
5	EC	6.7	**5**	**DFID**	**3.2**
6	China	3.6	**6**	**Netherlands**	**2.7**
7	UK MRC	3.4	**7**	**NORAD (Norway)**	**2.5**
8	NORAD (Norway)	3.3	**8**	**Wellcome Trust**	**1.6**
9	EDCTP	2.0	**9**	**Irish Aid**	**1.4**
10	Spain	1.9	**10**	**UK MRC**	**1.3**
11	Netherlands	1.7	**11**	**Denmark**	**0.9**
12	Denmark	1.7	**12**	**NHMRC**	**0.6**
13	Germany	1.3	**13**	**OFID**	**0.5**
14	Irish Aid	1.1	**14**	**Spain**	**0.4**
15	CDC	0.7	**15**	**ARC**	**0.4**

funders, such as the OPEC Fund for International Development (OFID) and the M.A.C. AIDS Fund, contributed over US$500,000 in 2011. OFID's total grant for microbicide research was US$1.5 million, to be allocated over the next few years.

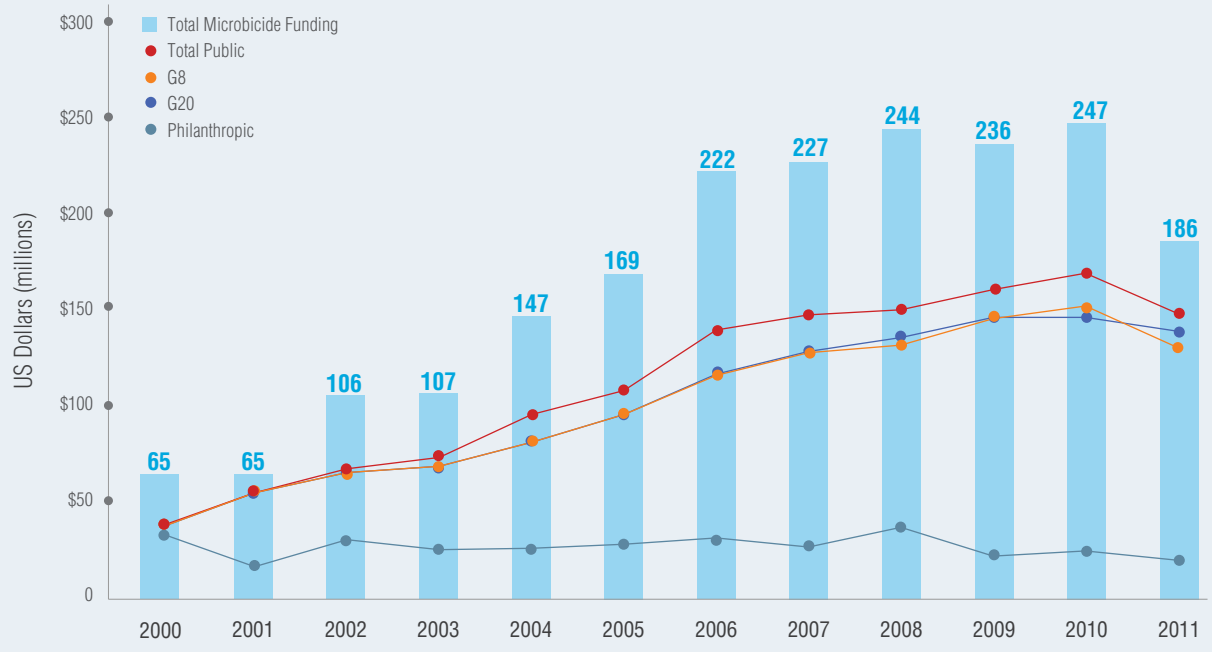
2.3.1 PUBLIC INVESTMENTS IN MICROBICIDE R&D

In 2011, public-sector investment accounted for 95 percent of the combined global funding for microbicide research, development and advocacy. The US continues to be the primary source of funding at US$148 million, representing 80 percent of total funding for microbicide R&D. US funding decreased by over US$39 million in 2011, a 21 percent drop. In 2010, the final disbursement of ARRA stimulus funds accounted for US$4.5 million of NIH investment in microbicide R&D, which explains in part the drop-off in US funding for 2011. European national governments and the EC together accounted for US$16 million (9 percent), a US$24.3 million (60 percent) decrease from 2010.

As the field moves further from the results of the CAPRISA 004 trial, which tested the effectiveness of 1% tenofovir gel, there is increasing clarity about next steps, along with new questions. In June 2011, USAID distributed a discussion draft of a strategic plan for microbicide introduction, and the South African and US governments announced full funding for the confirmatory multisite FACTS 001 trial, testing 1% tenofovir gel. With FACTS 001 scheduled to release results on the safety and effectiveness of 1% tenofovir gel in 2014, and the open-label implementation study CAPRISA 008, which is evaluating the effectiveness of distributing 1% tenofovir gel in communities where CAPRISA 004 took place, releasing results in 2013, advancements are being made in the microbicide field.

In November 2011, the field received disappointing news regarding the 1% tenofovir gel arm of the large-scale VOICE trial. The arm was dropped for futility after an independent Data and Safety Monitoring Board (DSMB) review found no effect in preventing HIV. The trial used a different dosing strategy from that of CAPRISA 004 and FACTS 001; participants were counseled to use the gel daily as opposed to before and after sex. In September 2011, the oral tenofovir arm of the VOICE trial was also stopped after the

Figure 11 **Microbicide Funding from 2000–2011** (US$ millions)



DSMB determined that it was not effective in the context of the trial.

The microbicide field continues to advance other candidates, with a robust pipeline of options that include a vaginal ring and rectally applied gel. The International Partnership for Microbicides (IPM) launched a clinical trial assessing the long-term safety and efficacy of a vaginal ring with the ARV dapivirine (The Ring Study), and the US NIH–funded Microbicide Trials Network (MTN) planned to start a parallel study of the dapivirine ring (ASPIRE). IPM and MTN are also collaborating on a Phase I study of maraviroc-based vaginal rings: a ring containing maraviroc alone and a combination dapivirine-maraviroc ring. A study testing 1% tenofovir gel used rectally is scheduled to begin in early 2013.[31] Looking ahead, the field has a number of late-stage studies set to begin.

A considerable research effort is being made to study a variety of other microbicide delivery systems, as well. The MTN 005 open-label trial, now enrolling, will test a placebo vaginal ring in an early-stage safety, adherence and feasibility study in India and two US sites, a collaboration between the Population Council and two NIH institutes. Both CONRAD and the Population Council are developing protocols for early clinical studies of combination approaches, increasingly referred to as "dual-protection" or "multipurpose technologies" (MPTs). Examples of these are the SILCS diaphragm and ARV-based gels, intravaginal rings (IVRs) and tablets combining ARVs and contraceptive agents, as well as a range of different dosing regimens for both ARV-based and combination ARV/contraceptive strategies, including dual-protection injectables. Finally, there are a range of studies exploring different aspects of microbicide safety, acceptability and adherence in both early clinical trials and discrete studies that include a pregnancy exposure registry, a cross-sectional resistance study, a bone mineral density sub-study, as well as feasibility studies in different populations, including sex workers, and a follow-up of HIV-1 seroconversion in microbicide trials.

While funding for basic research decreased between 2010 and 2011, candidates in the preclinical microbicide pipeline are receiving selective attention, with a focus on the potential of some candidates as MPTs. An "integrated MPT pipeline" that includes contraceptive agents and delivery systems, HIV entry and enzyme inhibitors and non-HIV anti-infective agents, is under review. The MPT pipeline is now integrated into US NIH and USAID strategies, and is being examined by the BMGF as an investment option. China is evaluating a CCR5 antagonist–based gel formulation in preclinical studies with funding from the Chinese Ministry of Health, Ministry of Science and Technologies and private sector; India's ICMR is pursuing preclinical and clinical studies of other drug substances; and the Combined Highly Active Anti-Retroviral Microbicides (CHAARM) project, a large collaboration co-funded by the EU under the Seventh Framework Programme, continues its wide-ranging basic research into specifically targeted combinations for topical application.

2.3.2 PHILANTHROPIC INVESTMENTS IN MICROBICIDE R&D

In 2011, the philanthropic sector provided US$9 million (5 percent) of the funds disbursed for microbicide R&D. The investment in 2011 represented a 42 percent decline from 2010, due in part to timing shifts in the investments of some funders. As in 2010, the majority of funding came from the BMGF and the Wellcome Trust. However, in 2011 the funder portfolio grew more diverse, with two new funders, the M.A.C. AIDS Fund and OFID, investing in microbicide R&D.

2.3.3 COMMERCIAL INVESTMENTS AND CONTRIBUTIONS TO MICROBICIDE R&D

Total commercial-sector microbicide investment in 2011 was estimated at US$1 million, mostly from biotechnology firms, with some large pharmaceutical investment, as well. As has been the case throughout the history of R&D for microbicides, the most significant contributions from the private sector were royalty-free transfers of ARVs for use as active agents in microbicide development. Microbicide developers continue to receive product information and technical support and advice from commercial partners. CONRAD, the Population Council and IPM also received

royalty-free licenses and material transfers from pharmaceutical companies, including licenses to develop ARVs as components of combination products. The biotechnology industry, through a variety of grant and contract mechanisms, has developed both ARV- and non-ARV-based products. Mapp Biopharmaceutical is engaged in R&D for microbicides using monoclonal antibodies.

The contribution of companies is not readily quantifiable, but includes a range of expertise and support such as legal support for material transfer agreements and licenses; regulatory and scientific advice; access to toxicology studies and safety data from clinical trials or surveillance; grants of product and product remanufacturing; advice regarding manufacture of microbicide delivery systems; participation in development meetings and teleconferences; and, timeline guidance.[32]

2.3.4 FUNDING ALLOCATIONS FOR MICROBICIDE R&D

In 2011, expenditures on microbicide R&D were allocated across the following seven categories: basic mechanisms of mucosal transmission (8 percent), preclinical testing (22 percent), formulations and modes of delivery (7 percent), clinical trials (48 percent), microbicide behavioral and social science research (3 percent), microbicide research infrastructure (7 percent), and policy and advocacy (4 percent).[33]

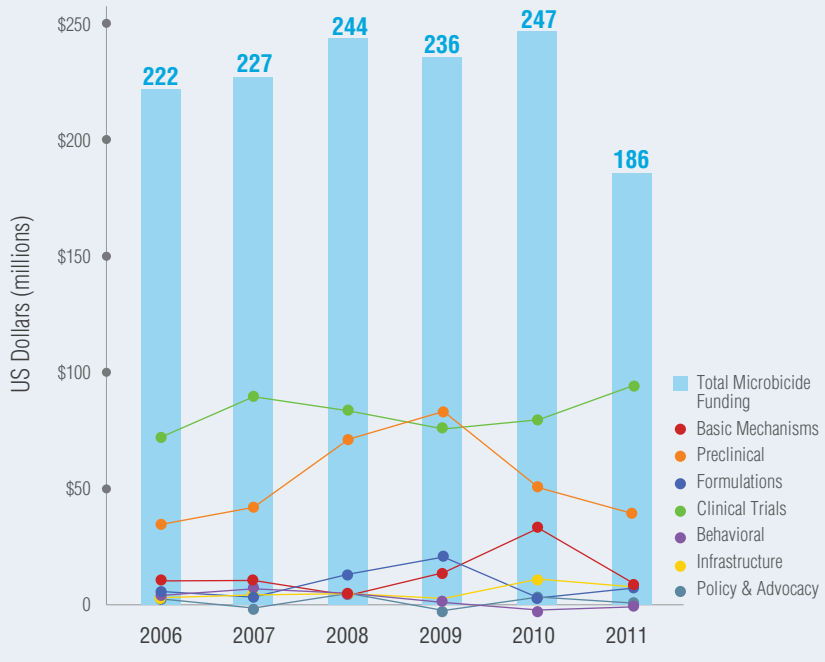
Preclinical testing and clinical trials remained the categories with the largest expenditures. Preclinical work declined from 25 percent in 2010 to 22 percent in 2011, as did research on basic mechanisms of mucosal transmission, from 18 percent in 2010 to 8 percent in 2011. There is hope that upcoming NIH funding announcements will infuse new investment and energy into this early research, since a number of fundamental questions remain regarding both topical and oral microbicides for PrEP. Not surprising, a large increase was seen in clinical trial expenditures, which rose from 38 percent in 2010 to 48 percent in 2011. Increases were also seen in allocations for formulations and modes of delivery, as well as for and behavioral and social science research.

2.3.5 INVESTMENTS IN RECTAL MICROBICIDE R&D

In 2011, R&D toward a rectal microbicide was funded at approximately US$4.1 million. Between 2001 and 2011, global spending on rectal microbicide research totaled US$30 million. In 2011, the majority of funding came from US sources and was dedicated to support preclinical development of rectal microbicide products and clinical testing of rectal microbicides.

Most of this work is funded by the NIH which, in 2009, established the Combination HIV Antiretroviral Rectal Microbicide Program (CHARM), a five-year, US$11 million, multi-center grant intended to advance candidate rectal microbicides from discovery into early clinical development. CHARM works through a multi-sector

Figure 12 **Microbicide Expenditures from 2006–2011** (US$ millions)



collaboration and seeks to develop rectal-specific products *de novo*, rather than simply testing existing vaginal microbicide formulations. Novel rectal-specific antiretroviral formulations are being evaluated in explant systems and a humanized mouse model optimized to evaluate microbicide efficacy. The first CHARM clinical studies with tenofovir will start in late 2012, and clinical evaluations of maraviroc products will start in late 2013. Three Phase I rectal safety trials of tenofovir have been completed, and the field is moving into later-stage trials. In 2011, MTN tested the safety and acceptability of 1% tenofovir gel, reformulated for rectal use and, based on positive results from that study, will proceed with a Phase II trial in Peru, South Africa, Thailand and the US in early 2013.

2.4 GLOBAL INVESTMENTS IN R&D AND OPERATIONS RESEARCH FOR OTHER HIV PREVENTION OPTIONS

A variety of other biomedical prevention strategies were explored in 2011, including PrEP and treatment as prevention. Funding also went to operations research for implementation of male circumcision for HIV prevention, to R&D to improve the female condom and to refining current strategies and developing new ones for preventing vertical transmission to infants at birth and during breastfeeding. The Working Group has also continued to track funding for HSV-2 vaccines because of their potential HIV prevention effect.

2.4.1 INVESTMENTS IN FOLLOW-UP STUDIES AND OPERATIONS RESEARCH RELATED TO ADULT MALE CIRCUMCISION

Global public-sector and philanthropic investment in R&D and operations research related to adult male circumcision totaled US$20.3 million in 2011.[34] While data from South Africa, Kenya and Uganda have already shown that male circumcision reduces the individual risk of HIV infection by 60 percent, there had been no evidence of a preventive effect at the community level before 2011. Results released in July 2011 from the ANRS Orange Farm randomized control study in South Africa indicated that rollout in the southern and eastern regions of Africa can markedly decrease the spread of HIV in high-prevalence areas. The results of this trial have spurred development agencies to invest in adult male circumcision for up to 15 million men in Africa as a highly cost-effective way to prevent the spread of HIV.[35]

President's Emergency Plan for AIDS Relief (PEPFAR) funding for implementation research related to adult male circumcision programs totaled US$500,000 in 2011. The US has provided support for three-quarters of the nearly one million male circumcisions performed for HIV prevention in recent years. PEPFAR announced that it will support more than 4.7 million procedures in the southern and eastern regions of Africa from 2012 to 2013.[37]

2.4.2 INVESTMENTS IN R&D RELATED TO PRE-EXPOSURE PROPHYLAXIS

Global public-sector, philanthropic and commercial investment in PrEP equaled US$62.3 million in 2011 and has totaled US$266 million over the past six years. There are currently nine ongoing or planned PrEP trials, most testing TDF

Box 3 Patient Capital

The New York–based Acumen Fund does not give grants. Instead, the charity provides loans, or equity, to businesses that in turn yield financial and social returns. The return on these loans is recycled into new investments.

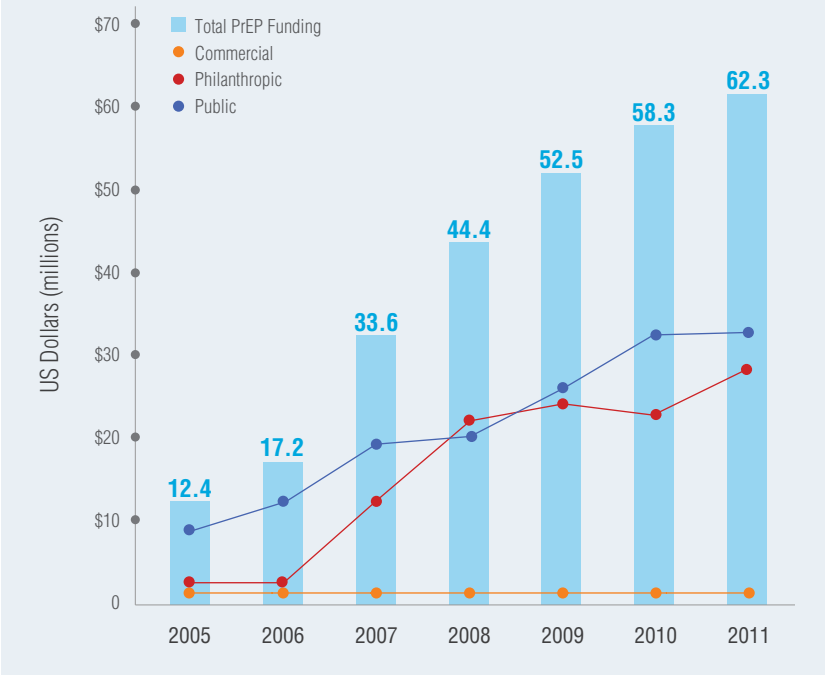
The key to Acumen is "patient capital", a debt or equity investment in an early-stage enterprise that works to provide low-income consumers with a basic necessity, such as healthcare, housing, water, alternative energy sources or agriculture. Acumen investments are typically in the range of US$300,000 to US$2.5 million, with payback expected after approximately seven to ten years. Acumen also provides services to help the enterprise grow and better serve the needs of those at the bottom of the pyramid.

In 2010, Acumen invested US$1.25 million in Circ MedTech, the developer of the non-surgical PrePex device used in performing male circumcisions. With the investment, Circ MedTech was able to prepare for WHO prequalification, get ready for launch in African markets and, in 2012, obtain US FDA approval.[36]

and/or TDF/FTC, one testing TMC278LA and another testing maraviroc in addition to TDF and FTC.

In February 2012, the FDA granted priority review to Gilead's application for once-daily TDF/FTC as PrEP in adults. The FDA has set September 2012 as the deadline to make a decision on Gilead's application.

Figure 13 **Investment in Pre-Exposure Prophylaxis from 2005–2011** (US$ millions)



Following the noteworthy results of the iPrEx trial in 2010—which showed the safety and effectiveness of TDF/FTC as PrEP among gay men, MSM and transgender women—came results on the effectiveness of PrEP in heterosexual men and women. In July 2011, the Partners PrEP trial announced that the DSMB had recommended that the placebo arm be discontinued and the study results released due to clear evidence of HIV protection from daily oral TDF/FTC and daily oral TDF. The study showed that both regimens reduced the risk of acquiring HIV in HIV-negative women and men in serodiscordant partnerships. Additionally, the smaller TDF2 expanded safety study reported a reduction in risk for both men and women who took daily oral TDF/FTC.

In 2011, two studies released differing results on the use of PrEP in women. In April, the FEM-PrEP study was stopped early, having found no evidence of benefit in women using daily-oral TDF/FTC. Analysis of the results, released in March 2012, suggests that inadequate adherence may have undermined the effectiveness of TDF/FTC. In September 2011, the VOICE oral TDF arm was dropped after a DSMB review found no reduction in risk of HIV. VOICE is continuing its evaluation of oral TDF/FTC, with final results expected in late 2012.

While proof-of-concept for PrEP has been demonstrated, ongoing trials are aiming to identify factors that may influence PrEP's efficacy among

Table 9 **Annual Investments in Pre-Exposure Prophylaxis from 2005–2011 (US$ millions)***

	2005	2006	2007	2008	2009	2010	2011
PUBLIC SECTOR							
Total public	8.7	13.5	19.7	20.6	26.6	33.8	32.3
PHILANTHROPIC SECTOR							
Total philanthropic	2.4	2.4	12.6	22.5	24.6	23.2	28.7
COMMERCIAL SECTOR							
Total commercial	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Total global investment	12.4	17.2	33.6	44.4	52.5	58.3	62.3

different populations, including young MSM, injection drug users and heterosexual men and women. Studies are also ongoing that look at different dosing strategies, including intermittent, time-driven and exposure-based use of PrEP.

2.4.3 INVESTMENT IN R&D RELATED TO TREATMENT AS PREVENTION

There is increasing evidence of the value of ART in prevention of HIV. Beginning in 2010, the prospective cohort analysis of serodiscordant couples in the Partners PrEP study showed a 92 percent reduction in infection.[38] Then, in 2011, results of the randomized clinical trial, HPTN 052, showed that immediate treatment and sustained adherence for healthy HIV-positive sexual partners with high CD4 counts reduced risk of transmission to their HIV-negative sexual partner by 96 percent and lowered TB infection rates in the HIV positive partner.[39] These results, and the important WHO, Swiss and Canadian consultations on treatment as prevention that preceded them, have laid the groundwork for an increase in treatment as prevention R&D.

Total global investment in treatment as prevention R&D in 2011 was US$79.4 million. Public-sector agencies from the US provided a significant portion of the funding with US$43.7 million coming from the NIH and an estimated US$11.3 million for combination prevention coming from PEPFAR. Canada provided a significant amount of funding, with CIHR investing US$2.0 million and the government of British Columbia investing an estimated $12.0 million. European funding came from France's ANRS, the UK's NIHR and MRC, SIDA, the Dream Fund of the Dutch Postcode Lottery and the Swiss-based Médecins Sans Frontières (MSF).

The majority of philanthropic funding comes from the BMGF, the Dream Fund of the Dutch Postcode Lottery, the Wellcome Trust and MSF. Clinical trials, sponsored by STOP AIDS/Clinton HIV AIDS Initiative (CHAI) in Swaziland, are being funded by the Dream Fund of the Dutch Postcode Lottery.

While there is no direct commercial investment in treatment as prevention R&D, a substantial amount of ARV drugs have been donated for clinical trials. In HPTN 052, for example, study drugs were donated by Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GSK and Merck & Co.

2.4.4 INVESTMENTS IN HIV PREVENTION R&D RELATED TO HSV-2 PREVENTION

Prevention of HSV-2 infections in HIV-negative people may be may be an effective element in an HIV prevention strategy. While HSV-2 suppression with acyclovir has not been shown to have an effect on HIV acquisition, research on other therapeutic and prophylactic methods is ongoing.

In 2011, a total of US$11.8 million was provided for HSV-2 vaccine research. While the US NIH provided the majority of funding, the ARC and Australia's NHMRC also provided funding for R&D.

Commercial investors were often subsidized or entirely funded by public-sector institutions. Vical was awarded a grant by the US NIH for its HSV-2 vaccine program, which is developing a plasmid DNA-based vaccine to inhibit recurring lesions in patients latently infected with HSV-2. Preclinical results from Vical show a significant reduction in viral lesion occurrence. Other pharmaceutical and biotechnology companies investing in HSV-2 vaccine R&D include GSK, Genocea Biosciences and Juvaris.

In 2010, GSK decided to halt its NIH-funded Phase III trial assessing the company's HSV vaccine, Simplirix, because the vaccine did not show efficacy against HSV-2. In mid-2012, results of the trial were published in the *New England Journal of Medicine*, validating GSK's decision to halt development of the vaccine. GSK and NIH investigators are conducting additional studies to gain further understanding of the results.

2.4.5 INVESTMENTS IN OPERATIONS RESEARCH RELATED TO VERTICAL TRANSMISSION PREVENTION

Funding for operations research related to prevention of vertical transmission from mother to child at birth and during breastfeeding was US$43.1 million in 2011. The public sector accounted for the majority of this funding, with the US, through the NIH and USAID, contributing 84 percent. Other public-sector agencies—ANRS, the Institut Pasteur, CHVI, CIDA and CIHR, SIDA and the UK Medical Research Council (MRC)—provided 15 percent of total funding. In 2011, studies testing vertical transmission prevention focused on transmission at birth and through breastfeeding, and on ARV resistance in HIV-positive women who were taking ARV regimens designed to prevent vertical transmission.

2.4.6 INVESTMENTS IN R&D AND OPERATIONS RESEARCH RELATED TO FEMALE CONDOMS

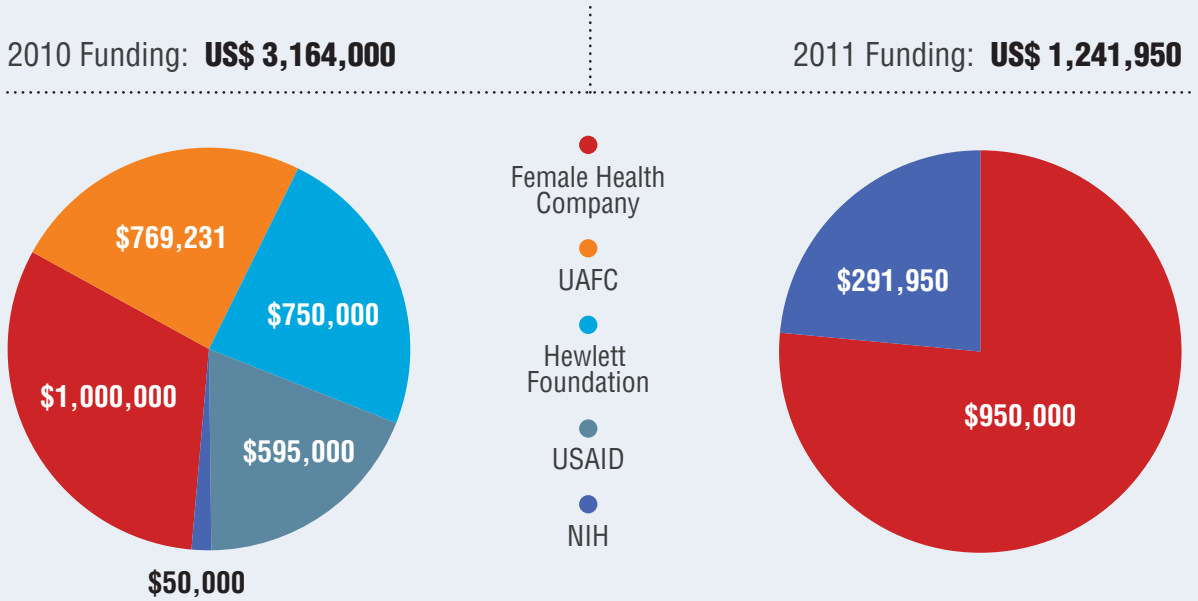
While the female condom has been available for 30 years, research questions remain in regards to design, rollout and implementation. R&D work—including product development efforts, basic HIV research, clinical trial preparation, community education and advocacy—continues. In 2011, global investment in R&D related to the female condom totaled US$1.2 million, coming from the US NIH and the Female Condom Company.

Table 10 **Funding for Vertical Transmission Prevention from R&D 2008–2011 ((US$ millions)**

		2008	2009	2010	2011
PUBLIC SECTOR					
France	ANRS	3,429,400	1,820,100	418,900	203,100
	Institut Pasteur	0	0	0	384,900
Canada	CHVI	0	0	0	3,956,400
	CIDA	0	0	1,250,000	570,600
	CIHR	0	0	0	634,000
US	CDC	1,716,900	488,100	0	0
	NIH	8,533,600	44,101,000	55,348,000	34,012,000
	USAID	0	0	1,600,000	2,225,000
Sweden	SIDA	128,000	263,299	1,127,800	102,800
UK	MRC	374,600	448,100	0	448,000
EDCTP		3,393,500	3,393,500	0	0
Total public		**17,576,000**	**50,514,000**	**59,744,700**	**42,613,700**
PHILANTHROPIC SECTOR					
Total philanthropic		**3,641,800**	**904,100**	**0**	**500,700**
Total global investment		**21,217,800**	**51,418,000**	**59,744,700**	**43,114,300**

* Numbers may be rounded.

Figure 14 **Funding for Female Condom R&D in 2010 and 2011**



In 2012, results from a cost-effectiveness study in Washington, DC served to increase interest in female condoms. Conducted by the Johns Hopkins Bloomberg School of Public Health, the study found a cost savings of roughly US$20 per person when female condoms were distributed to women in neighborhoods with high rates of HIV. The study was part of the "DC's Doin' It!" campaign, a collaboration of the DC Department of Public Health, the Female Health Company, CVS/Caremark and the Washington AIDS Partnership. The study authors concluded that provision and promotion of female condoms was a highly productive use of public health investment in DC.

2.5 INVESTMENTS BY TRIAL PARTICIPANTS IN HIV PREVENTION R&D

As of December 2011, there were 126,589 participants in HIV prevention research trials. These trials were predominantly based in countries and communities with high HIV burden, so as to ensure that new tools are more immediately tested in, and therefore appropriate for, the populations that most need them. Trial participants may be the first to receive a product that proves safe and effective, but they also take on the risks inherent in biomedical research. Without their generous contribution to the field, research could not move forward. Participants from South Africa, Uganda and the US accounted for the majority of trial participants.

Trials testing HIV prevention interventions in areas of high HIV burden provide an invaluable contribution to the HIV prevention field. While the trials benefit these countries and communities through provision of health care and other services, and by offering potential HIV prevention options, they require extraordinary time and commitment from the host countries and participants. While not quantifiable, the contribution of participants in clinical trials is the most essential element of HIV prevention R&D and goes beyond any financial investment.

3.0 Discussion

Measureable progress is being made toward ending the epidemic. The number of new infections dropped by 15 percent between 2001 and 2010, bringing the number down 21 percent from the peak of the epidemic in 1997. HIV incidence has fallen in 33 countries, 22 of them in sub-Saharan Africa, the region most affected by AIDS. The number of people living with HIV/AIDS and accessing ARV therapy rose to 6.6 million in 2010, and the number of low- and middle-income countries providing universal access to treatment continues to rise. The number of new HIV infections among children is decreasing, and the rate of vertical transmission of HIV from mother to child has dropped.[40] *The world has maintained its commitment to combating the epidemic, and there is widespread understanding of the need to sustain funding for HIV programs and research.*

Global leaders are taking charge. Former US President George W. Bush initiated PEPFAR in 2003, a program that continues to be a world leader in providing HIV prevention and AIDS treatment and care services. In 2011, US President Barack Obama committed to expanding access to treatment globally, continuing research for an HIV vaccine and microbicides and utilizing the combined impact of male circumcision, treatment as prevention, prevention of vertical transmission and other effective existing strategies. UK Prime Minister David Cameron committed to providing access to treatment in sub-Saharan Africa and to prevention of vertical transmission. Brazilian President Luiz Inácio Lula da Silva was recognized by UNAIDS for building partnerships and encouraging South-South cooperation in his contribution the AIDS response. In December 2011, China pledged to fill its HIV treatment gap, and in July 2011 India announced that it would work to ensure availability of generic ARVs and passed guidelines on new health insurance coverage for HIV patients. In October 2011, the Russian Federation convened a high-level forum on Millennium Development Goal 6, focused specifically on universal access to treatment for HIV/AIDS. Public policy shifts in South Africa were notable in recent years, and included a 22 percent increase in public spending on AIDS, support for microbicide research and the launch of an HIV testing campaign.

The year was not just one of global commitment to expanding access to existing tools, but also one of promising scientific results across a range of new prevention options.

- ***Treatment as prevention*** saw positive results in May, when the US-funded HPTN 052 trial established that ART initiated in HIV-positive individuals at an early stage and maintaining adherence substantially protected their HIV-negative partners from acquiring HIV infection, with a 96 percent reduction in risk of HIV transmission.
- ***Pre-exposure prophylaxis*** had similarly positive news in July, with results from the Partners PrEP and TDF2 trials showing the effectiveness of PrEP for heterosexual couples.
- ***Microbicide*** trials are underway that could provide the results needed to license and deliver a marketable product. In October, the FACTS 001 trial began testing the safety and effectiveness of 1% tenofovir gel in preventing HIV and HSV-2 in women. The results of FACTS 001 will be crucial to our understanding of the effectiveness of 1% tenofovir gel.

Additionally, two Phase III trials are underway evaluating the safety and effectiveness of dapivirine-based vaginal rings. The rings could prove an effective long-term option, offering women protection for a month, two months or longer—and may eventually combine an ARV with a contraceptive hormone to provide women with dual protection. Yet 2011 also included some disappointing news for the field. In November the VOICE trial discontinued its 1% tenofovir gel arm. The field continues to forge ahead with the FACTS trial, and has learned from, and moved forward with, new innovative candidates.

- ***HIV vaccine*** research moved forward in 2011, with a new finding from the correlates analysis of RV144 researchers, as well as the important new discoveries regarding broadly neutralizing antibodies, including their structures, evolution and interactions with the virus itself. These discoveries have given the field useful insights into new strategies toward powerful new vaccine candidates.

The advancements made in 2011 provided scientific hope that the end of the epidemic might truly be in sight. Despite a growing optimism based on exciting discoveries, researchers continued to face the challenge of delivering results while their budgets are under increasing pressure. Resource tracking data for HIV prevention R&D supports the following conclusions:

- ***Resources need to be directed to capitalize on areas of progress.*** Last year, the Working Group report emphasized the need to plan for success as was demonstrated in the wake of promising results from the RV144, CAPRISA 004, iPrEx and HPTN 052 trials. This year, results from Partners PrEP and TDF2 brought new promise but further underscored the importance of preparing for success. Funding for planned clinical trials that build upon recent results is not guaranteed. The prevention field continues to need funding structures that can adapt quickly and are sufficiently generous to allow for rapid expansion in the event of positive outcomes.
- ***Resources need to be directed to capitalize on areas of promise.*** The HIV prevention field needs to explore next-generation approaches. There are a number of next-stage research strategies—involving vaccines, microbicides, PrEP and adult male circumcision—that need to be pursued just as urgently as those that follow up on RV144, CAPRISA and iPrEX. This is particularly so in microbicide development, as the decline in funding since 2009 appears to have come principally at the expense of preclinical research. Advancement of, and funding for, the HIV prevention pipeline ten years ago is what has made it possible to achieve the many successes noted in this report.
- ***Implementation research has to become a significant focus of R&D.*** After a number of years without new additions, the HIV prevention toolbox has started to fill up. We now have clinically validated HIV prevention approaches using female condoms, voluntary medical male circumcision (now including nonsurgical circumcision), treatment as prevention and PrEP. For answers to core questions around the potential and real effectiveness of new prevention technologies and tools, there will have to be much more substantial investment by funders in theoretical, qualitative and quantitative behavioral and social research. Further, such investment will need to be driven by strategies that define and prioritize core questions, as well as commitments to explicit collaborations that aim to answer these questions.

A small group of countries and philanthropies have embraced this important work. Canada, the EC, France and the US have all funded implementation research, as have a number of foundations. It will be important for additional funders and countries to step forward, particularly from the most affected areas, to support this work. Only through global participation in implementation research will trial results be tested and adapted to different settings and for maximum effectiveness. Large funding agencies currently funding and managing HIV programs need to be engaged with new HIV prevention options currently in the R&D stage. As these new options are added to the menu of existing prevention tools, discussions need to start on whether, when and how these tools should be rolled out in specific countries and populations.

- ***Funding structures need to accommodate the costs of important late-stage research.*** The high cost of HIV prevention trials, which can exceed US$100 million, continues to be a concern for funders and researchers. New funding structures outside of existing R&D funding sources need to be developed to address these costs.
- ***Funding is highly concentrated among few funders.*** The HIV prevention field continues to be vulnerable to funding shifts among the small group of investors that provide the majority of support, including the US government and the BMGF. Recent deficit control efforts in the US threaten to decrease NIH funding in 2013 and beyond. Some European funders increased their investments in 2011, but due to the economic downturn, changes in government administrations and structures and debt and austerity programs, overall European funding lags more than 40 percent beneath its peak a few years ago.
- ***The expertise of the commercial sector is now more fully engaged.*** The commercial sector has become increasingly involved in HIV prevention research. RV144, CAPRISA, iPrEx and HPTN 052 each involved collaboration and support from industry partners in developing the vaccines and drugs used in those trials. Upcoming trials of the TDF gel and the dapivirine ring, research into broadly neutralizing antibodies and follow-on trials to RV144 each involved critical contributions of product or IP for those trials. While these contributions do not include funding for preclinical and clinical trial expenses, there are often agreements with industry to ensure broader access or low-cost development should trials be successful.
- ***There is increased responsibility within the field.*** Many PDPs and product developers have become more focused and responsible, aligning their efforts with the field as a whole. They have improved efficiency, which is especially important during a time of limited resources, placed a premium on partnerships and increased collaboration to move research forward in the most cost-efficient way (e.g., by leveraging centers of excellence maximizing available resources and working to deliver value for money), demonstrating that funds invested have real benefit both in terms of the end goal and tangible interim goals.

Box 4 Conclusions

Resource tracking data support the following conclusions, which address change, continuing challenges, and needs for HIV R&D going forward:

- Resources need to be directed to capitalize on areas of progress;
- Resources need to be directed to capitalize in on areas of promise;
- Implementation research has to become a significant focus of R&D;
- Funding structures need to accommodate the costs of important late-stage research;
- Funding is highly concentrated among few funders;
- The expertise of the commercial sector is now more fully engaged; and,
- There is increased responsibility within the field.

Global commitment to HIV prevention research has brought us to the point where the HIV prevention research field has made multiple tectonic advances in the fight against AIDS, but realizing the full potential of those advances will demand sustaining, and perhaps even increasing, funding levels in the years ahead. ARV-based prevention options, HIV vaccines and microbicides will each require further trials and time to complete their development and ensure that they are made available to those who need them most. To sustain the momentum achieved so far, HIV prevention advocates, researchers, policy makers, developing countries, the private-sector and donors will need to make an intelligent, realistic, strategic, integrated case for the long-term need for sustained and flexible funding for each prevention option. If that case is not well made and a lack of focused and flexible funding persists, the debut of new HIV prevention tools will be delayed in the short term and, in the longer term, continue to leave millions of people at risk of HIV infection. The best case is that new HIV prevention tools will become available and turn the 2011 rallying cry of "ending AIDS" into reality.

Appendix

Methodology

This report was prepared by Emily Donaldson (AVAC) with contributions from Kevin Fisher (AVAC), Michael Green (IPM), Thomas Harmon (IAVI), Polly Harrison (AVAC), Robert Lande (IPM) and Mitchell Warren (AVAC) of the HIV Vaccines and Microbicides Resource Tracking Working Group (the Working Group). The report is authored by AVAC with other members of the Working Group—IAVI, IPM and UNAIDS—providing editorial guidance and reviewing drafts of the report. A systematic approach to data collection and collation has been used since 2004. These methods were employed to generate the estimates of funding for R&D presented in this report. A detailed explanation of the methodology can be found on the Working Group website (*www.hivresource tracking.org*). The two sets of categories used to describe different R&D activities—one for HIV vaccines and one for HIV microbicides—were derived from those developed by the US NIH and are shown in the following tables.

Table 11 **Categories Used to Classify Preventive HIV Vaccine R&D Funding**

Basic research	Studies to increase scientific knowledge through research on protective immune responses and host defenses against HIV.
Preclinical research	R&D efforts directed at improving preventive HIV vaccine design. This includes vaccine design, development and animal testing.
Clinical trials	Support for Phase I, II and III trials, testing the safety, immunogenicity and efficacy of suitable preventive HIV vaccine candidates or concepts in domestic and international settings (including the costs of producing candidate product lots for clinical trials).
Cohort & site development	Support to develop strategies, infrastructure and collaboration with researchers, communities, government agencies, regulatory agencies, NGOs and industry that are necessary to identifying trial sites, building capacity, ensuring adequate performance of trials and addressing the prevention needs of at-risk populations in trial communities.
Advocacy & policy development	Efforts directed at educating, mobilizing public and political support for preventive HIV vaccines, and addressing potential regulatory, financial, infrastructure and/or political barriers to their rapid development and use.

Table 12 **Categories Used to Classify Microbicide R&D Funding**

Basic mechanisms of mucosal transmission	Elucidate basic mechanisms of HIV transmission at mucosal/epithelial surfaces that are important for microbicide research and development in diverse populations.
Discovery, development & preclinical testing	R&D efforts directed at the discovery, development and preclinical evaluation of topical microbicides, alone and/or in combination.
Formulations & modes of 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.
Clinical trials	Conduct clinical studies of candidate microbicides to assess safety, acceptability and effectiveness in reducing sexual transmission of HIV in diverse populations in domestic and international settings.
Microbicide behavioral & social science research	Conduct basic and applied behavioral and social science research to inform and optimize microbicide development, testing, acceptability and use, domestically and internationally.
Microbicide research infrastructure	Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide research, domestically and internationally.
Policy & advocacy	Efforts directed at educating and mobilizing public and political support for microbicides, and at addressing potential regulatory, financial, infrastructure and/or political barriers to their rapid development and use.

List of Acronyms

AECID	Spanish Agency for International Development Cooperation
amfAR	American Foundation for AIDS Research
ANRS	National Agency for Research on AIDS and Viral Hepatitis, France
ARC	Australian Research Council
ARRA	American Recovery and Reinvestment Act
ART	Anti-retroviral therapy
ARV	Anti-retroviral
BMGF	Bill & Melinda Gates Foundation
BMS	Bristol Myers Squibb
BRICS	Brazil, Russia, India, China and South Africa
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CDC	US Centers for Disease Control and Prevention
CHAARM	Combined Highly Active Anti-Retroviral Microbicides Project
CHVI	Canadian HIV Vaccine Initiative
CIDA	Canadian International Development Agency
CIHR	Canadian Institutes of Health Research
DAIDA	Danish International Development Agency
DFID	Department for International Development
DOH	Department of Health, South Africa
DST	Department of Science and Technology, South Africa
EC	European Commission
EDCTP	European and Developing Countries Clinical Trials Partnership
EGPAF	Elizabeth Glazer Pediatric AIDS Fund
ESF	Estonia Science Foundation
FACTS	Follow-on African Consortium for Tenofovir Studies
FDA	US Food and Drug Administration
FHI	Family Health International, US
GSK	GlaxoSmithKline
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IRMA	International Rectal Microbicides Advocates
J&J	Johnson & Johnson
MHRP	United States Military HIV Research Program
MSF	Médecins Sans Frontières
MRC	Medical Research Council
MTN	Microbicide Trials Network
NAC	Neutralizing Antibody Consortium
NCAIDS	National Center for AIDS/STD Control and Prevention, China
NHMRC	Australian National Health & Medical Research Council
NIAID	US National Institute of Allergy and Infectious Diseases
NIH	US National Institutes of Health
NIHR	UK National Institutes of Health Research
OFID	OPEC Fund for International Development
PDP	Product Development Partnership
PEPFAR	US President's Emergency Plan for AIDS Relief
SBIR	Small Business Innovation Research
SIDA	Swedish Agency for International Cooperation Development
TDF	Tenofovir
TDF/FTC	Tenofovir/Emtricitabine
UK	United Kingdom
UK MRC	United Kingdom Medical Research Council
US	United States
USAID	US Agency for International Development
VRC	Vaccine Research Center
WHO	World Health Organization

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Endnotes

[1] UNAIDS. "Progress Report on the Global Response to the HIV/AIDS Epidemic, 2003: Follow-up to the 2001 United Nations General Assembly Special Session on HIV/AIDS." Geneva (2003).

[2] HIV Vaccines and Microbicides Resource Tracking Working Group. "Tracking Funding for Preventive HIV Vaccine Research and Development: Estimates of Annual Investments and Expenditures 2000 to 2005." (2006).

[3] N. Padian et al. "HIV prevention transformed: the new prevention research agenda." The Lancet 378: 269–78(2011).

[4] M. Chan. "The increasing importance of global health: Success, shocks, surprises, and moral vindication." Address at the Chatham House (13 June 2011).

[5] G. Ramjee. "Issues surrounding the implementation of multiple product development partnership clinical trials in developing countries." Global Forum for Health Research (2008).

[6] The Working Group has only been tracking treatment as prevention since 2010; reporting from funders was more thorough in 2011 than in 2010. Assumptions regarding investments over time should be made with this awareness.

[7] The decline in 2011 funding for vaccines and microbicides may reflect an actual decline or may be a "perceived decline", reflecting the cyclical nature of clinical trials and the disbursement timing of multi-year grants. Annual fluctuations in funding can often be driven by the timelines of large-scale clinical trials, which require large investments during concentrated periods of time.

[8] See Table 2, Investment Snapshot for 2011.

[9] M. Cohen et al. "Prevention of HIV-1 Infection with Early Antiretroviral Therapy." New England Journal of Medicine (11 August 2011).

[10] M.C. Thigpen et al. "Daily oral antiretroviral use for the prevention of HIV infection in heterosexually active young adults in Botswana: Results from the TDF2 study." 6th IAS Conference on HIV Pathogenesis and Treatment (2011).

[11] J. Baeten et al. "Antiretroviral pre-exposure prophylaxis for HIV-1 prevention among heterosexual African men and women: The Partners PrEP study." 6th IAS Conference on HIV Pathogenesis and Treatment (2011).

[12] R. Grant et al. "Pre-exposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men." New England Journal of Medicine (30 December 2010).

[13] B.F. Haynes. "Case control study of the RV144 trial for immune correlates: The analysis and way forward." AIDS Vaccine Conference. New England Journal of Medicine (2011).

[14] Policy Cures. "Neglected Disease Research & Development: Is innovation under threat?" G-FINDER (December 2011).

[15] See Appendix for discussion of the approach used.

[16] J.D. Auerbach. "Optimizing social science knowledge in the fight against HIV/AIDS." 6th National Meeting of the CFAR SBSRN. Chapel Hill, NC, USA (1 March 2012).

[17] UNAIDS. "Combination HIV Prevention: Tailoring and Coordinating Biomedical, Behavioural and Structural Strategies to Reduce New HIV Infections—Discussion Paper." JC2007 (English original, September 2010).

[18] Commercial estimates are not available prior to 2004. Commercial funding figures included here are based on reporting and, in a number of cases, estimates are based on a review of HIV vaccine programs at companies.

[19] The original protocol was amended to include HIV infection as a primary end point after nonhuman primate studies showed that a simian immunodeficiency virus (SIV) vaccine regimen similar to the HIV vaccine regimen used in HVTN 505 had a protective effect when given to macaques.

[20] Figures are inclusive of all public agencies providing funding in each country.

[21] The members of the G8 are: Canada, the EU, France, Germany, Italy, Japan, the UK and the US.

[22] The members of the G20 are: Argentina, Australia, Brazil, Canada, China, the EU, France, Germany, Italy, India, Indonesia, Japan, Korea, Mexico, Russia, South Africa, Saudi Arabia, Turkey, the UK and the US.

[23] See appendix for list of acronyms.

[24] Commercial funding figures are estimates based upon a review of HIV vaccine programs at each company. While in recent years, fewer companies have been willing to provide actual figures for their programs, in 2011 more companies either reported exact investment figures or reported higher ranges of spending than in previous years. Where companies decline to report financial information, the Working Group develops estimates are based on interviews with company staff and third parties, and on publicly filed documents. The amounts described here are estimated commercial investments of companies' own funding and do not include the financial support that many of these companies receive from the public sector and through public-private partnerships.

[25] The mission of the AVIP is to develop novel preventive and therapeutic vaccines to be tested in Phase I trials in Europe and that will be suitable for future testing in Phase II and III trials in developing countries. The AVIP also aims to foster training, technology transfer and community involvement among the EU and developing countries.

[26] UNIDO. "Italy funds UNIDO project aimed at helping South Africa locally produce HIV/AIDS vaccine." (January 2012).

[27] With the exception of "policy and advocacy", these are the categories used by the NIH to classify allocations for HIV vaccine research. Because not all data from funders can be parsed according to these five categories, these percentages were estimated based on an US$792 million subset that allowed for determining allocations. These expenditure estimates do not include therapeutic vaccines.

[28] The change from 2010 to 2011 may reflect more robust reporting in 2011. The Working Group has had difficulty obtaining complete data on commercial investment, so changes from year to year may reflect differences in reporting.

[29] In 2011, GeoVax was the only company to report its investment, independent of NIH and other public-sector grants. Some biotechnology companies have had success with their therapeutic HIV vaccine trials.

[30] See Appendix for list of acronyms.

[31] See p. 21 for information regarding rectal microbicide R&D funding.

[32] Quantifying in-kind contributions, technical assistance, IP transfers and other non-direct financial contributions is challenging for pharmaceutical companies; thus, it is often not possible for companies to report this information to the Working Group.

[33] With the exception of "policy and advocacy", these are the categories used by the NIH to classify allocations for microbicide research. Further information on these categories can be found in the Appendix.

[34] The Working Group tracks investment in R&D and operations research for adult male circumcision; however, the Working Group but does not track investment in rollout and scale-up of the procedure. "Operations research" aims to develop solutions to current operational problems of specific health programs or specific service delivery components of the health system. "Implementation research" aims to develop strategies for available or new health interventions in order to improve access to, and the use of, these interventions by the populations in need. (Definitions from J.H.F. Remme et al. "Defining Research to Improve Health Systems." PLoS Med 7(11)(16 November 2010).]

[35] B. Auvert B et al. "Effect of the Orange Farm (South Africa) male circumcision rollout (ANRS-12126) on the spread of HIV." 6th IAS Conference on HIV Pathogenesis, Treatment, and Prevention. (July 2011).

[36] Acumen Fund. "Circ MedTech: Non-surgical male circumcision to combat HIV/AIDS." Health Portfolio. (2011).

[37] The White House, Office of the Press Secretary. "Fact Sheet: The Beginning of the End of AIDS." (1 December 2011).

[38] D. Donnell et al. "Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: A prospective cohort analysis." The Lancet (2010).

[39] M.S. Cohen et al. "Prevention of HIV-1 infection with early antiretroviral therapy." New England Journal of Medicine (2011).

[40] UNAIDS Data Tables (2011).

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HIV Vaccines & Microbicides Resource Tracking Working Group

AVAC
Global Advocacy for HIV Prevention
www.avac.org

IAVI
International AIDS Vaccine Initiative
www.iavi.org

IPM
International Partnership for Microbicides
www.ipmglobal.org

UNAIDS
Joint United Nations Programme on HIV/AIDS
www.unaids.org

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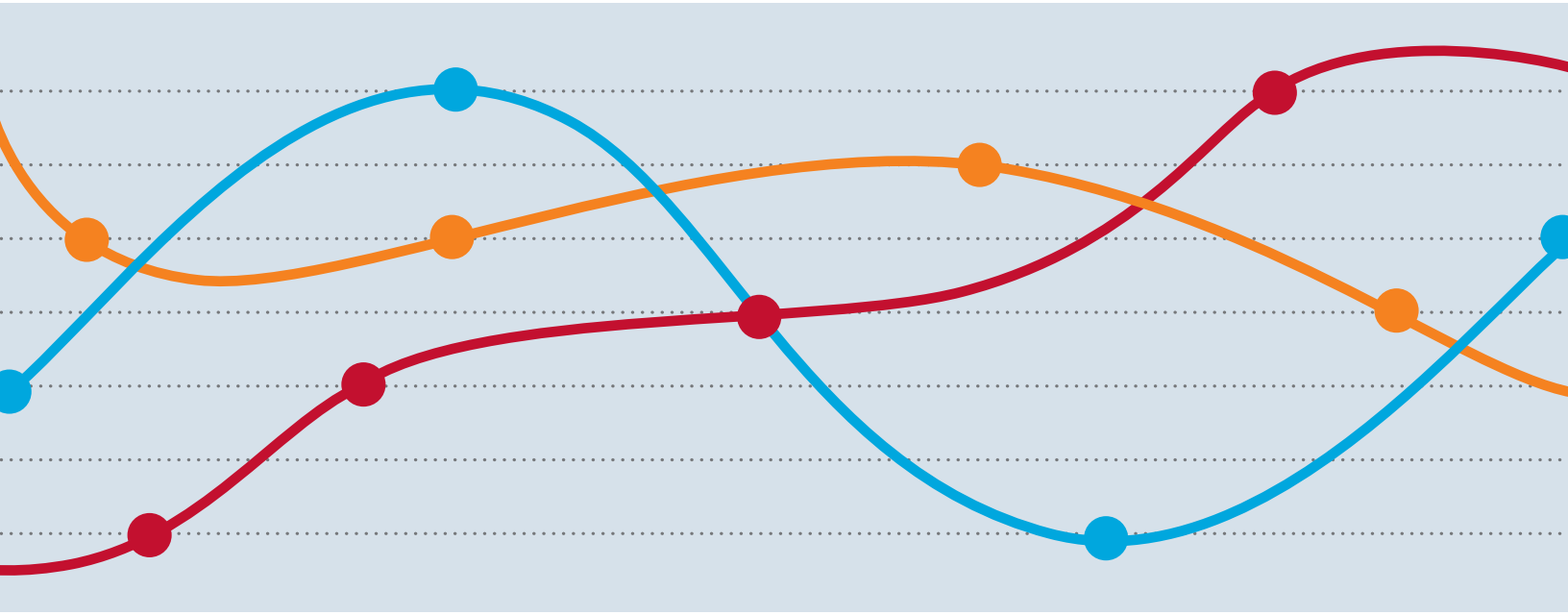

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