HIV VACCINES
& MICROBICIDES
RESOURCE TRACKING
WORKING GROUP

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Capitalizing on Scientific Progress:
Investment in HIV Prevention R&D in 2010

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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1.0 Introduction

2010 has been a year of retrospection, a time for looking back over the 30 years since the first published report of the mysterious illness that would come to be known as AIDS. As sobering as this anniversary has been, it has also been a time for some optimism and calls to end the epidemic. These calls may not be simply wishful thinking, fueled as they have been by promising research results over the past two years in vaccines, microbicides, pre-exposure prophylaxis using antiretrovirals (PrEP), and antiretroviral treatment as prevention—results that have energized the entire HIV prevention field.

The first good news came at the end of 2009, when researchers in the RV 144 Thai vaccine trial reported that a vaccine combination had reduced risk of infection by 31 percent—the first clinical evidence that a preventive AIDS vaccine would be possible. Then, in July 2010, the CAPRISA 004 trial team announced its findings–that use of 1% tenofovir (TDF, also known as Viread®) vaginal gel reduced women's risk of HIV infection by 39 percent—providing the first proof that a microbicide would be possible. This news was followed in November 2010 by the announcement from the iPrEx trial team that daily oral tenofovir/emtricitabine (TDF/FTC, also known as Truvada®) had reduced risk of HIV infection by an estimated 44 percent overall in men who have sex with men (MSM) and transgender women, and proved for the first time that HIV prevention using PrEP would be possible. And finally, in early 2011, the HIV Prevention Trials Network (HPTN) 052 trial established that use of antiretroviral therapy (ART) by HIV-positive individuals reduced transmission to their partners

Investment Snapshot for 2010

HIV Prevention Option	Amount	Change from 2009	Headlines
Preventive Vaccines	US$859 million	-US$9 m (-1%)	• Lower U.S. public-sector investment; US stimulus package expires in 2011 • Lower European investment offset by higher philanthropic investment • Long-term nature of vaccine research will require sustained investments
Microbicides	US$247 million	+US$11 m (+ 5%)	• Higher U.S. public-sector investment • Support needed for follow-up licensure trials after CAPRISA success
Pre-exposure Prophylaxis	US$58.3 million	+US$5.9 m (+11%)	• 44% efficacy seen in iPrEx trial • Seven ongoing trials
Adult Male Circumcision	US$21.7 million	+US$12 m (+124%)	• Additional investments by the Bill & Melinda Gates Foundation
Treatment as Prevention	US$19.6 million	*First year of reporting*	• Potentially transformative impact of HPTN 052 results in 2011
All HIV Prevention R&D	US$1.27 billion	+US$40 m (+3.1%)	• Increased investments in some prevention options, new inclusion of treatment as prevention, and improved reporting

by 96%, proving—another first—that treatment could also act as prevention.

However, the funding story for HIV prevention research in 2010 was mixed. Funders, as a whole, can be commended for continuing their support for HIV prevention research in the light of budget constraints triggered by the onset of the global recession in 2008. In 2010, funders invested a total of US$1.19 billion in research and development (R&D) for four key prevention options: preventive HIV vaccines, microbicides, pre-exposure prophylaxis using ARVs, and operations research related to male circumcision. Even in the face of global recession, this investment approached the previous historical high of US$1.23 billion reached in 2007 for these four research areas.

Yet all of the promising results that have emerged over the past two years will require additional investment, research, and development before they can be realized as effective, accessible HIV prevention options. The ultimate costs of what is needed to in effect "close the deal" on vaccines, microbicides, PrEP, and other prevention technologies, are unknown. Thus, although funding stability is especially welcome in challenging economic times, it is nevertheless unclear whether current funding levels will be sufficient to address future R&D needs, given the opportunities for real progress that have appeared over the past two years.

1.1 Executive Summary

HIV Preventive Vaccines

Global preventive HIV vaccine R&D investment totaled US$859 million in 2010, with the public sector providing US$726 million (85%), the philanthropic sector providing US$103 million (12%), the commercial sector contributing US$30 million (3%). This total represents a decline of US$9 million (1%) from 2009 and a US$102 million (11%) decrease from 2007, when HIV vaccine R&D funding peaked at US$961 million. [Table 1]. Investment by European governments was US$61 million in 2010, down by US$4 million (6%) from the previous year, and down 26% from a US$82 million peak in 2006. Philanthrophic investments in HIV vaccine R&D saw an upswing of 12% from US$92 million in 2009 to US $103 million in 2010.

Microbicides

Total global investment in microbicide R&D was US$247 million in 2010, with the public sector providing US$230 million (93%), the philanthropic sector providing US$16 million (6%), and the commercial sector contributing US$1 million (<1%). [Table 5] Four European public-sector funders decreased their contributions, resulting in a US$4 million (9%) reduction in European contributions from 2009. However, the US government increased its funding by US$9 million (5%); the philanthropic sector led by the Bill & Melinda Gates Foundation (BMGF) increased its funding by US$9 million; and China, the European Commission (EC), and South Africa increased their 2010 funding, amounting to an overall increase of US$11 million (5%) in microbicide R&D funding from 2009.

Other Prevention Options

Public and philanthropic funders contributed US$162 million in 2010 to support HIV prevention R&D activities other than HIV vaccines or microbicides. These investments were directed toward one or more of the following five HIV prevention options: male circumcision, reducing vertical transmission at birth and during breast-feeding, treatment as prevention, female condom R&D, and PrEP. Of that total, public-sector sources provided US$120 million (75%) and the philanthropic sector provided US$41 million (25%), whereas the commercial sector provided in-kind assistance in the form

of antiretroviral drugs (ARVs) to be tested in preclinical and clinical research, and R&D directed at the next-generation female condom.

Key Conclusions

This year's resource tracking and analysis found that funders as a whole had maintained support for HIV prevention research in both 2009 and 2010, an encouraging finding given global economic challenges and corresponding reductions in public-sector funding in many countries. Yet funders continue to confront budgetary constraints, and some funders have reduced or eliminated their HIV prevention research programs altogether. Thus, care must be taken that the stability seen over this period not lead to a false sense of security about future funding trends. This fragility is especially concerning just as the HIV prevention field is poised to pursue new scientific directions and capitalize on the scientific opportunities generated by recent promising research results.

The Structure of Funding

Funder Concentration. Funding for HIV prevention remains highly concentrated among relatively few funders, which contributes to the potential for more fragile support going forward. The public-sector funding stability seen in 2010 resulted primarily from increased or sustained funding by the US and fewer European countries than hitherto, and the philanthropic organizations now comprise relatively few, though generous, contributors. The sustained public-sector participation of the BRICS (Brazil, Russia, India, China, and South Africa) countries and Thailand among HIV prevention research funders is therefore critical to broadening the prevention research funding base and expanding cross-country collaborations. And, since all funders have to deal with more constrained budgets, a broader, more varied spectrum of funders will be essential to ensuring that funding levels remain both stable and adequate.

Commercial Engagement. As for the commercial sector, while there is increasing and vibrant participation among small and medium-size biotechnology companies, their participation was at lower levels of investment or through in-kind contributions and the engagement of large pharmaceutical companies has not increased. That engagement, however, remains instrumental as a source of large-scale product development expertise and capacity that are currently a significant deficit in HIV prevention.

Capacity to Capitalize. The scientific successes of the past two years demonstrate the need to direct resources so as to convert promise into progress with all deliberate speed. Funding structures are required that are flexible, agile, and generous enough to adapt rapidly to new opportunities, both in earlier translational research and late-stage clinical research. With positive clinical evidence and new scientific knowledge now available in several important areas, the lack of long-term funding particularly threatens to impede progress, most critically when the next essential step is a late-stage confirmatory trial.

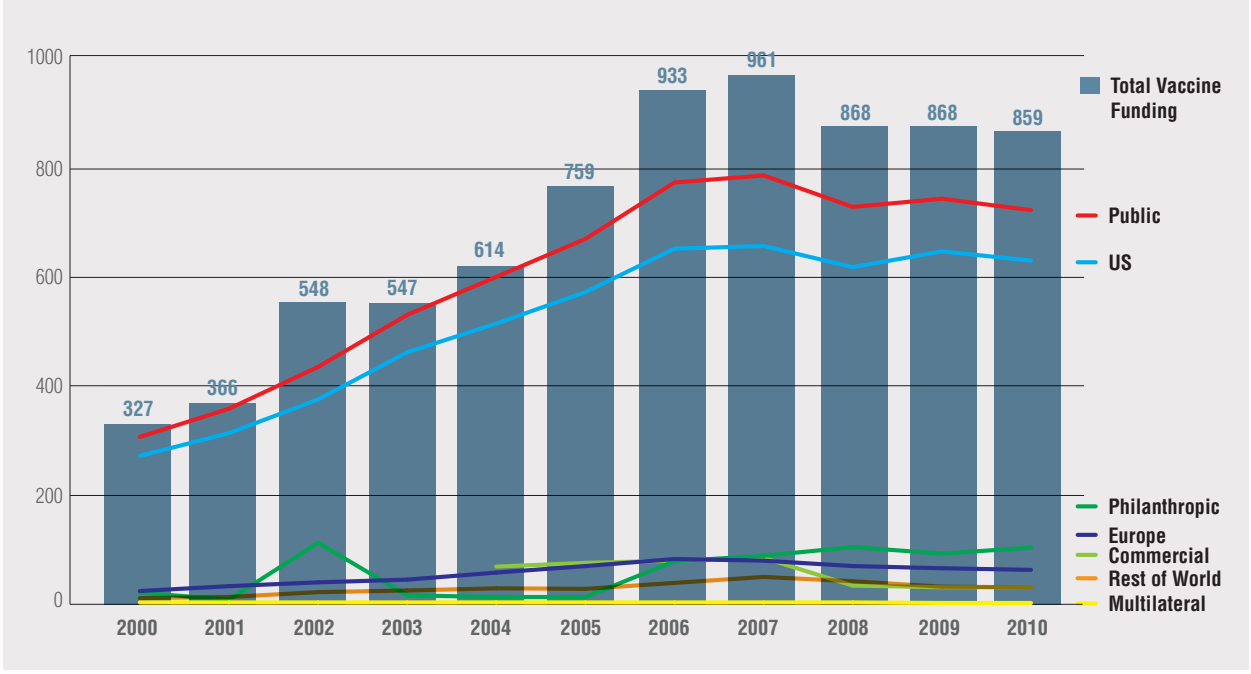
Research Emphases. In general, the HIV prevention field has tended to view unanswered scientific questions, rather than funding, as the primary roadblocks to progress. While scientific questions still predominate as the primary challenges for HIV vaccine R&D, for other fields, notably microbicides and PrEP, scarcity of funding for clinical and implementation research is coming to be the crucial issue. Yet HIV prevention will still require basic research. Recent advances did not emerge from a vacuum but from the early discovery and preclinical research that takes place largely in academic settings and PDPs, and is primarily funded by the public sector. Such research could be at risk if forced to compete with the new wave of follow-on trials, at the same time that it will be need to build on their outcomes or fill the void that might ensue should they fail to produce the results around which there is now so much hope.

2.0 HIV Prevention R&D

2.1 Global Investments in HIV Vaccine R&D

In 2010, total global investment in HIV vaccine R&D was US$859 million, a US$9 million (1%) decrease from the previous year. As in past years, public-sector funders provided the largest part of the investment, followed by the philanthropic sector and the commercial sector.

Figure 1: HIV Vaccine Funding for 2000–2010 (US$ millions)



* Commercial estimates not available prior to 2004.

Table 1. Annual Investments in HIV Vaccine R&D 2006–2010 (US$ millions)					
	2006	2007	2008	2009	2010
PUBLIC SECTOR					
US	654	659	620	649	632
Europe	82	79	69	65	61
Other	38	49	41	31	32
Multilaterals	2	2	1	1	1
Total public	776	789	731	746	726
PHILANTHROPIC SECTOR					
Total philanthropic	78	88	104	92	103
NON-COMMERCIAL SECTOR					
Total non-commercial	854	877	835	838	829
COMMERCIAL SECTOR					
Total commercial	79	84	33	30	30
Total global investment	**933**	**961**	**868**	**868**	**859**

2.1.1 Public Investments in HIV Vaccine R&D

Public agencies and institutions dominate R&D funding for HIV vaccines. In 2010, public agencies in the United States accounted for 74% of HIV vaccine R&D funding. Public agencies in 13 other countries invested more than US$1 million each. The European Commission and China were the second- and third-largest contributors investing US$18.5 million and US$18.3 million, respectively.[1] Although the US had the largest decline in funding from 2009 to 2010 in dollar terms (US$17 million), the percentage of decline was actually small (3%).

2010 was the second and final year of stimulus funds from the American Recovery and Reinvestment Act (ARRA), which accounted for US$26.7 million of the National Institutes of Health (NIH) investment in HIV vaccine R&D in 2010. Total US contributions to HIV vaccine R&D in 2010 were 4% higher than they otherwise would have been without ARRA. Even though HIV vaccine research saw only a 1% drop overall in 2010, the vaccine field could be facing larger decreases when ARRA funding ends in 2011. Additionally, the current US government budget debates could affect funding for the NIH and United States Agency for International Development (USAID) funding in 2012, which given the primacy of those funders could have magnified impacts on HIV vaccine funding.

[1] The Working Group figure for investment by the Government of China is based on direct reporting and third-party estimates.

All members of the G8[2] and 13 members of the G20[3] have supported HIV prevention research in the past two years, with China, the European Union, France, Russia, the United Kingdom, and the United States having contributed more than US$5 million a year to support either vaccines or microbicides. Support by Canada, China and France increased in 2010.

Table 2. Top HIV Vaccine Funders for 2009 and 2010 (US$ millions)*

2009 Rank	Funder	Amount	2010 Rank	Funder	Amount
1	NIH	596.0	1	NIH	561.6
2	BMGF	76.8	2	BMGF	80.9
3	USAID	28.7	3	MHRP	41.6
4	MHRP	24.3	4	USAID	28.7
5	EC	20.1	5	EC	18.4
6	DFID	16.3	6	China (est.)	18.3
7	China	14.4	7	DfID	16.6
8	Ragon Institute	10.0	8	Ragon Institute	10.0
9	Russia	10.0	9	ANRS	6.6
10	Netherlands	6.6	10	Wellcome Trust	5.1
11	Spain	5.6	11	UK MRC	5.0
12	Sweden	3.6	12	Netherlands MFA	4.8
13	Norway	3.3	13	CIDA	3.8
14	Canada	3.2	14	Spain & Basque Community	3.3
15	ANRS	2.3	15	Norwegian AID	2.5

* Excludes commercial funders.

As encouraging as the RV144 results were for the HIV vaccine field, there remain significant scientific questions many of which were raised but not answered by the RV144 results. In many ways the path forward for HIV vaccines is less scientifically clear than it is for other prevention research in areas such as microbicides, PrEP and treatment as prevention. As of this report's publication, there are 30 HIV vaccine clinical trials underway.[4] Most HIV vaccine research efforts are at least partially supported through public-sector funding. Areas of research that have shown the potential to move the field forward in the foreseeable future include:

RV144 follow-up. A number of actors from across sectors, most notably the NIH, the U.S. Military HIV Research Program (MHRP), the BMGF and private-sector partners receiving US government funding, have been performing studies to attempt to identify correlates of immunity from the RV144 study, with results expected to be released in September 2011. Additionally, consideration is being given to up to three efficacy trials involving candidates utilizing a similar prime-boost mechanism to that used in RV 144 which would take place in South Africa and Thailand. Candidate vaccines for these

[2] The members of the G8 are Canada, European Union, France, Germany, Italy, Japan, United Kingdom, and US.
[3] The members of the G20 are Argentina, Australia, Brazil, Canada, China, European Union, France, Germany, Italy, India, Indonesia, Japan, Korea, Mexico, Russia, South Africa, Saudi Arabia, Turkey, United Kingdom, and US.
[4] IAVI Report *AIDS Vaccine Trials Database* (2011) accessed at http://www.iavireport.org/trials-db/Pages/default.aspx.

Public-sector Funding in Context

The recession that began in 2008 has led to growing public-sector budget deficits and in turn to a political movement in a number of donor countries to limit public-sector spending. Since 2007, overall European funding for HIV vaccines has declined by 23%, and has declined 32% for microbicides. Countries that provided early support have reduced their investment. Funding by the Canadian government, an important early supporter of HIV prevention research, has declined since 2008 for HIV vaccines and ended completely for microbicides. Vaccine funding by the Swedish and Russian governments declined significantly in 2010. The United States, which is the largest funder of HIV prevention R&D, is facing pressure from congressional leaders to cut spending.

trials are being developed by Sanofi Pasteur and Novartis Vaccines.

Moving forward with antibody discoveries. Since 2009, a number of broadly neutralizing antibodies against HIV have been discovered by a number of key players, including the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID) and IAVI. Focus on these efforts has begun to shift toward the design of antigens to elicit such antibodies in humans. One such effort to further preclinical and clinical development of an antibody-eliciting HIV vaccine candidate is based at the University of Maryland's Institute of Human Virology and is being funded by a consortium including the BMGF, the MHRP, and the NIH. Additionally, several parties are exploring the possibility of passive delivery of antibodies to protect against HIV infection.

Replicating vectors. In May of 2011, data were released by a team at the Oregon Health and Science University supported by the IAVI, BMGF, NIH and USAID showing that a vaccine candidate based on a replicating cytomegalovirus vector largely controlled replication of simian immunodeficiency virus (SIV). Other efforts across the public and private sectors to investigate replicating vectors, including the Tiantan candidate being tested as part of the Chinese government's HIV vaccine megaproject, could have long-term implications for both preventive and therapeutic vaccines.

Other candidates moving forward. The HIV vaccine study farthest along the development pathway is the HVTN 505 Phase II trial evaluating the safety and effectiveness of a candidate designed to either prevent infection or to lower viral load in HIV-positive individuals. The study is sponsored by the HIV Vaccine Trials Network (HVTN) and the NIH, and is expected to provide results in 2013. Also, a collaboration among Harvard University, the Ragon Institute, Crucell, NIAID, and IAVI is currently supporting a Phase I trial of an Ad35/Ad26 candidate with the intention of moving within the next three years into a test-of- concept Phase IIB trial involving a new "mosaic" antigen set.

2.1.2 Philanthropic Investments in HIV Vaccine R&D

Table 3. Philanthropic Investment in HIV Vaccine R&D by Foundations and Commercial Philanthropy in 2010	
US$81 million	Bill & Melinda Gates Foundation
US$10 million	Ragon Institute
US$5 million	Wellcome Trust
US$2 million	OPEC Fund for International Development, Starr Foundation
US$600,000	Foundation for NIH
US$500,000 to US$1 million	Pfizer
< US$250,000	amFAR, BMS Foundation, Continental Airlines, Gilead Sciences Foundation, Google, Henry M. Jackson Foundation, Obra Social Fundación "La Caixa", White & Case, WWR Foundation

The philanthropic sector accounted for US$103 million (about 12%) of the total funds disbursed for HIV vaccine R&D in 2010, with the BMGF contributing US$81 million (79%) of that total. Philanthropic contributions actually rose, owing to increases in 2010 by the BMGF, Wellcome Trust, and OPEC Fund. Recent significant additions to the philanthropic funding pool include the Ragon Institute's 10-year, $100 million commitment to a collaboration among Harvard University, Massachusetts General Hospital (MGH), and the Massachusetts Institute of Technology (MIT) that is based at MGH.

2.1.3 Commercial Investments in HIV Vaccine R&D

Table 4. Commercial Engagement in HIV Vaccine R&D by Company in 2010	
US$5 million to US$10 million	GlaxoSmithKline
	Merck & Co.
	Novartis International AG
	Sanofi Pasteur
US$1 to US$5 million	ESTEVE, GeoVax, Inc.
US$100 thousand to US$1 million	Argos Therapeutics
	Advanced BioScience
	AlphaVax
	Bionor Immuno
	Crucell
	FIT-Biotech
	Genvec
	Ichor
	Inovio Pharmaceuticals
	Vical

Commercial sector funding remained level in 2010, with an increase in small-level activity on the biotechnology side.[5] The majority of private-sector investments in HIV vaccine research funding come from large pharmaceutical companies.

Four pharmaceutical companies currently have HIV vaccine programs GlaxoSmithKline, Merck & Co, Novartis Vaccines, and Sanofi Pasteur. Sanofi Pasteur and Novartis, both headquartered in Europe, are working together on components of the vaccine combinations to be tested in the follow up studies to RV144. Merck has an active program developing an envelope-based protein vaccine designed to elicit broadly neutralizing antibodies. GlaxoSmithKline is developing both preventive and therapeutic vaccine candidates utilizing their proprietary adjuvants.

[5] Commercial funding figures are estimates based upon a review of HIV vaccine programs at each company. In recent years, fewer companies have been willing to provide actual investment figures for their programs. Where companies decline to report financial information, the Working Group develops estimates for companies based upon interviews with company staff and third parties, and 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.

A number of biotechnology companies have vaccine programs that support NIH research through the Vaccine Research Center (VRC), such as GenVec and Crucell or are developing vaccine candidates of their own such as GeoVax and Inovio Pharmaceuticals. A more detailed description of these commercial programs can be found in the Appendix.

Commercial Investments in Context

Overall, R&D investment by US pharmaceutical companies appears to be on an upswing. US pharmaceutical research companies invested a record $67.4 billion last year in the R&D of new medicines and vaccines—an increase of $1.5 billion from 2009, according to analyses by the Pharmaceutical Research and Manufacturers of America (PhRMA).[6]

However little of this investment is occurring in HIV prevention research. The lack of a lucrative commercial market in high-income countries for many HIV prevention technologies is seen as a major disincentive for privately funded research by companies needing to justify risky and expensive research efforts to shareholders. This risk was underscored by the cancellation of Merck's Step HIV vaccine trial in 2007. A few companies—Merck, Sanofi Pasteur, Novartis, and GlaxoSmithKline—invest in HIV vaccines, but at levels we estimate to be US$10 million annually or less. In the field of ARV-based prevention, Gilead Sciences is the primary actor, providing its drugs TDF and TDF/FTC for use in preclinical and clinical work. In addition, several other companies are providing ARV drugs for use as active agents in microbicides.

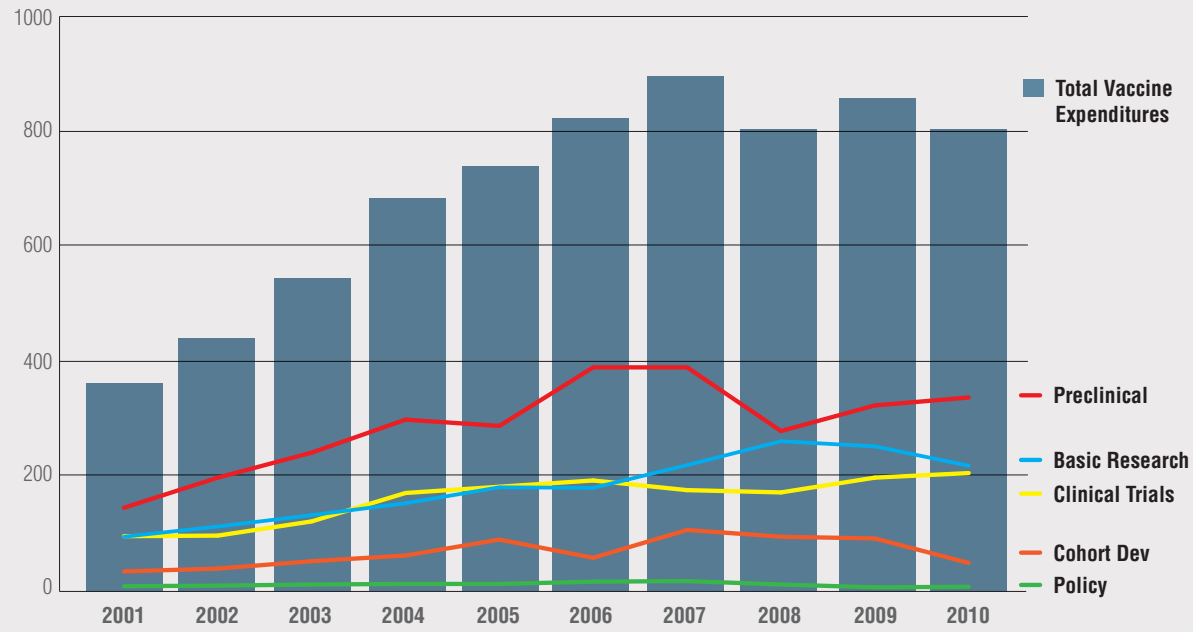
Targeted efforts by the public sector and other non-commercial entities to bring private sector expertise to the HIV prevention field have begun to show positive results while self-funding from the commercial sector has leveled off. In the case of HIV vaccines, the United States government's Small Business Innovation Research (SBIR) program has funded a number of small biotechnology companies in HIV prevention research. IAVI's Innovation Fund seeks out and funds innovative technologies not traditionally applied to HIV research, with a number of those biotechnology companies playing a major role in the discovery of new broadly neutralizing antibodies.

[6] Pharmaceutical Research and Manufacturers of America, *2011 Profile Pharmaceutical Industry* (2011)

2.1.4 Funding Allocations For HIV Vaccine R&D

Spending by the public and philanthropic sectors in 2010 on preventive HIV vaccine R&D was allocated to five categories: basic research (27%), preclinical research (41%), clinical trials (25%), cohort and site development (6%), and advocacy and policy development (<1%). The percentage distribution of investment among the five categories was similar to that in 2009, with some increases for preclinical and clinical activities and small decreases in basic research and cohort development. Further information about the categories used to define R&D can be found in the Appendix.[7]

Figure 2. Vaccine Expenditures for 2001–2010 (US$ millions)



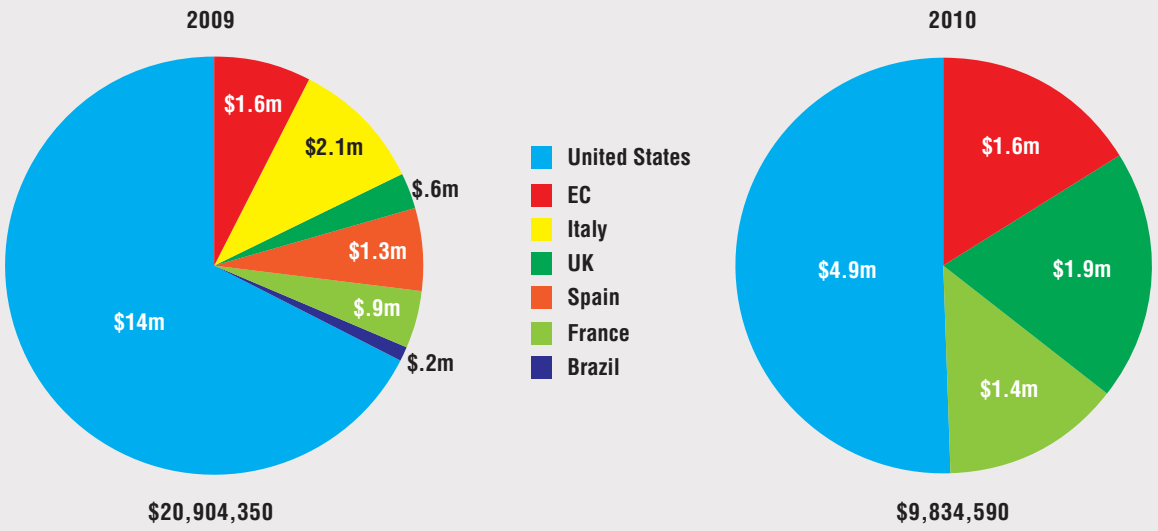
[7] With the exception of "policy and advocacy," these are the categories used by the NIH to categorize HIV vaccine research. Because not all data from funders permits the allocation according to these five categories, these percentages were estimated from an US$808 million subset that did permit such allocations. These expenditure figures do not include therapeutic vaccines.

2.1.5 Global Investments in Therapeutic HIV Vaccine R&D

Investment also went into research into therapeutic HIV vaccines for HIV-positive individuals. Therapeutic vaccines are designed to enhance immune responses to HIV to better control the infection. There are three HIV therapeutic vaccines now in clinical trials. In 2010, therapeutic HIV vaccine R&D received an estimated US$9.8 million, with the US and Europe each contributing 50% of this total.

Therapeutic HIV vaccine R&D also received an undetermined amount of funding in 2010 from pharmaceutical companies and biotech companies. Companies involved in therapeutic vaccine research include: Argos Therapeutics, Bionor Immuno, FIT Biotech, GeoVax, GlaxoSmithKline, Inovio Pharmaceuticals, Profectus Biosciences, and VIRxSYS.[8]

Figure 3. Investments in Therapeutic HIV Vaccines in 2009 and 2010

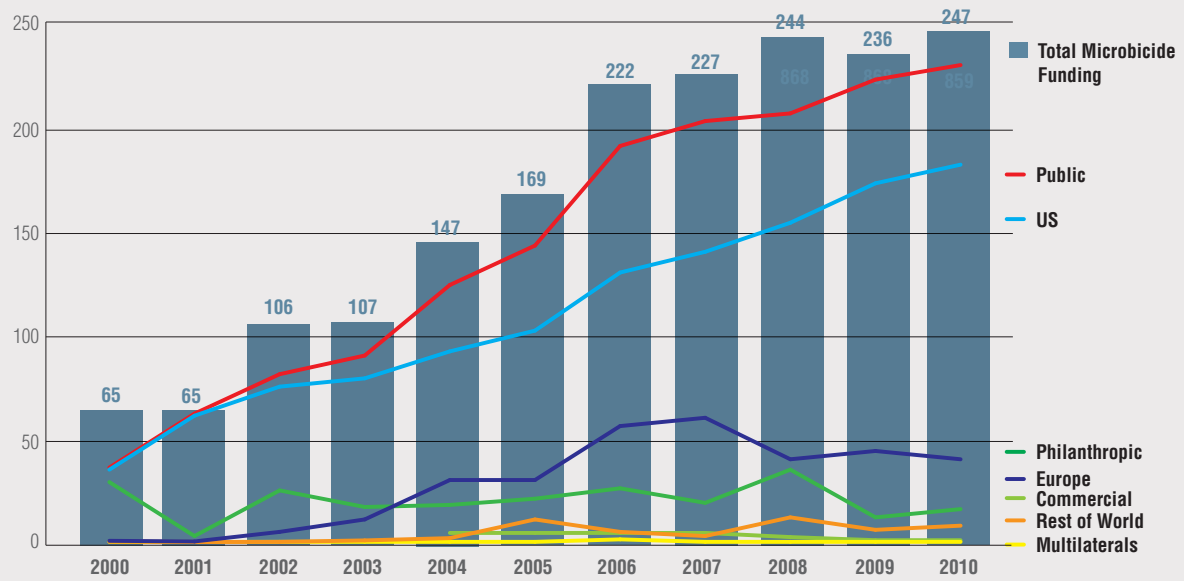


[8] This year's estimate of US$9.8 million falls significantly short of the 2009 investment of US$21 million, but our conclusion is that this change is largely due to limited responses from the commercial sector.

2.2 Global Investments in Microbicide R&D

In 2010, total global investment in microbicide R&D was US$247 million, a US$11 million (5%) increase from 2009. This increase returned microbicide funding to a level that exceeded its highest previous level of funding equalling US$244 million achieved in 2008.

Figure 4. Microbicide Funding for 2000–2010 (US$ millions)



* Commercial estimates not available prior to 2004.

Table 5. Annual Investments in Microbicide R&D for 2006–2010 (US$ millions)

	2006	2007	2008	2009	2010
PUBLIC SECTOR					
US	129.7	139.8	154.4	172.6	181.7
Europe	56.3	59.6	39.9	44.4	40.3
Rest of World	4.7	3.4	12.1	5.7	8.3
Multilaterals	1.4	0.2	0.2	0.2	0.1
Total public	192.1	203	206.6	222.9	230.4
PHILANTHROPIC SECTOR					
Total philanthropic	26.2	19	34.6	11.8	15.9
COMMERCIAL SECTOR					
Total commercial	4.5	4.5	2.5	1	1
Total global investment	**222.8**	**226.5**	**243.7**	**235.7**	**247.3**

CAPRISA 004 Funding

In July 2010, researchers from the Centre for the AIDS Programme of Research in South Africa (CAPRISA) announced the results of their groundbreaking microbicide trial involving 1% TDF formulated as a microbicide gel. CAPRISA 004 provided proof of concept that TDF gel can protect women from HIV infection, offering the first statistically significant evidence of effectiveness for a vaginal microbicide. In addition, the trial showed that TDF gel provided 51% protection against infection by HSV-2.

The trial was groundbreaking in its implementation, funding, and, most recently, its progress along the critical path to access. Among its distinguishing features, it was:

- conducted by a consortium that included CAPRISA, located at the University of KwaZulu-Natal; Family Health International (FHI) in North Carolina, USA; and CONRAD in Virginia, USA
- jointly funded by the South African and United States governments through the US Agency for International Development (USAID), which provided US$16.5 million, and through TIA, the Technology and Innovation Agency of the South African Department of Science and Technology (DST), which provided US$1.1 million—the first direct funding a microbicide trial has received from a host country
- supported by Gilead Sciences in California, USA, the pharmaceutical company that developed TDF; which donated drug product for initial batches for the trial and granted co-exclusive licenses to CONRAD and the International Partnership for Microbicides to develop the gel for use in resource-limited countries
- advanced by CONRAD, which in turn granted a non-exclusive license to TIA; with both groups now collaborating in an innovative public-private partnership, both groups collaborated with Cipla Medpro and iThemba Pharmaceuticals to manufacture and distribute TDF gel in Southern Africa.

This mosaic of contributions to the advancement of a product for deployment and use in a developing country is unusual in its constituents and in the integration of its objectives. If those partners continue to coalesce and expand strategically and transparently, it could serve as a highly beneficial model at a time when new approaches to advancing HIV prevention research are severely needed.

2.2.1 Public Investments in Microbicide R&D

In 2010, public-sector investment accounted for 93% of the combined global funding for microbicide research, development, and advocacy. The US continues to be the primary source of funding at US$181.7 million (74%). European national governments and the European Commission together accounted for US$40.3 million (17%) of funding, a 9% decrease from 2009. In 2010, the second and final year of ARRA stimulus funds, ARRA accounted for US$4.5 million of NIH investment in microbicide R&D.

In the year since the historic CAPRISA 004 trial results were announced, the microbicide field has grappled with defining the best next steps and how to support them in a time of financial constraint and uncertainty. Regulatory strategy has been largely clarified and USAID has just distributed a discussion draft of a strategic plan for microbicide introduction;[9] and recommended ancillary studies have begun. In June 2011, the South African and US governments announced full funding for the confirmatory multi-site "FACTS 001" trial to be launched this summer by the Follow-on African Consortium for Tenofovir Studies (FACTS). The trial, proposed for several sites in South Africa and one in Kenya, would be similar to CAPRISA 004. It would involve women ages 16 to 30, and—pending approvals and funding—could begin enrollment by mid-2011. The South African government and USAID have committed funding, and other support is pending.

The microbicide field continues to advance other candidates as well. Next in line is the IPM-developed monthly vaginal ring containing dapivirine, an ARV licensed from Tibotec/J&J. The dapivirine ring is designed as a long-acting product intended to ensure more consistent use and therefore improved effectiveness. Discussions of how to most efficiently advance this candidate led to the announcement in June 2011 that, pending regulatory approval, the NIH-funded Microbicide Trials Network (MTN) will conduct a single pivotal efficacy trial in 2012 of the dapivirine ring in approximately 4,000 participants in southern Africa and that IPM will conduct a parallel trial in at least 1,000 women in order to provide licensure-quality safety data. Progress in the earlier portions of the microbicide pipeline are supported by the NIH, primarily through strategically linked program announcements, and by USAID support for dual- and multi-purpose reproductive health technologies with microbicide components. Importantly, the first microbicides containing the ARV maraviroc and a combination of maraviroc and dapivirine will be evaluated this year in humans through a partnership between IPM and the MTN. Finally, plans are proceeding to test the safety and acceptability of 1% TDF gel as a rectal microbicide.

[9] United States Agency for International Development *USAID Proposal for a Shared Vision and Strategic Plan for Microbicide Introduction.* Washington, DC, 3 June 2011 *(draft for discussion).*

2.2.2 Philanthropic Investments in Microbicide R&D

In 2010, the philanthropic sector provided US$15.9 million (6%) of the funds disbursed for microbicide development. This increase over the US$11.8 million for 2009 was due to an increase in funding by the BMGF. All philanthropic funding came from three foundations: the BMGF, Wellcome Trust, and amfAR.

Philanthropic Funding in Context

Funding trends in HIV prevention research can be compared with those in the wider world of philanthropy. A 2010 report from the Foundation Center revealed that among 75,000 foundations tracked, total funding in 2009 was 8.4% lower than in 2008, the largest year-to-year decrease on record.[10] Those foundations had forecast that their funding would remain flat in 2010, but this did not in fact occur. Giving was instead robust, just 2.1% below the record high of US$ 46.8 billion awarded by foundations in 2008, despite the fact that foundation assets were still close to 10% below their 2007 peak.

Table 6. Top Microbicide Funders in 2009 and 2010 (US$ millions)*

2009 Rank	Funder	Amount	2010 Rank	Funder	Amount
1	NIH	133.3	1	NIH	147.0
2	USAID	39.0	2	USAID	38.0
3	DfID	21.5	3	DfID	16.5
4	EC	7.1	4	BMGF	15.7
5	BMGF	6.9	5	EC	6.7
6	Canada	4.9	6	China	3.6
7	Wellcome Trust	4.4	7	UK MRC	3.4
8	Norway	4.3	8	Norway	3.3
9	Spain	2.0	9	EDCTP	2.0
10	Denmark	1.9	10	Spain	1.9
11	Sweden	1.8	11	Netherlands	1.7
12	Belgium	1.4	12	Denmark	1.7
13	Netherlands	1.4	13	Germany	1.3
14	Ireland	1.4	14	Ireland	1.1
15	ANRS	1.3	15	CDC	0.7

* Excludes commercial funders and USAID excludes FEM-PrEP trial.

[10] The Foundation Center, *Foundation Growth and Giving Estimates* (2010 and 2011 Editions)

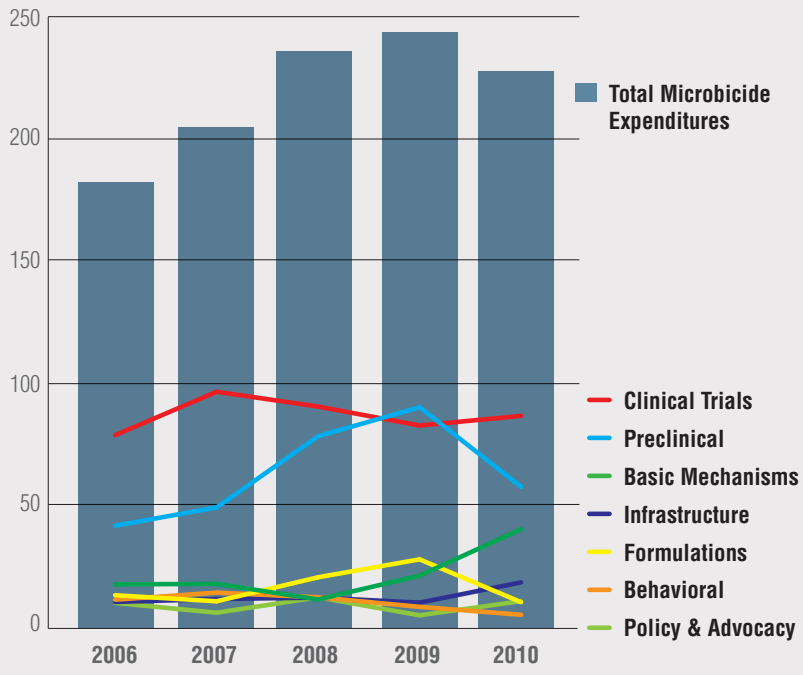
2.2.3 Commercial Investments in and Contributions to Microbicide R&D

Total commercial sector microbicide investment in 2010 was estimated at US$1.0 million, all of which came from the biotechnology industry. The most significant contribution from the commercial sector came in the form of non-exclusive, royalty-free transfers of ARVs for use as active agents in microbicide development. Microbicide developers continue to receive valuable product data and technical advice from commercial partners. IPM received non-exclusive, royalty-free licenses for ARVs from Bristol-Myers Squibb Co. (gp120 binder), Gilead Sciences (NRTI), Johnson & Johnson subsidiary Tibotec (NNRTI), Merck & Co. (CCR5 blocker & gp41 binder), and Pfizer (CCR5 blocker). CONRAD and the Population Council also received material transfers and licenses for similar purposes, including licenses to develop ARVs as components of combination products. Commercial support has also included licenses to develop ARVs as components of combination products. The microbicide field has benefited from the active participation of the following biotechnology companies, which offered ARV and non-ARV-based products and support for follow-on development through a variety of NIH grant and contract mechanisms: ImQuest BioSciences (pyrimidinediones (ARV)), Mapp Biopharmaceutical (monoclonal antibodies), Osel (probiotics), and Starpharma Holdings (VivaGel). There has been substantial commercial participation and collaboration with nonprofit developers and partnerships, such as CONRAD, IPM, and the Population Council. This collaboration has included a broad range of expertise and support from companies such as: legal support connected with 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 microbicide development meetings and teleconferences, and timeline guidance.

2.2.4 Funding Allocations for Microbicide R&D

In 2010, expenditures on microbicide R&D were allocated across the following seven categories: basic mechanisms of mucosal transmission (18%); preclinical testing (25%); formulations and modes of delivery (5%); clinical trials (38%); microbicide behavioral and social science research (2%); microbicide research infrastructure (8%); and policy and advocacy (4%).[11] Preclinical testing and clinical trials were the two largest categories, as they were in 2009, though preclinical work declined from 36% of investment in 2009 to 25% of investment in 2010. Increases were seen in investments in basic mechanisms, clinical research, and research infrastructure. Further information on the categories used to define R&D can be found in the Appendix.

Figure 5. Microbicide Expenditures for 2006–2010 (US$ millions)



[11] With the exception of "policy and advocacy," these are the categories used by the NIH to categorize microbicide research. Because not all data from funders permits the allocation according to these seven categories, these percentages were estimated from an US$237 million subset that did permit such allocations.

2.2.5 Investments in Rectal Microbicide R&D

In 2010, R&D toward a rectal microbicide was funded at approximately US$7.2 million according to the International Rectal Microbicide Advocates (IRMA). Between 2007 and 2010, global spending on rectal microbicide research totaled US$25 million. Of this amount, the US public sector contributed 91.6%, European public-sector contributions represented 5.3%, and the philanthropic sector contributed 3.0%.[12] In 2010, the majority of funds came from US sources (both public and philanthropic) and went toward support of preclinical development of rectal microbicide products and clinical testing of rectal microbicides through the NIH's MTN. The MTN is testing the safety and acceptability of 1% TDF gel reformulated for rectal use. If the gel proves safe, acceptable and effective, this may pave the way for the first rectal Phase II expanded microbicide safety trial.

2.3 Global Investments in R&D and Operations Research for Other HIV Prevention Options

Other biomedical prevention strategies were explored in 2010, 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 refinement and expansion of strategies for preventing vertical infection of infants at birth and during breastfeeding. One experimental prevention approach that the Working Group has tracked in the past—HSV-2 vaccines—received little funding in 2010.

[12] International Rectal Microbicide Advocates *From Promise to Product: Advancing Rectal Microbicide Research and Advocacy* (2010). The Working Group did not develop a separate estimate for rectal microbicide funding in 2010, and instead refers the reader to the IRMA report cited here.

2.3.1 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$59 million over the last five years. Investment in circumcision operations research grew significantly in 2010, due to an eightfold increase in contributions from the BMGF.

Figure 6. Investment in Medical Male Circumcision for 2001–2010 (US$ millions)

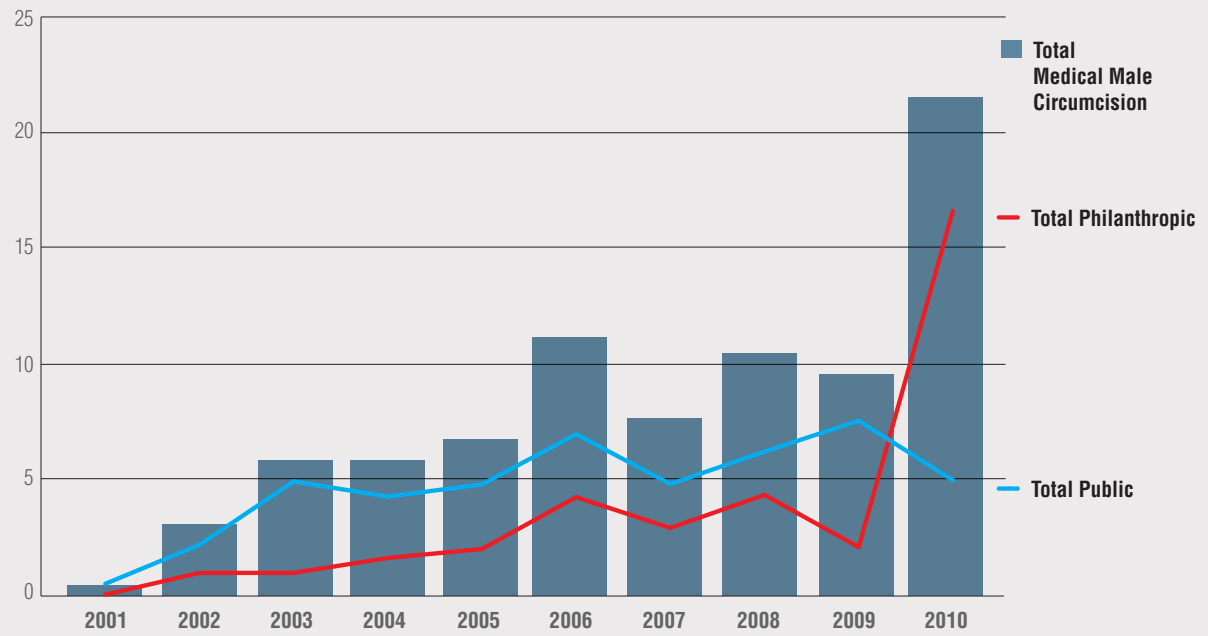


Table 7. Annual Investments in Adult Male Circumcision 2006–2010 (US$ millions)

	2006	2007	2008	2009	2010
PUBLIC SECTOR					
Total public	6.9	4.8	6.2	7.5	5.0
PHILANTHROPIC SECTOR					
Total philanthropic	4.3	2.9	4.3	2.1	16.7
Total investment	**11.2**	**7.7**	**10.5**	**9.6**	**21.7**

President's Emergency Plan for AIDS Relief (PEPFAR) funding for implementation research related to adult male circumcision programs totaled US$1.6 million in 2010. From October 2009 to September 2010, PEPFAR allocated US$70.9 million to adult male circumcision rollout in a number of countries in Africa.

2.3.2 Investments in R&D Related to Pre-exposure Prophylaxis

Global public-sector and philanthropic investment in pre-exposure prophylaxis (PrEP) equalled US$58.27 million in 2010, and totaled US$205 million over the last 5 years. There are five ongoing or planned PrEP trials involving TDF or TDF/FTC, and there is one involving the ARV TMC278LA injected intramuscularly.

In 2010, the iPrEx trial released results regarding the safety and effectiveness of PrEP using a TDF/FTC tablet. The trial data showed that once-daily oral TDF/FTC reduced risk of HIV infection by approximately 44% among gay men, other MSM, and transgender women.

The FEM-PrEP trial, involving heterosexual women in sub-Saharan Africa, also tested the use of once-daily oral TDF/FTC, but it was stopped before its anticipated end date after a scheduled interim data review by an independent data monitoring committee (IDMC) concluded that even if the trial ran to completion, it was highly unlikely to show a benefit.

Two other ongoing trials in sub-Saharan Africa are evaluating oral PrEP among heterosexuals. The VOICE trial is evaluating oral TDF and TDF/FTC as well as 1% TDF vaginal gel in 5,000 women in sub-Saharan Africa. The Partners PrEP trial is evaluating oral TDF and TDF/FTC in the HIV-negative partner in couples in which one partner is HIV-positive.

Figure 7. Investment in Pre-exposure Prophylaxis for 2002–2010 (US$ millions)

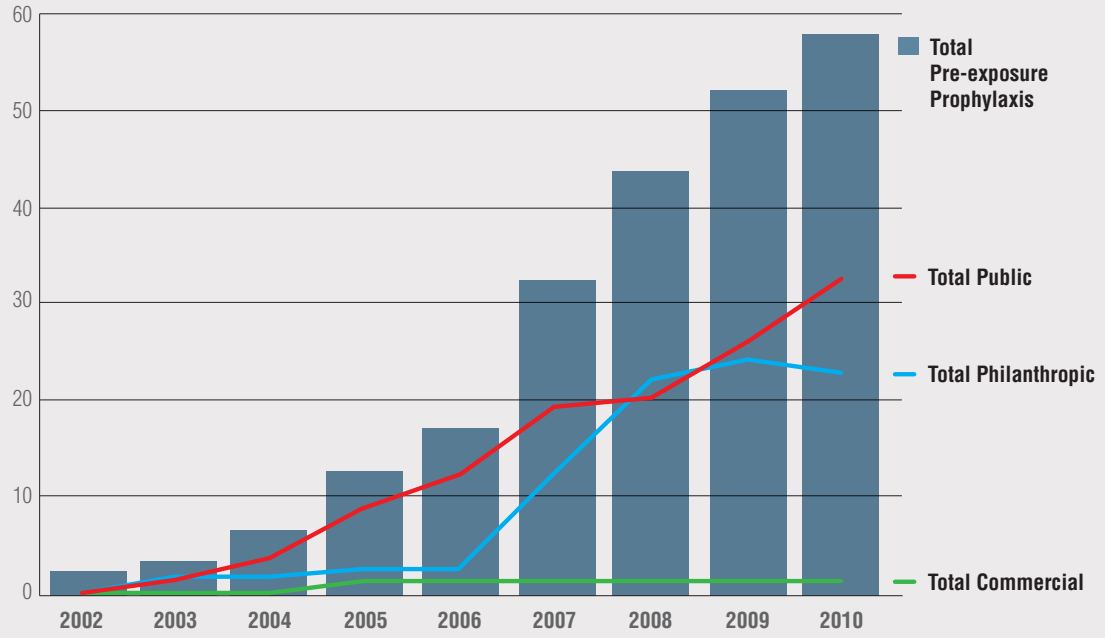


Table 8. Annual Investments in Pre-exposure Prophylaxis 2005–2010 (US$ millions)						
	2005	2006	2007	2008	2009	2010
PUBLIC SECTOR						
Total public	8.7	13.5	19.7	20.6	26.6	33.8
PHILANTHROPIC SECTOR						
Total philanthropic	2.4	2.4	12.6	22.5	24.6	23.2
COMMERCIAL SECTOR						
Total commercial	1.3	1.3	1.3	1.3	1.3	1.3
Total investment	**12.4**	**17.2**	**33.6**	**44.4**	**52.5**	**58.3**

2.3.3 Investments in R&D Related to Treatment as Prevention

The treatment-as-prevention or test-and-treat approaches to HIV prevention refer to the use of ARVs by people living with HIV to lower their viral load and hence the potential to transmit HIV. In 2010, R&D invested toward interventions testing the prevention effect of ARV treatment equaled US$19.6 million. This funding went toward the NIH funded HIV Prevention Trials Network (HPTN) 052 and HPTN 065 trials.

In May 2011, HPTN 052, upon the recommendation of its data and safety monitoring board (DSMB), released results from 13 sites in Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, the United States, and Zimbabwe. HPTN 052 is a randomized trial examining the HIV prevention effect of early initiation of treatment in couples where one partner is HIV-positive and the other is not. The trial found a 96% reduced risk of transmission in those couples, as well as a reduction in extra pulmonary tuberculosis among HIV-positive participants in the delayed treatment group. The HPTN 065 community-level trial taking place in the District of Columbia and the Bronx, New York, which is designed to test strategies to increase community HIV testing, improve referrals to treatment, and increase adherence to treatment regimens.

A number of treatment-as-prevention studies are planned but as yet unfunded. In South Africa, the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) announced plans for a trial providing universal HIV testing and treatment in order to study the impact it would have on HIV transmission. As part of the PopART program, the Imperial College London is planning a study in Uganda and Zambia that tests the effectiveness of universal HIV voluntary counseling and testing (VCT) with immediate access to antiretroviral therapy (ART) as an intervention to reduce transmission. In Malawi, HIV-positive individuals in acute infection are being offered early treatment and

behavior interventions in the NIH-funded MP3 study, which is also examining the impact on HIV incidence. Finally, in Swaziland, a Clinton Foundation project is under consideration which would offer universal HIV testing and treatment to all those living with HIV in order to examine the effect on national HIV incidence. The results of the HPTN 052 trial may affect the study design of these trials and whether they receive funding.

Cure Research

Timothy Ray Brown, the so-called "Berlin Patient," was living in Berlin in 2007 when, in addition to being HIV-positive, he had a relapse of leukemia. His doctor recommended a bone marrow transplant using cells from a donor with a rare genetic mutation resistant to HIV. The transplant had an unprecedented result, making Mr. Brown the only human ever to be cured of HIV. He has no replicating virus and isn't taking antiretroviral medication. Although Mr. Brown's treatment is not a practical protocol for treating the general population of HIV-positive individuals his case has helped revitalize research into a cure for HIV. The interest in understanding the mechanism of protection could lead to more broadly applicable treatment options.

Public-sector investment in cure research looking at elimination of viral reservoirs in HIV-positive individuals equaled US$4.9 million in 2010 and is likely to increase in coming years. This year's funding came from the NIH (79%), ANRS (19%), National Health and Medical Research Council (NHMRC) (1%), and Swedish International Development Cooperation Agency (SIDA) (1%).[14]

The NIH is asking for proposals for an US$8.5 million collaborative research grant to search for a cure, and amfAR has just announced its first round of four grants to research "to develop strategies for eradicating HIV infection." Finally, some commercial sector companies, such as Gilead Sciences, Merck and Pfizer, have also begun research into this area.

[14] This estimate is only for cure research directed only at eliminating viral reservoirs in HIV-positive individuals. As this research develops and its parameters become clearer, there may be additional areas of research that can and should be included under the category of cure research.

2.3.4 Investments in HIV Prevention R&D Related to HSV-2 Prevention

Although HSV-2 suppression with acyclovir has not been shown to affect HIV acquisition, prevention of HSV-2 infection in HIV-negative people may be an effective HIV prevention strategy. The NIH provided all of the public sector investment for research into HSV-2 vaccines in 2010, a total of US$908,000. HSV-2 vaccines have also received modest commercial investment from pharmaceutical companies (such as GSK) and from biotech companies (such as BioVex, Genocea Biosciences, Juvaris, and Vical).

Results from the NIH funded a Phase III trial to assess GSK's HSV vaccine released in September 2010 showed that the vaccine did not prevent HSV-2 infection. These disappointing trial results may further discourage investment in this area despite its warranting further research and the need for an HSV-2 vaccine.

One unexpected and exciting finding from CAPRISA 004 was that among women who were uninfected with HSV-2 at the start of the trial, those who used 1% TDF gel were at 51% lower risk of acquiring HSV-2, as compared to HSV-2 negative women using placebo. This finding may guide new research and suggests an additional important benefit to women using the 1% TDF gel.

2.3.5 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 breast feeding was US$59.7 million in 2010. The public sector accounted for all of this funding, with the United States, through the NIH and USAID, contributing 95% and ANRS, the Canadian International Development Agency (CIDA), and SIDA providing additional funding. There were eight active clinical trials testing vertical transmission prevention in 2010. These studies focused on issues related to prevention of vertical transmission at birth and through breastfeeding, and to ARV resistance in HIV-positive women taking ARV regimens designed to prevent vertical transmission.

The US-funded International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) began its PROMISE study in 2010. By testing antepartum and postpartum interventions to reduce vertical transmission, PROMISE aims to determine the optimal antenatal and postnatal intervention.

Table 9. Funding for Vertical Transmission Prevention R&D in 2008–2010 (US$)

	2008	2009	2010
PUBLIC SECTOR			
EDCTP	3,393,500	3,393,500	0
ANRS	3,429,355	1,820,086	418,890
UK	374,600	448,105	0
SIDA	128,041	263,158	1,127,820
CIDA	0	0	1,250,000
CDC	1,716,928	488,132	0
USAID	0	0	1,600,000
NIH	8,533,594	44,101,000	55,348,000
Total public	17,576,018	50,513,981	59,744,709
PHILANTHROPIC SECTOR			
Total philanthropic	3,641,800	904,065	0
Total global investment	**21,217,800**	**51,418,000**	**59,744,700**

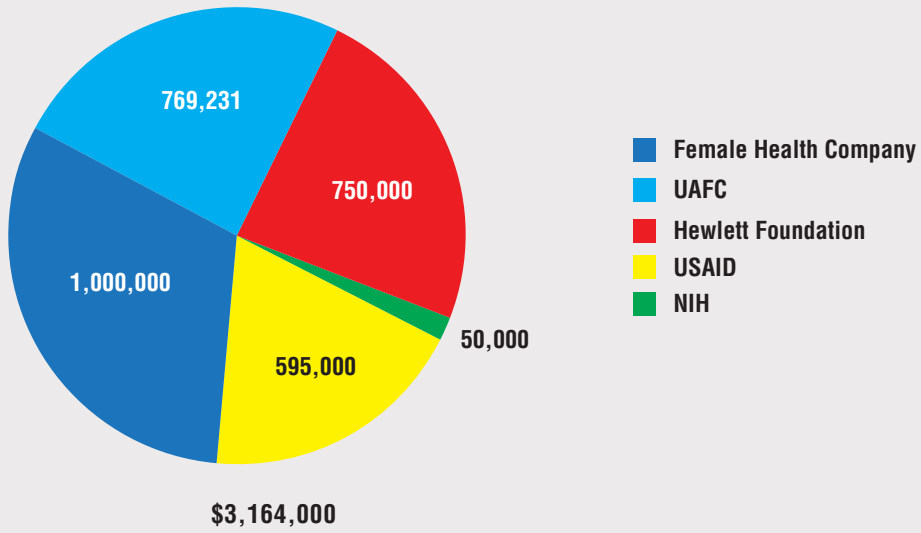
Funder Profile: ANRS

The French National Agency for Research on AIDS and Viral Hepatitis (ANRS), based in Paris, is an important funder of HIV prevention research and supporter of early career HIV/AIDS researchers. ANRS supports HIV prevention research in academic institutions: institutes, universities and hospitals and in international teams, mostly from limited resource countries, carrying out basic and clinical research on experimental and existing HIV prevention methods. ANRS' research programme has had an early role in involving social and public health scientists, as well as integrating community leaders in HIV and AIDS research. Despite an annual budget of approximately €48 million, ANRS has been responsible for important research contributions regarding both HIV treatment and prevention over the past decade. In 2010, the ANRS contributed €6.2 million toward HIV prevention (13% of its budget), including €4.9 million for HIV vaccine research, as well as €707,000 for adult male circumcision research and €316,000 for basic research related to prevention of vertical transmission. Prior research by the ANRS has demonstrated the benefits of ARV treatment for vertical transmission prevention and, more recently, the protective effects of adult male circumcision. ANRS is focusing on research into new HIV vaccines in ways that encourage a diversification of candidate vaccines. The candidate vaccines under ANRS evaluation include lipopeptides, naked DNA, recombinant vectors, and fusion proteins of human monoclonal antibodies directed against dendritic cells coupled to HIV epitopes. In 2011 the ANRS vaccine research programme was selected by an international scientific jury for the creation of a Vaccine Research Institute. ANRS also has trials planned to examine the efficacy of intermittent oral PrEP use in France and Canada and treatment as prevention in South Africa. An additional ANRS area of focus is the establishment and control of latent reservoirs, which has implications for research into a cure for HIV infection.

2.3.6 Investments in R&D and Operations Research Related to Female Condoms

There remain a number of implementation and research questions around design, rollout, and uptake of the female condom.[16] R&D work in this area includes product development efforts, as well as basic HIV research, clinical trial preparation, community education, and advocacy—all of which are being funded by both the public and philanthropic sectors. Global investment in R&D related to the female condom totaled US$3.1 million in 2010 coming from the Female Condom Company, the Hewlett Foundation, the Universal Access to Female Condom (UAFC) Joint Programme and the NIH, The UAFC Joint Programme is a partnership among four Dutch organizations: Oxfam Novib, World Population Foundation, i+solutions, and the Dutch Ministry of Foreign Affairs.

Figure 8. Funding for Female Condom R&D in 2010



[16] Although a female condom has been available for some years, its design has continued to be improved. The original FC female condom was made of polyurethane. Subsequently, the manufacturer released second-generation FC-2 version, made of cheaper nitrile material. Production of the original FC female condom has stopped and large-scale production of the FC2 began in 2007. The FC2 female condom received FDA approval in March 2009 and is now available in the US.

2.4 Investments by Trial Participants in HIV Prevention R&D

As of November in 2010, there were 35,600 participants in HIV prevention research trials. These trials were predominantly based in countries and communities with high HIV burden. Participants from Kenya, South Africa and Uganda accounted for 16%, 15% and 23% of all trial participants, respectively.

Trials in areas of high HIV burden tend to offer rapid results, providing 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. The Working Group has not placed a financial value on this contribution, but it unquestionably represents a major and incalculable investment in HIV prevention research.

Table 10. Trial Participants by Country

Rank	Country	Number
1	Uganda	8101
2	Kenya	5723
3	South Africa	5416
4	Zimbabwe	4330
5	United States	2982
6	Thailand	2824
7	Malawi	2003
8	Botswana	1200
9	Tanzania	1006
10	Peru	529
11	Brazil	417
12	Ecuador	416
13	Zambia	233
14	Rwanda	120
15	China	80
16	Switzerland	80
17	Belgium	64
18	India	32
19	Sweden	24
20	Russia	15

3.0 Discussion

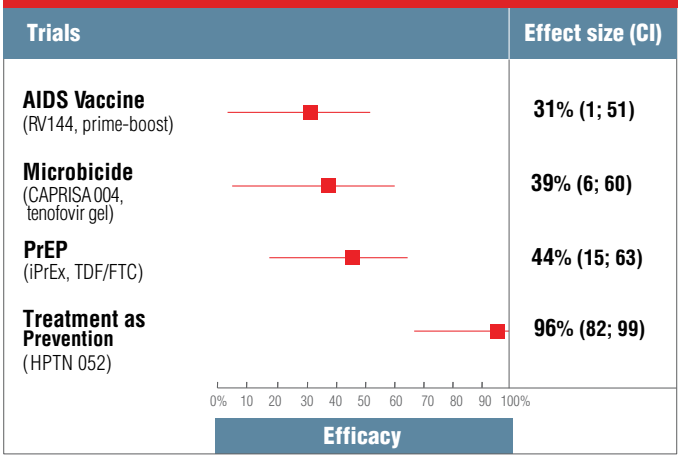
In the 30 years since the first reported cases of AIDS, researchers have made extraordinary advances in understanding, treating, and preventing HIV infection. There are now more than 20 approved antiretroviral drugs, and in 2010 the number of people receiving ART grew by 25% from 2009, from 5.3 million to 6.6 million. At the same time, there has been recent global success in promoting HIV prevention through safer sexual practices. During the last decade, HIV incidence has declined in 33 countries, and HIV prevalence among young people has fallen in 15 countries.[17]

Until recently, scientific progress in developing new prevention options had come slowly. In the last two years, however, there have been a number of promising trial research results in HIV vaccines, microbicides, PrEP, and treatment as prevention.

- **October 2009:** The US- and Thailand-funded Phase III HIV vaccine clinical trial, RV 144, tested the prime-boost combination of two vaccines: ALVAC (the prime) and AIDSVAX (the boost) with 16,000 Thai trial participants. The trial demonstrated that the vaccine regimen was safe and modestly effective, lowering the rate of HIV infection by 31.2%.
- **July 2010:** The US- and South Africa-funded CAPRISA 004 microbicide trial, showed that 1% TDF vaginal gel reduced women's risk of acquiring HIV from their male sexual partners by an estimated 39% overall in South African women and also showed a 51% reduction in acquisition of HSV-2.
- **November 2010:** The US- and BMGF-funded iPrEx trial results showed that in gay men, other MSM, and transgender women, daily PrEP using TDF/FTC reduced the risk of HIV by 44%.
- **May 2011:** The US-funded HPTN 052 trial established that immediate versus delayed initiation of ART by HIV-positive individuals substantially protected their HIV-negative partners from acquiring HIV infection, with a 96% reduction in risk of HIV transmission.

Some of these new interventions remain experimental (RV 144); others require confirmatory trials (CAPRISA 004); and others have as yet unarticulated pathways to implementation (iPrEx and HPTN 052). Each requires further research, either to build upon or confirm results or to test implementation strategies. Each of the results is cause for

Figure 9. Proof of Concept Trial Results (2009–2011)



[17] UNAIDS *Report On The Global Aids Epidemic* 2010.

optimism. The challenge is still to build on current momentum when many HIV prevention R&D funders, especially in government agencies, find themselves under increasing pressure to reduce spending.

In 2010, public-sector, philanthropic, and commercial funders invested US$1.27 billion toward R&D for preventive HIV vaccines, microbicides, pre-exposure prophylaxis (PrEP) using ARVs, and operations research related to male circumcision, treatment as prevention, female condom R&D, and vertical transmission prevention in 2010. Funders invested US$1.19 billion in 2010 in four key prevention options (preventive HIV vaccines, microbicides, PrEP and adult male circumcision), which approaches the previous historical high of US$1.23 billion for investment in these prevention options, reached in 2007.

Compared to 2009, prevention research experienced small funding increases for microbicides and PrEP and a small decrease for vaccines. Overall, funding for HIV prevention research as a whole has remained stable over the past two years, and the field overall has regained funding that was lost in the years immediately following the cancellation of the Step HIV vaccine trial in 2007 and the initial impact of the global recession. This trend of stability parallels global investments in both HIV prevention and treatment generally. For example, a recent report from UNAIDS and the Henry J. Kaiser Family Foundation found that funding for the global HIV epidemic from country governments totaled US$7.6 billion in 2009, virtually equal to the US$7.7 billion spent in 2008—and in direct contrast to the trend of double-digit percentage increases in funding in previous years.[18] Thus, while funding for research into some interventions has dropped and for others it has increased following promising results, overall support for HIV prevention R&D has kept pace with overall HIV funding.

Yet, at no previous time during the pandemic has the HIV prevention research field found itself in a better position to capitalize on so many promising opportunities. And it is as yet unclear whether sufficient resources have been allocated to make the rapid and strategic decisions that the field needs to move forward. On the 30th anniversary of the first reported cases of AIDS, there is serious consideration as to how we might put these recent results to use in developing a plan to end AIDS. The HIV prevention field will need to focus its existing resources strategically for maximum impact by addressing the following areas of concern:

- **Resources Need to Be Directed to Capitalize in Areas of Progress.** The promising results of the RV 144, CAPRISA 004, iPrEx, and HPTN 052 trials have demonstrated the need to plan for success. Yet, doing so will require funding structures that can adapt quickly and are sufficiently generous to allow for rapid expansion in the event of positive outcomes. Funding structures also need to be able to react to new developments in real time, rather than requiring researchers to wait for existing programs or grants to end in order to free up research funds. Beyond that, these resources must support the next clinical phases of each intervention, from the transformation of recent discoveries into new HIV vaccine candidates to ensuring appropriate funding levels for confirmatory microbicide trials.

[11] UNAIDS and Kaiser Family Foundation, *Financing the Response to AIDS in Low and Middle-Income Countries: International Assistance from the G8, European Commission and Other Donor Governments in 2009* (June 2010).

- **Funding Structures Need to Accommodate the Costs of Important Late-Stage Research.** In prior years, the HIV prevention field saw unanswered scientific questions, rather than funding, as the critical obstacle to progress. Now that new scientific knowledge is being brought to bear in a number of areas, funding levels are constraining that progress, particularly where the next step required is a late-stage trial.

- **Funding Is Highly Concentrated among Few Funders.** In 2010, much as was the case in 2009; public-sector funding stability was largely the result of increased or sustained funding by the US and a few European countries (France, the European Commission, Netherlands, Spain, and the UK). Canada also increased its contribution to HIV vaccines in 2010 after years of cutbacks in its HIV prevention research support. It is therefore encouraging that a number of the BRICS countries have continued to allocate resources to HIV prevention research in recent years. The investment by public-sector funders of HIV prevention research this year—by China, Thailand, and South Africa—is critical to broadening the funding base and promotion of greater R&D collaboration across countries. At the same time Russia has significantly decreased investment. A very small number of generous funders (amfAR, BMGF, Ragon Institute, and Wellcome Trust) provide the bulk of support from the philanthropic sector.

- **The Expertise of the Commercial Sector Is Not Fully Engaged.** Each of the recent trials reporting promising results—RV 144, CAPRISA, iPrEx and HPTN 052—involved collaboration and support from industry partners in developing the vaccines and drugs used in those trials. Despite those successful collaborations, HIV prevention R&D by large pharmaceutical companies has not increased. However, a number of biotech actors are bringing new vitality to the field. Many of their efforts focus on mid-stage development, such as GeoVax's Phase IIA HIV vaccine trial. A number of biopharmaceutical companies have forged new business models that include providing a level of in-kind support to HIV prevention trials via compound licensing. Research success in the biotech sector often inspires further engagement by large pharmaceutical entities, which are best positioned to contribute large-scale development expertise. Nevertheless, there is a need to broadly engage the commercial sector in HIV prevention R&D. Targeted efforts by public-sector and non-profit research entities to leverage biotechnology expertise not previously applied to HIV science have been instrumental in recent discoveries that will lead to the candidates of the future.

- **The Future of HIV Prevention Research Will Require Further Early-Stage Research.** Trial advances in HIV prevention R&D have not emerged from a vacuum. The continuing efforts of academia in basic HIV research primarily funded by the public sector will likely be especially at risk when NIH stimulus funding expires. Programs to translate basic scientific discoveries into viable products have been funded by development agencies whose budgets could be reduced should foreign assistance be deprioritized in austerity measures. Existing research efforts and inquiries into new avenues will require sustained support in order to improve upon the partial success of recent trials, turn promising basic science into candidates for trials, and potentially create new families of HIV prevention tools, such as the potential application of neutralizing antibodies to induce "passive immunity" in uninfected individuals.

The global commitment to HIV prevention research remains. It was most recently evidenced by the Declaration of Commitment on HIV/AIDS and the Political Declaration on HIV/AIDS draft resolution submitted to the General Assembly after the High-Level meeting on HIV-AIDS held in June of 2011. That Declaration asserts the goal of "investing in accelerated basic research on the development of sustainable and affordable….microbicides and other new prevention technologies, including female-controlled prevention methods, ….[and] research and development for a safe, affordable, effective and accessible vaccine." Cognizant that development of new technologies will be useless without proper implementation, the Declaration also sets the goal of "Deploying new biomedical interventions as soon as they are validated, including female-initiated prevention methods such as microbicides, HIV treatment prophylaxis, earlier treatment as prevention, and an HIV vaccine."

That HIV prevention research has not suffered significant declines in investment in the aftermath of the global recession that began in 2008 speaks to the commitment of funders to creating a comprehensive toolbox of HIV prevention tools. This commitment has brought us to the point where the HIV prevention research field could make game-changing advances in the 30-year-old fight against AIDS, but making those advances will demand continuing, perhaps greater, resources in the years ahead. While time frames vary, ARV-based prevention options, HIV vaccines, and microbicides will require years and further trials 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 will need to make an intelligent, realistic, strategic, integrated case for the long-term need for sustained and flexible funding, for each technology and across the range of technologies in that toolbox. 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, keep millions at continued risk of HIV infection. The best case is that new HIV prevention tools will become available and turn the UNAIDS 2010 rallying cry of "zero new infections" into reality.

APPENDIX

Methodology

This report was prepared by Kevin Fisher (AVAC), Thomas Harmon (IAVI), Polly Harrison (AVAC) and Wadzanayi Muchenje (AVAC), with contributions from LMichael Green (IPM), Robert Lande (IPM), Wilson Lee (IAVI), and Mitchell Warren (AVAC) of the HIV Vaccines and Microbicides Resource Tracking Working Group (Working Group). The Working Group developed and has utilized a systematic approach to data collection and collation 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.hivresourcetracking.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 National Institutes of Health and are shown in the following tables.

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

Category	Definition
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 the strategies, infrastructure, and collaborations with researchers, communities, government agencies, regulatory agencies, NGOs, and industry necessary to identify trial sites, build capacity, ensure adequate performance of trials, and address the prevention needs of at-risk populations in trial communities.
Advocacy & Policy Development	Efforts directed at educating and mobilizing public and political support for preventive HIV vaccines and at 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	
Category	Definition
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.

APPENDIX

Commercial Sector Research Programs

Table 13. Commercial Sector HIV Vaccine R&D in 2010	
PHARMACEUTICAL COMPANIES	
GlaxoSmithKline	**GlaxoSmithKline** is currently pursuing three separate vaccine strategies. Its HIV vaccine candidate, F4/AS01, is being evaluated for safety and efficacy in HIV-positive individuals in Phase II clinical trials. In a collaborative effort with IAVI, GSK's F4/AS01 vaccine candidate will also be combined with a recombinant ad35 vector. And GSK is working with the Pasteur Institute in Paris and other partners to develop a vaccine by fusing genes from the HIV virus onto a measles vaccine vector. A Phase I clinical trial of this candidate started in 2010.
Merck & Co.	**Merck**, working with multiple partners, supports an extramural collaborative discovery R&D program that aims to identify an HIV envelope-based protein vaccine capable of producing broadly neutralizing antibodies against HIV infection. This program is being conducted with multiple partners. Merck continues to explore implications for vaccine design based on results from the STEP trial of its adenovirus vaccine and the development of antigens to elicit protective antibodies to HIV.
Novartis Vaccines	**Novartis Vaccines** continues its alphavirus vector program, and is also developing different envelope proteins as well as adjuvants for use either as a boost to ALVAC prime in the follow-up trials to the Thai RV 144 trial or with other candidates.
Sanofi Pasteur	**Sanofi Pasteur**, the vaccines division of Sanofi-Aventis Group, is discussing follow-up studies to RV 144 with multiple partners in Thailand and South Africa. Following the results of RV 144, the Thai study partnership is supporting research to both better understand why the RV 144 vaccine worked and what the best next steps for that candidate should be. A related partnership, spearheaded by Sanofi Pasteur, is focusing on how the Thai study can be repeated and improved upon in Africa.
BIOTECHNOLOGY COMPANIES	
Alphavax	**AlphaVax** is developing a multigene alphavirus vector vaccine.
Bavarian Nordic	**Bavarian Nordic** is developing an MVA-based HIV vaccine.
Crucell	**Crucell** continues to work with the VRC to develop a preventive vaccine using Crucell's Ad26 adenovector.
Genvec	**Genvec** continues to work with the VRC to develop a preventive vaccine using Genvec's adenovirus vector delivery technology.
GeoVax	**GeoVax** has progressed to Phase II tests of its MVA/DNA prime boost regimen as a preventive and therapeutic vaccine.
Inovio Pharmaceuticals	**Inovio Pharmaceuticals** is developing a DNA-based preventive and therapeutic vaccines and combining it with an MVA candidate.

LIST OF ACRONYMS

amfAR	American Foundation for AIDS Research
ANRS	National Agency for Research on AIDS and Viral Hepatitis, France
BMGF	Bill & Melinda Gates Foundation
BRICS	Brazil, Russia, India, China, and South Africa
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CDC	Centers for Disease Control and Prevention
CHVI	Canadian HIV Vaccine Initiative
CIDA	Canadian International Development Agency
CIHR	Canadian Institutes of Health Research
DFID	Department for International Development
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
FACTS	Follow-on African Consortium for Tenofovir Studies
FHI	Family Health International, US
HPTN	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 and Johnson
MHRP	United States Military HIV Research Program
MRC	Medical Research Council
MTN	Microbicide Trials Network
NHMRC	National Health & Medical Research Council
NIAID	National Institute of Allergy and Infections Diseases
NIH	National Institutes of Health
PDP	Product Development Partnership
PEPFAR	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
UAFC	Universal Access to Female Condom Joint Programme
USAID	United States Agency for International Development

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HIV Vaccines and 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 Microbicide
www.ipmglobal.org

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

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