Advancing the Science in a Time of Fiscal Constraint: Funding for HIV Prevention Technologies in 2009

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HIV Vaccines and Microbicides Resource Tracking Working Group
www.hivresourcetracking.org

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

HIV VACCINES AND MICROBICIDES RESOURCE TRACKING WORKING GROUP

Since 2004, the HIV Vaccines and Microbicides Resource Tracking Working Group (Working Group) has generated estimates of research and development (R&D) investment that can be compared year to year, from one HIV prevention technology to another, and across funding sources. This effort supports the 2001 United Nations General Assembly Special Session (UNGASS) Declaration of Commitment on HIV/AIDS, which called for the development of sustainable and affordable prevention technologies, such as HIV vaccines and microbicides.[1] Information collected in previous years has also been used by the Working Group and others to monitor levels of effort, to analyze the significance of investment trends, and to assess the impact of public policies aimed at accelerating scientific progress.

The Working Group was founded by the Alliance for Microbicide Development (AMD), AVAC: Global Advocacy for HIV Prevention (AVAC), the International AIDS Vaccine Initiative (IAVI), and the Joint United Nations Programme on HIV/AIDS (UNAIDS). In late 2009, after five years of support for and participation in the Working Group, AMD closed its doors and withdrew from the Working Group. In 2010, the International Partnership for Microbicides (IPM) joined the Working Group.

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EXECUTIVE SUMMARY

- In 2009, public-sector, philanthropic and commercial funders invested US$1.165 billion toward **HIV prevention R&D** for preventive vaccines, microbicides, pre-exposure prophylaxis (PrEP) using antiretroviral drugs (ARVs) and operations research related to male circumcision.

- Despite the onset of a global recession, **preventive HIV vaccine R&D investment** remained steady between 2008 and 2009. In 2009, total global investment in **preventive HIV vaccine R&D** was an estimated US$868 million, the same level as 2008. Of that total, the public sector provided US$746 million (86%), the philanthropic sector provided US$92 million (11%), and the commercial sector accounted for US$30 million (3%). This year of stable funding followed a 10% decrease in preventive HIV vaccine R&D from 2007 to 2008. [Table 2]

- In 2009, **preventive HIV vaccine R&D** investment by the European Commission (EC) and European countries declined 5%, and investment by countries outside of Europe and the US declined 23%. The US increased its investment in preventive HIV R&D by 5%, attributed to US$35 million in American Recovery and Reinvestment Act (ARRA) stimulus funds directed to the US National Institutes of Health (NIH). Without these funds, total investment in preventive HIV vaccine R&D would have declined by 3%.

- **Preventive HIV vaccine R&D** funds were invested predominantly in basic and preclinical research, which together accounted for 66% of the funds spent. [Figure 6]

- Investment in **therapeutic HIV vaccine R&D** is estimated at US$38.6 million in 2009. [Figure 5]

- In 2009, total global investment in **microbicide R&D** was US$236 million, a US$8 million (3%) decrease from 2008. Of that total, the public sector provided US$223 million (94%), the philanthropic sector provided US$12 million (5%), and the commercial sector accounted for US$1 million (<1%). [Table 4]

- From 2008 to 2009, US funding for **microbicide R&D** increased by US$18 million (12%) and European funding increased by US$4 million (11%). However, philanthropic funding declined by 66%.

- Funds invested for **microbicide R&D** predominantly supported preclinical and clinical research, which together accounted for 70% of the funds spent. [Figure 8]

- In 2009, public and philanthropic funders contributed US$111 million to support R&D activities directed toward one or more of the following **HIV prevention options**: male circumcision, reducing vertical transmission at birth or during breast feeding,

and PrEP. Of that funding, public-sector funders provided US$84 million (76%) and the philanthropic sector provided US$27 million (24%), whereas the commercial sector provided ARVs for research.

- Funding for **R&D for HIV vaccines, microbicides, and other HIV prevention options** came primarily from the US National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation (BMGF). [Figure 13, 14, 15]

- Although all members of the G8 and most members of the G20 have supported HIV prevention research in the past few years, the support from some countries has declined from five years ago in real terms and as a percentage of their national Gross Domestic Product (GDP).[2] [Table 1]

- Given the onset of a global recession beginning in 2008, level funding for HIV prevention is positive news. This stability in funding is encouraging, but it masks some reasons for concern about funding for HIV prevention. These concerns have to do with the structure of funding sources and the implications of level or "flat" funding.

    - *Current Funding Levels and Structures Do Not Adequately Anticipate the Costs of Potential Late-stage Research*. Scientific momentum is imperiled when funding is not available to test new prevention approaches in human clinical trials

    - *Funding Stability is Concentrated in a Few Funders*. Funding stability in 2009 was largely the result of increased or sustained funding by the US and the BMGF. The introduction of new public-sector funders such as China, and new philanthropic funders such as the Phillip and Susan Ragon Institute, may contribute to stabilizing and ultimately increasing funding for discovery and clinical research.

    - *A Diversity of Funders is Needed to Supplement Resources and to Diversify Research Approaches*. New funders are clearly needed, not just for the supplementation of funding but for their important voices, alternative perspectives, and fresh approaches to global HIV prevention research and development.

    - *Flat Funding Does Not Account for Increases in the Costs of Biomedical Research*. With biomedical research costs rising 3–4% annually, the real value of existing funding commitments diminishes over time.

    - *Current Funding Levels May Not Be Indicative of Future Commitments*. This report highlights R&D funding investment for the development of HIV prevention products in 2009. As current funding commitments come to an end, the concern will be whether donors will renew commitments at existing funding levels or whether cost cutting measures will result in reductions in HIV prevention R&D funding.

TABLE 1. TOTAL INVESTMENT IN HIV VACCINES, MICROBICIDES AND OTHER HIV PREVENTION OPTIONS AS A PERCENTAGE OF COUNTRY GROSS DOMESTIC PRODUCT IN 2000, 2005 AND 2009*

.006-.007%		Ireland	
.005-.006%		United States	United States
.002-.003%	United States	Canada, United Kingdom	Norway, United Kingdom
.001-.002%	Norway	Netherlands, Norway, Sweden	Netherlands, Sweden
.0005-.001%	France	Denmark, South Africa, Thailand	Canada, Denmark, Ireland, Russia, South Africa, Thailand
<.0005%	Australia, Brazil, China, Canada, Denmark, Finland, Germany, India, Ireland, Italy, Japan, Netherlands, Russia, Sweden, Thailand, United Kingdom	Australia, Belgium, Brazil, China, Finland, France, Germany, India, Italy, Japan, Russia	Australia, Brazil, China, France, Germany, India, Italy, Japan, Spain
	2000	2005	2009

*Percentages represent total investment in HIV prevention research as a percentage of national gross domestic product.

FIGURE 1. HIV VACCINE PUBLIC-SECTOR FUNDING 2000–2009 (US$MILLION)

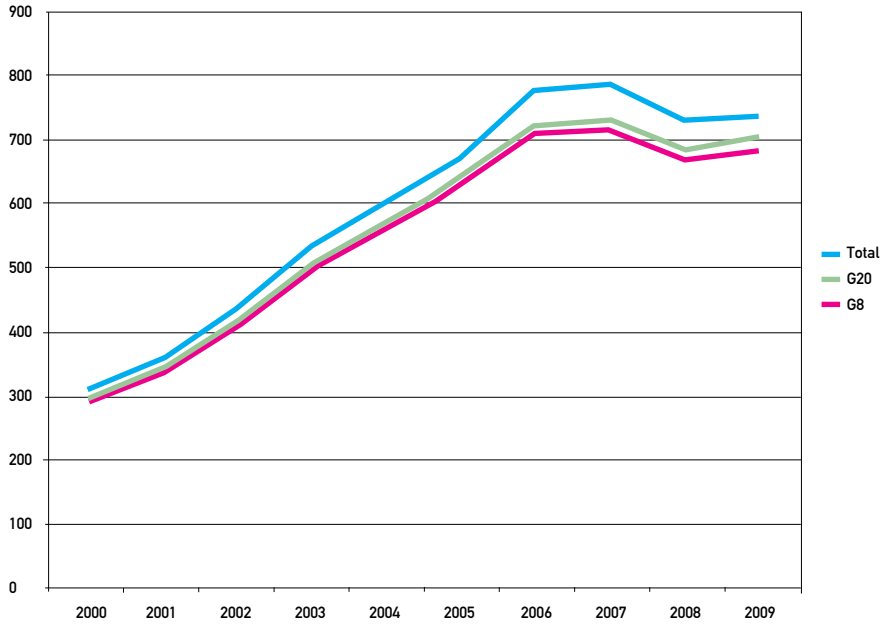
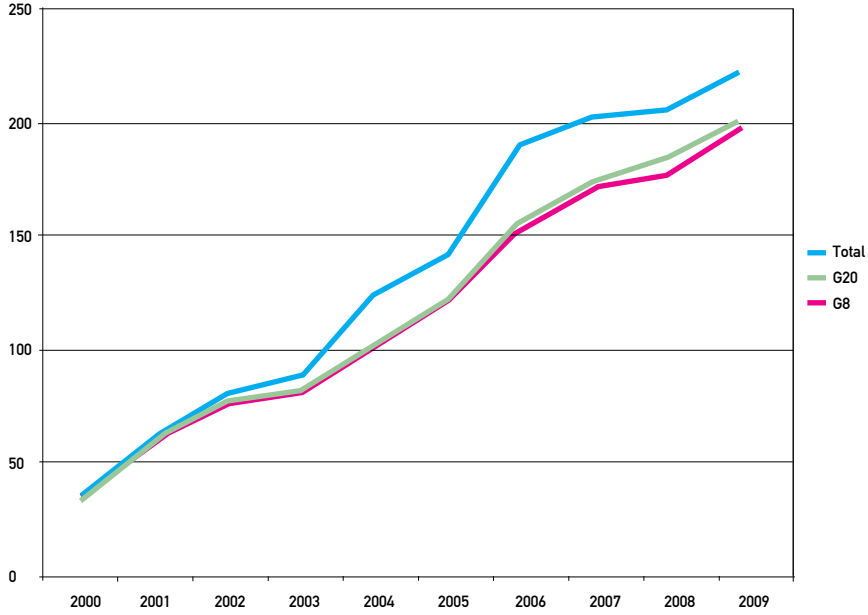


FIGURE 2. MICROBICIDE PUBLIC-SECTOR FUNDING 2000–2009 (US$MILLION)



INVESTMENT IN HIV VACCINE R&D

In 2009, total global investment in R&D for HIV preventive vaccines was US$868 million, the same level as the previous year. This funding level followed a 10% decrease from 2007 to 2008. [Table 2] Public-sector agencies and institutions continued to dominate investment in HIV vaccine R&D in 2009.

Four countries (China, the Russian Federation, the United Kingdom, and the United States) each invested US$10 million or more in public-sector funds in 2009, and an additional eight countries invested more than US$1 million each. The United Kingdom was the second largest public funder after the US, at US$24 million. Although US funding in 2009 increased by US$29 million over 2008, US$35 million was received through stimulus funding under the American Recovery and Reinvestment Act (ARRA) which is due to expire after 2011. Without ARRA funding, total HIV vaccine investment in 2009 would have declined 3% from 2008.

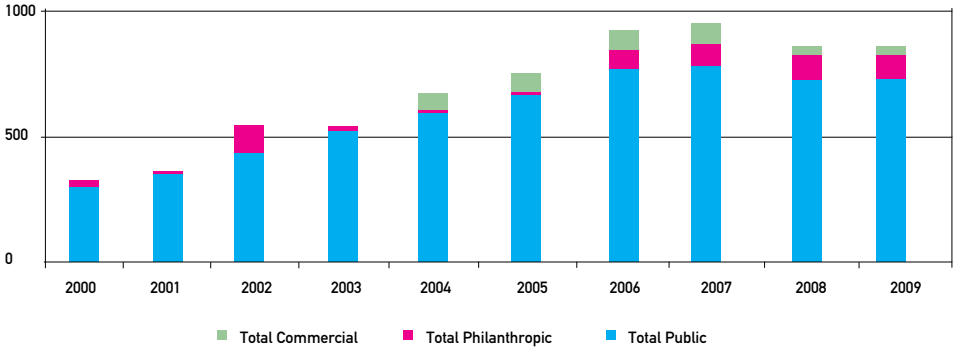
TABLE 2. ANNUAL INVESTMENT IN HIV VACCINE R&D 2005–2009 (US$MILLION)

	2005	2006	2007	2008	2009
US	574	654	659	620	649
Europe	69	82	79	69	65
Other	27	38	49	41	31
Multilaterals	2	2	2	1	1
Total Public	672	776	789	731	746
Total Philanthropic	12	78	88	104	92
Total Commercial	75	79	84	33	30
Total Global Investment	759	933	961	868	868

In 2009, results of the RV 144 trial conducted by several partners, including the NIH, the US Military HIV Research Program (USMHRP) and the Thai Ministry of Public Health, demonstrated modest protection by the ALVAC/gp120 candidate vaccine, but perhaps more importantly showed for the first time that an HIV vaccine was possible. The recent discovery of novel broadly neutralizing antibodies by a research consortium led by the International AIDS Vaccine Initiative (IAVI) and by the NIH Vaccine Research Center (VRC) have also generated new excitement.

These recent scientific breakthroughs in the vaccine field have led to planning for new efficacy trials. One such trial would use a prime-boost candidate to attempt to improve upon the modest efficacy found in the RV 144 trial. Such a trial could cost from US$30 million to over US$100 million, depending upon trial size and the number of vaccine regimens being tested.[3] In addition, the NIH and others are considering a passive antibody clinical trial as part of the development process for an antibody-based HIV vaccine.

FIGURE 3. HIV VACCINE FUNDING BY SECTOR 2000–2009 (US$MILLION)*



*Data used to prepare this graph can be found in Table 2. Data were not collected for commercial investment before 2004.

PHILANTHROPIC INVESTMENT IN HIV VACCINE R&D

The philanthropic sector accounted for US$92 million (11%) of the total funds disbursed for HIV vaccine R&D in 2009. The Bill & Melinda Gates Foundation (BMGF) accounted for US$76 million (83%) of all philanthropic investment [Table 3]. In 2009, Phillip T. Ragon became an important new HIV vaccine funder, with a US$100 million grant over 10 years to the Phillip and Susan Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University.

TABLE 3. PHILANTHROPIC INVESTMENT BY FOUNDATIONS AND COMPANIES TOWARD HIV VACCINE R&D IN 2009

Over US$75 million	Bill & Melinda Gates Foundation
US$5 million to US$10 million	Phillip and Susan Ragon Institute
US$1 million to US$2 million	Starr Foundation
US$500,000 to US$1 million	Elizabeth Glaser Pediatric AIDS Foundation
US$250,000–US$500,000	Wellcome Trust, Fundació La Caixa, Becton Dickenson, GlaxoSmithKline, Pfizer
< US$250,000	amfAR, Kovler Foundation, Continental Airlines, James B. Pendleton Trust, Duke University, W.M. Keck Foundation, Henry M Jackson Foundation, John D Evans Foundation

COMMERCIAL INVESTMENT IN HIV VACCINE R&D

Commercial investment in HIV vaccine R&D remained level in 2009, with several continuing and important HIV vaccine development partnerships involving the private, public and philanthropic sectors.

- Merck & Co. continues to explore the results from the Step trial of its adenovirus vaccine and to fund research into development of antigens to elicit protective antibodies.

- Sanofi-Aventis, through its vaccine division, Sanofi Pasteur, is working with the NIH and the USMHRP on follow-up to RV 144.

- Novartis continues its alphavirus vector program and is also developing a protein for possible use in the follow-up trial to RV 144.

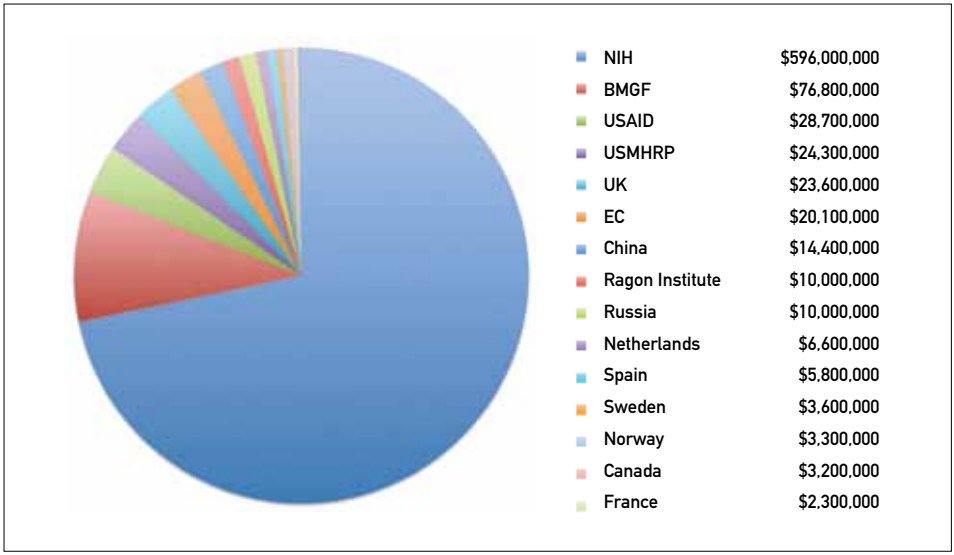
- GlaxoSmithKline (GSK) has programs to develop HIV vaccines using its proprietary adjuvants combined with proteins.

GSK, Merck, Novartis, and Sanofi are all continuing to support programs feeding into timely clinical trial work across the vaccine field. Although Europe lags behind the US in public-sector investment, three of the four pharmaceutical companies with active HIV programs are headquartered in Europe.

Biotechnology companies that have HIV vaccine programs include Alphavax, Argos Therapeutics, Bavarian Nordic, Crucell, Elevation Biotech, EpiVax, Genvec, GeoVax, ImmunoGenix, Inovio Pharmaceuticals, Maxygen, Profectus Biosciences, Progenics Pharma, and United Biomedical. Several biotech companies are supported in their work on HIV vaccines through grants from the NIH or the IAVI Innovation Fund. In 2009, GeoVax, with support from the NIH, began an HIV Vaccine Trials Network (HVTN) Phase IIa trial of its MVA/DNA vaccine candidate.

The year 2008 saw a reassessment of, and in some cases a retrenchment from, commercial investment in the HIV preventive vaccine field. Much of this was prompted by the early halting in 2007 by the Data Safety Monitoring Board (DSMB) of the Step trial of the Merck Ad5 adenovirus vaccine for lack of efficacy. Results from the RV 144 trial could change this dynamic and engage new partners from the commercial sector, but the modest levels of protection shown suggest that optimism should be cautious. If anything, the global recession that began in 2008 will likely further constrain such investment in the immediate future.

FIGURE 4. TOP 15 PUBLIC AND PHILANTHROPIC HIV VACCINE FUNDERS IN 2009

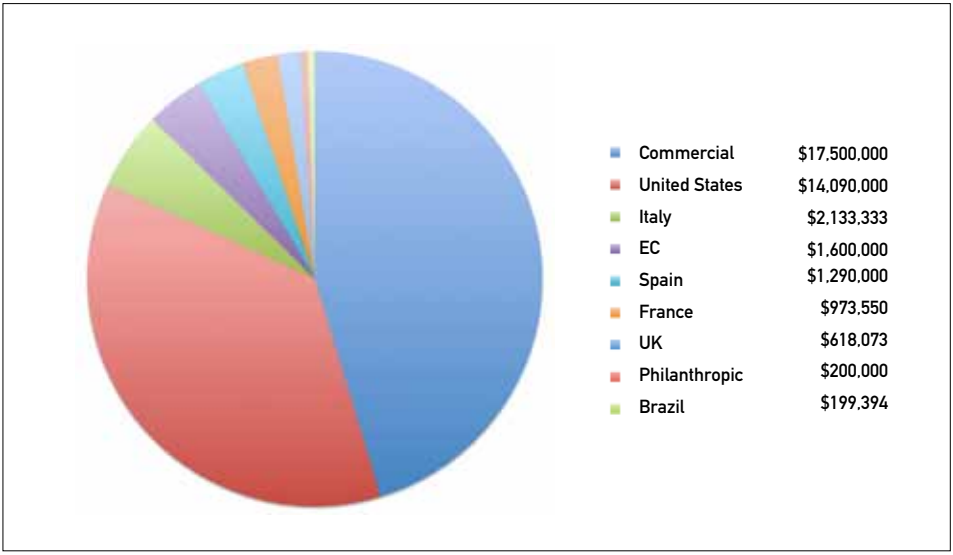


FUNDING FOR THERAPEUTIC HIV VACCINE R&D

Therapeutic vaccines aim to treat HIV infection by enhancing immune responses to HIV. Therapeutic HIV vaccine research started in the early 1990s, with several trials in the US and Europe. Several HIV vaccine candidates are being tested both as preventive vaccines in HIV-negative individuals and as therapeutic vaccines in HIV-positive individuals.

In 2009, therapeutic HIV vaccine R&D received an estimated US$39 million, with the US contributing 36% and Europe contributing 17%. [Figure 5] As was the case in 2008, the EC and European funders provided a greater percentage of the total global R&D support for therapeutic HIV vaccines (17%) than they did for preventive HIV vaccines (8%). Therapeutic HIV vaccine R&D received almost half of its funding (44%) from pharmaceutical companies such as GSK and biotech companies such as Argos Therapeutics, GeoVax, Inovio Pharmaceuticals, and ImmunoGenix.[4]

FIGURE 5. HIV THERAPEUTIC VACCINE INVESTMENT IN 2009

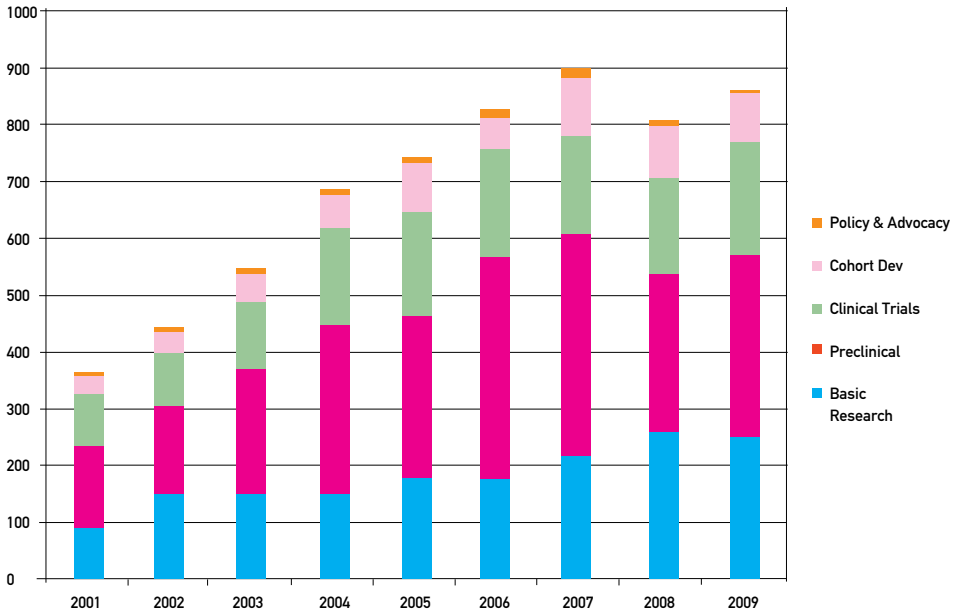


Funders have also started to look toward research examining whether HIV infection could be "functionally eradicated" so that HIV-positive persons might live without ARV drugs for years or possibly for the rest of their lives. The NIH has recently announced a program to fund interventions that will develop "functional cure" strategies. At the same time, amfAR, the Foundation for AIDS Research, announced in 2010 the first round of grants to researchers developing strategies for eradicating HIV infection.

EXPENDITURES ON VACCINE R&D

For this report, spending by the public and philanthropic sectors on preventive HIV vaccine R&D in 2009 was allocated to five categories (See Appendix). Preclinical research (37%), and basic research (29%) account for the majority of expenditures. In order of magnitude, the other three categories receiving funding were clinical trials (23%), cohort and site development (10%), and policy and advocacy development (<1%). [Figure 6] Preclinical research, basic research, and clinical trials saw increases in funding for 2009, with preclinical research seeing the largest percentage change at 16%.[5]

FIGURE 6. EXPENDITURE DISTRIBUTION FOR PUBLIC AND PHILANTHROPIC FUNDING FOR HIV VACCINE R&D IN 2001-2009 (US$MILLION)*



*Based upon a total expenditures for which allocations could be calculated.

INVESTMENT IN MICROBICIDE R&D

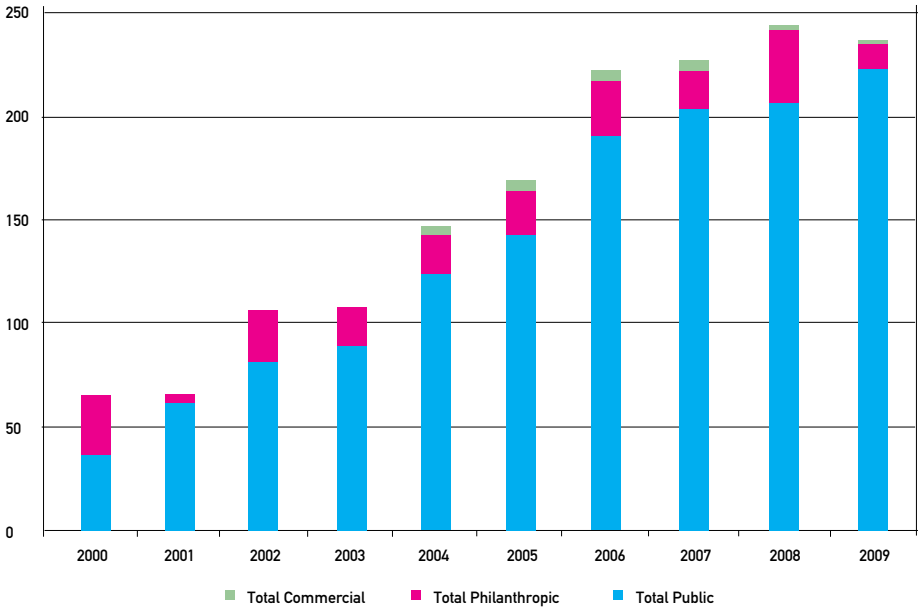
In 2009, total global investment in microbicide R&D was US$236 million, a 3% decrease from 2008. [Table 4] This small decline came from lower philanthropic investment in 2009, and represents the first year-to-year decline in microbicide funding since 2000. This funding continued to be dominated by public agencies and institutions led by the UK and the US, each of which invested more than US$10 million in public-sector funds. The EC was the third largest funder, at US$7 million, and an additional 10 countries invested more than US$1 million each [Figure 9].

CAPRISA 004, a Phase IIb clinical trial of tenofovir gel used as a coitally-dependent microbicide, will report results in July 2010. Tenofovir is an ARV-based nucleotide reverse transcriptase inhibitor (NRTI). If CAPRISA shows that the tenofovir gel is effective in preventing HIV infection, a confirmatory trial may be required for licensure. The International Partnership for Microbicides' (IPM) most clinically advanced candidate, a long-acting monthly dapivirine ring, continues to progress and is scheduled to enter Phase III evaluation in 2011. Dapivirine is an ARV-based non-nucleoside reverse transcriptase inhibitor (NNRTI). The evaluation would cost approximately US$ 90 million.[6]

TABLE 4. ANNUAL INVESTMENT IN MICROBICIDE R&D 2005–2009 (US$MILLION)

	2005	2006	2007	2008	2009
US	101.6	129.7	139.8	154.4	172.6
Europe	30.3	56.3	59.6	39.9	44.4
Other	10.5	4.7	3.4	12.1	5.7
Multilaterals	0.2	1.4	0.2	0.2	0.2
Total Public	142.6	192.1	203	206.6	222.9
Total Philanthropic	21.3	26.2	19	34.6	11.8
Total Commercial	4.5	4.5	4.5	2.5	1
Total Global Investment	168.4	222.8	226.5	243.7	235.7

FIGURE 7. MICROBICIDE FUNDING BY SECTOR 2000–2009 (US$MILLION)*



*Data used to prepare this graph comes from Table 4.

PUBLIC INVESTMENT IN MICROBICIDE R&D

In 2009, the public sector accounted for 94% of the combined global funding for microbicide R&D. A 12% increase in funding (US$19 million) from 2008 by the US was partially accounted for by a US$4.7 million infusion of ARRA stimulus funds. The US continued to maintain the largest presence, providing US$173 million (73%) of total investment. European governments and the EC together accounted for US$44.4 million, an 11% increase from 2008. [Table 4].

PHILANTHROPIC INVESTMENT IN MICROBICIDE R&D

In 2009, the philanthropic sector provided US$12 million (6%) of the funds disbursed for microbicide development. This was 66% lower than in 2008 and due largely to fluctuation caused by the funding of multi-year grants which can produce wide fluctuations between years when grants are made and how they are paid out. The vast majority of the philanthropic funding for 2009 came from the BMGF, followed by the Wellcome Trust, the Ford Foundation, and amfAR.

COMMERCIAL INVESTMENT IN MICROBICIDE R&D

The most significant contribution from the commercial sector comes in the form of non-exclusive royalty-free transfers of ARVs for use as active agents in microbicide development. That sector also provides microbicide developers with valuable product data and technical advice. From 2004 to 2009, IPM obtained non-exclusive royalty-free licenses for ARVs from Gilead Sciences (NRTI), Johnson & Johnson subsidiary Tibotec (NNRTI), Pfizer (CCR5 blocker), Merck & Co. (CCR5 blocker & gp41 binder), and Bristol-Myers Squibb Co. (gp120 binder). CONRAD and the Population Council have also received material transfers and licenses for similar purposes, including licenses to develop ARVs as components of combination products.

The microbicide field has also benefited over this period from the active participation of the following biotechnology companies for the following products: Endo Biopharmaceuticals (PRO 2000), ImQuest Biosciences (pyrimidinediones), Mapp Biopharmaceuticals (monoclonal antibodies), Osel (probiotics), ReProtect (BufferGel), and Starpharma Holdings (VivaGel)—all with support for follow-on development through a variety of NIH grant and contract mechanisms. There has been substantial commercial participation and collaboration with non-profit developers and partnerships such as CONRAD, IPM, and the Population Council, which has included a broad range of expertise: 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 related to manufacture of microbicide delivery systems, participation in microbicide development meetings and teleconferences, and timeline guidance.

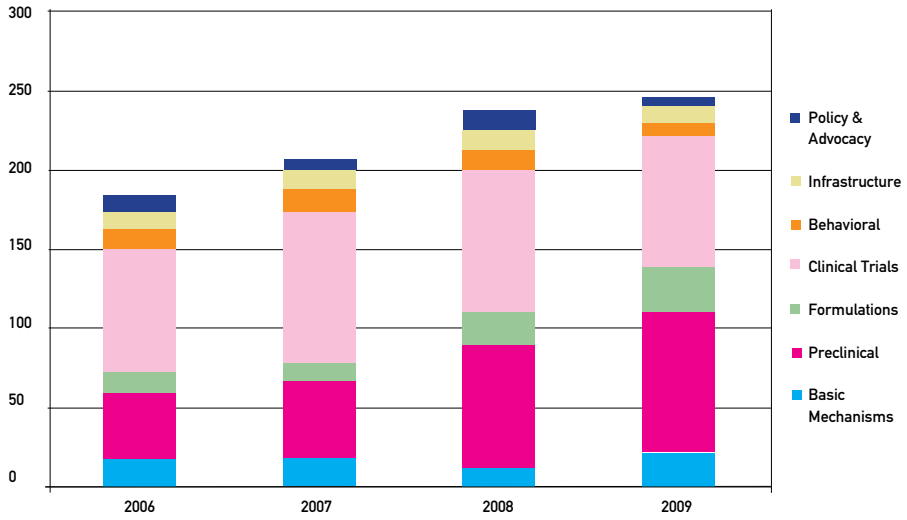
FUNDING FOR RECTAL MICROBICIDE R&D

The 2010 report by the International Rectal Microbicide Advocates (IRMA), *From Promise to Product: Advancing Rectal Microbicide Research and Advocacy*,[7] estimates that R&D toward developing a microbicide for rectal use was funded at a little over US$7 million in 2009, with most of this coming from US sources, specifically amfAR and the NIH.[8]

FUNDING ALLOCATIONS FOR MICROBICIDE R&D

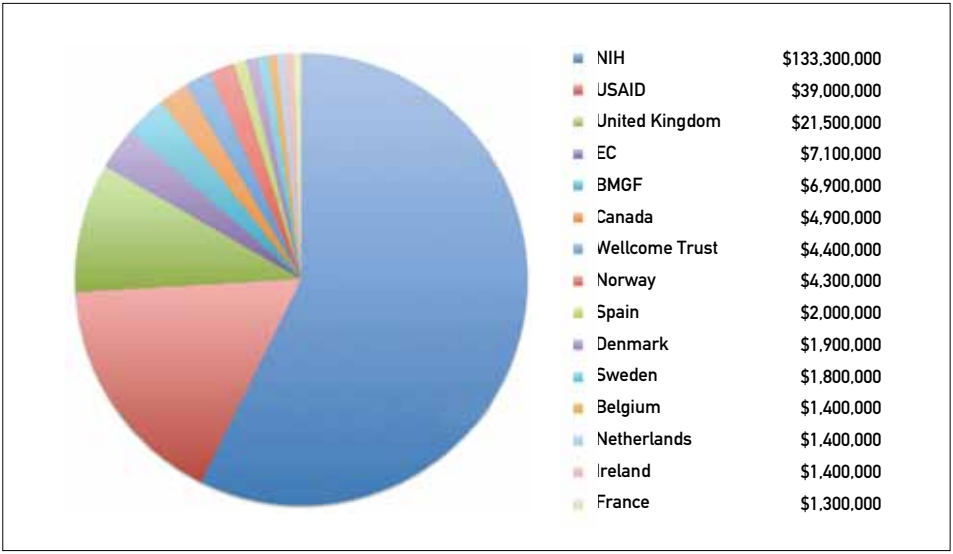
In 2009, expenditures on microbicide R&D were allocated across the following seven categories (see Appendix)[9]: basic mechanisms of mucosal transmission (9%); discovery, development and preclinical testing (36%); formulations and modes of delivery (11%); clinical trials (34%); microbicide behavioral and social science research (4%); microbicide research infrastructure (4%); and policy and advocacy (2%). [Figure 7] Basic mechanisms of mucosal transmission, formulations and preclinical work saw increased investment from 2008 to 2009.

FIGURE 8. EXPENDITURE DISTRIBUTION FOR PUBLIC AND PHILANTHROPIC FUNDING FOR MICROBICIDE R&D IN 2006-2009 (US$MILLION)*



*Based upon expenditures for which allocations could be calculated.

FIGURE 9. TOP 15 PUBLIC AND PHILANTHROPIC MICROBICIDE FUNDERS IN 2009



INVESTMENT IN HIV PREVENTION R&D RELATED TO PRE-EXPOSURE PROPHYLAXIS

TABLE 5. ANNUAL INVESTMENT IN PRE-EXPOSURE PROPHYLAXIS 2005–2009 (US$MILLION)

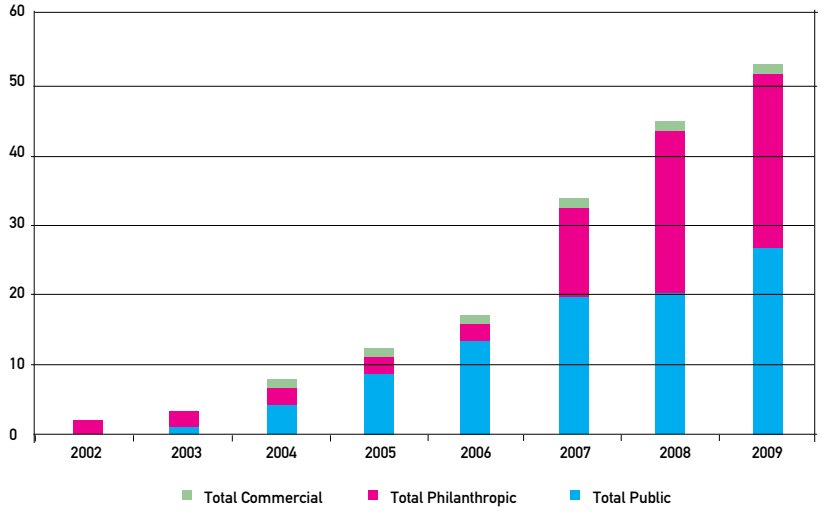
	2005	2006	2007	2008	2009
Total Public	8,853,200	13,473,100	19,710,900	20,599,481	26,583,123
Total Philanthropic	2,357,900	2,357,900	12,561,700	22,505,700	24,600,446
Total Commercial	1,250,000	1,250,000	1,250,000	1,250,000	1,250,000
Total	12,461,100	17,081,000	33,522,600	44,355,181	52,433,569

Global public-sector and philanthropic investment in pre-exposure prophylaxis (PrEP) over the last eight years totaled US$173 million and has been increasing steadily, with annual funding more than quadrupling from 2005 to 2009. [Table 5] In 2009, funding for oral PrEP was US$52 million, or US$8 million more than in 2008. There are five ongoing oral PrEP effectiveness trials and four ongoing safety trials. In 2009, the St. Stephens AIDS Trust began a BMGF funded safety trial of Tibotec's antiretroviral TMC278 (rilpivirine) injected intramuscularly, as a possible long-acting PrEP drug which is also included in these totals.

The iPrEx study, testing the safety and effectiveness of daily tenofovir/emtricitabine in preventing HIV transmission in 3000 HIV-negative men who have sex with men (MSM), is expecting to release results in early 2011. In addition, a study funded by the CDC testing daily dosage of tenofovir (CDC 4323) to prevent HIV infection in injection drug users in Bangkok, Thailand is expecting to release results by early 2011. These trials will provide the first effectiveness results for daily oral use of ARVs for HIV prevention.

Depending upon the results in PrEP trials of tenofovir or tenofovir/emtricitabine (CDC 4323, iPrEx), a second confirmatory trial for licensure may be needed. If these trials provide proof of concept for ARV prophylaxis as a method of HIV prevention, there may be a movement to find an ARV that is not currently used in treatment programs for use as a PrEP drug. Thus, additional ARVs may need to be tested as PrEP agents to address safety or resistance concerns. The cost of additional PrEP trials could equal US$40-60 million each based upon the cost of current PrEP trials.[10]

FIGURE 10. PRE-EXPOSURE PROPHYLAXIS FUNDING 2002–2009 (US$MILLION)*



*Data used to prepare this graph can be found in Table 5.

INVESTMENT IN FOLLOW-UP STUDIES AND OPERATIONS RESEARCH RELATED TO MALE CIRCUMCISION

Over the past nine years, global public-sector and philanthropic investment in R&D and operations research related to male circumcision has totaled US$61 million. [Figure 11] In 2009, funding for male circumcision research declined by US$1 million from 2008. [Table 6] Investment in circumcision research has slowed since completion in 2006 of the NIH-funded trial in Rakai, Uganda and the BMGF-funded trial in Kisumu, Kenya, which established the effectiveness of male circumcision for HIV prevention.

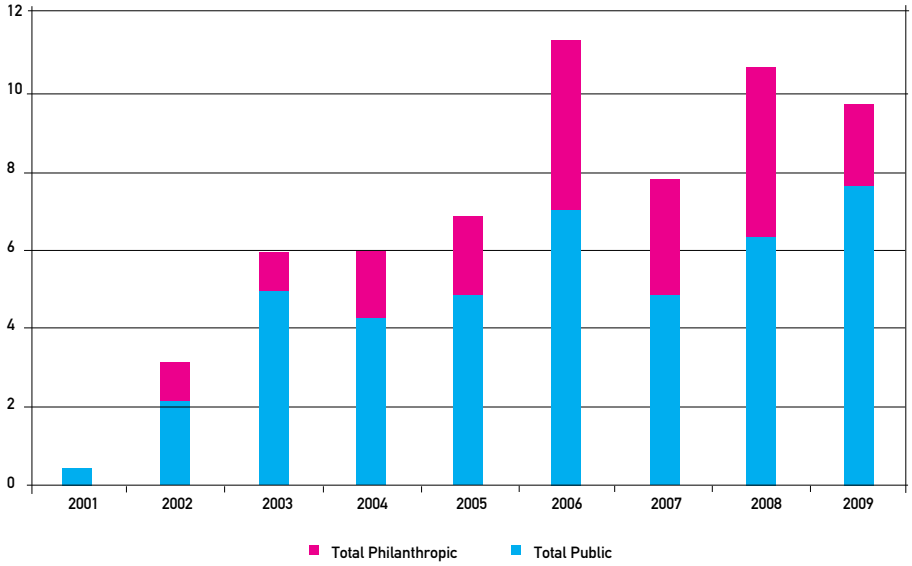
TABLE 6. ANNUAL INVESTMENT IN MALE CIRCUMCISION 2005–2009 (US$)

	2005	2006	2007	2008	2009
Canada	414,695	0	0	0	42,533
France	268,963	1,000,000	1,000,000	1,738,526	1,334,520
UK	-	-	-	-	115,930
US	4,118,300	5,984,441	3,817,337	4,487,573	6,080,451
Total Public	4,801,958	6,984,441	4,817,337	6,226,099	7,573,434
Total Philanthropic	1,988,814	4,246,979	2,905,668	4,344,627	2,070,850
Total	6,790,772	11,231,420	7,723,005	10,570,726	9,644,284

These trials, along with the study in Orange Farm, South Africa funded by the French Agence Nationale de Recherches sur le Sida (ANRS), provided rationale for investing in introducing male circumcision as an HIV prevention strategy. As scale-up has proceeded, investment has increased in follow-up studies by the ANRS, BMGF, and NIH.

In addition, the United States President's Emergency Plan for AIDS Relief (PEPFAR) has begun funding rollout of adult male circumcision programs. WHO and UNAIDS also invested resources in materials, technical assistance and policy development to translate the research findings into programs with public health impact.[11]

FIGURE 11. MALE CIRCUMCISION FUNDING 2001–2009 (US$MILLION)*



*Data used to prepare this graph can be found in Table 6.

INVESTMENT IN HSV-2 SUPPRESSION AND HSV-2 VACCINES

Global public-sector and philanthropic investment in HSV-2 suppression for HIV prevention using acyclovir totaled US$51 million from 2002 to 2008. In May 2009, results were released from the Partners in Prevention trial conducted at fourteen sites in seven African countries. The trial found that ongoing suppressive acyclovir therapy for HSV-2 in HIV-positive people did not reduce their risk of transmitting HIV to their HIV-negative partners. Although HSV-2 suppression with acyclovir has not been shown to affect HIV acquisition, there is a scientific basis for the view that prevention of HSV-2 infection in HIV-negative people may prove to be an effective HIV prevention strategy.

The Working Group has identified over US$7 million in investment in HSV-2 vaccine research. [Figure 12] HSV-2 vaccines have received commercial investment from pharmaceutical companies such as GSK and Sanofi Pasteur and from biotech companies such as BioVex, GenVec, and Vical. Because the Working Group was unable to verify investment by some companies engaged in HSV-2 vaccine research, US$7 million is likely an underestimation of this investment. Future commercial investment may be positively or negatively affected by the results from the Phase III trial of its HerpeVac vaccine as a preventive HIV vaccine for genital herpes in HSV-1– and -2 seronegative young women. This NIH-funded trial expects to release results in late 2010.

INVESTMENT IN ANALYSIS AND RESEARCH ON HIV TREATMENT AS PREVENTION

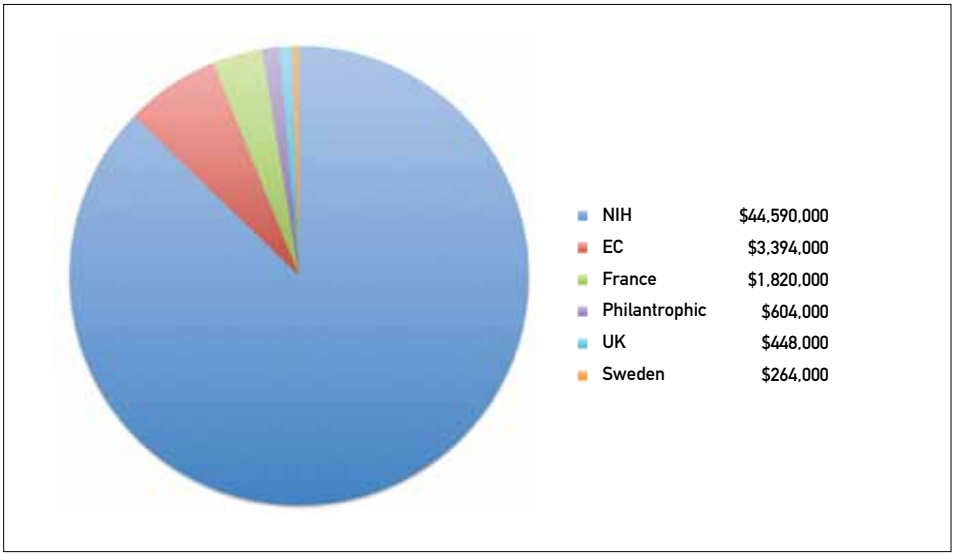
Ongoing research aims to evaluate HIV treatment as a means of HIV prevention, an approach known as "test-and-treat" or "treatment as prevention." The approach is based on the idea that new HIV infections in a community can be reduced if all community members have access to voluntary HIV testing, and all individuals who are HIV-positive are promptly referred to medical care and placed on a treatment regimen to reduce levels of HIV in their system. Evidence indicates that informing individuals about whether they are HIV-positive or HIV-negative can reduce risky behavior. Ongoing studies are examining the prevention effect of HIV treatment—whether early treatment can reduce community incidence by reducing community viral loads. In addition to this clinical work, several modeling projects are examining the prevention effect of greater linkage to HIV treatment.

The NIH is funding two trials examining the prevention effect of HIV treatment. The HIV Prevention Trials Network (HPTN) 052 Phase III trial is designed to determine the effectiveness of early treatment in preventing the sexual transmission of HIV in HIV-serodiscordant couples in eight countries in a 78-month study. The HPTN 065 trial will evaluate the feasibility, effectiveness and prevention effect of community-focused expanded HIV testing and linkage to care in the United States. In Europe, Imperial College London is planning an as-yet unfunded trial, entitled PopArt (Population effects of AntiRetroviral Therapy), which will determine the effect and feasibility of test-and-treat programs in South Africa. Finally, the ANRS has funded a study entitled TasP (Treatment as Prevention), to begin in 2010, which will examine the feasibility and acceptability of the test-and-treat concept in South Africa.

INVESTMENT IN OPERATIONS RESEARCH RELATED TO VERTICAL TRANSMISSION PREVENTION

In 2009, the Working Group identified US$51 million in funding for research into prevention of vertical transmission of HIV. [Figure 12] The public sector accounted for almost all of this funding (99%), with the philanthropic sector providing the remainder. In 2009, there were 10 active clinical trials related to prevention of transmission at birth or through breastfeeding, funded by the ANRS, CDC, through the EC, the European & Developing Countries Clinical Trials Partnership (EDCTP), and NIH.[12]

FIGURE 12. VERTICAL TRANSMISSION PREVENTION FUNDING IN 2009



INVESTMENT BY TRIAL PARTICIPANTS IN HIV VACCINE, MICROBICIDE AND PrEP RESEARCH

In 2009, there were almost 46,000 participants in HIV prevention research trials. [Table 7] Although the RV 144 trial in low-risk Thai men and women are an important exception, these trials were predominantly in countries and communities at highest risk. Trial sites in these settings offer rapid answers to HIV prevention research and provide a critical and irreplaceable contribution to the HIV prevention field. These trials benefit these countries and communities through provision of health and other services and the potential for new HIV prevention options. Nevertheless, these trials require extraordinary time and commitment of countries and participants. The Working Group has not placed a financial value on this contribution, but it unquestionably represents a major investment in HIV prevention research.

TABLE 7. HIV PREVENTION RESEARCH TRIAL PARTICIPANTS BY COUNTRY IN 2009

	Country	Number of Participants	Type of Prevention
1	Thailand	19,243	PrEP and vaccines
2	Uganda	6,011	PrEP, microbicides and vaccines
3	Kenya	5,863	PrEP, microbicides and vaccines
4	South Africa	2,968	PrEP, microbicides and vaccines
5	US	2,691	PrEP, microbicides and vaccines
6	Malawi	1,967	PrEP and microbicides
7	Zambia	1,887	PrEP, microbicides and vaccines
8	Botswana	1,200	PrEP
9	Tanzania	1,068	PrEP, microbicides and vaccines
10	Zimbabwe	1,060	PrEP
11	Peru	574	PrEP and vaccines
12	Brazil	417	PrEP
13	Ecuador	417	PrEP
14	UK	163	PrEP and vaccines
15	China	80	Vaccines
16	Belgium	64	Microbicides
17	Sweden	38	Vaccines
18	Germany	35	Vaccines
19	Switzerland	35	Vaccines
20	France	35	Vaccines
21	India	32	Vaccines
22	Dominican Republic	25	Microbicides
23	Russia	15	Vaccines

*In a few cases the actual number of participants per country could not be determined for specific trials. In these cases, the number of trial participants were divided equally among trial sites.

DISCUSSION

In 2009, UNAIDS released its annual AIDS Epidemic Update, which indicated that annual new HIV infections have been reduced from 3.2 million to 2.7 million since 2001. While the reason for this decline is unclear and may be the result of a number of complex factors, UNAIDS found "growing evidence of HIV prevention successes in diverse settings."[13] Yet, despite these advances, 2.7 million people became HIV-positive in 2008 and funding for HIV prevention has become the smallest percentage of the HIV budgets of many countries. Thus, there is a clear "prevention gap" between what has been achieved and what is needed to drive incidence to zero. Although that can be partly filled by better access to existing prevention approaches, many believe that new prevention options are needed. This need for new prevention tools has fueled the clinical testing of the first ARV-based microbicides and PrEP, a richer microbicide pipeline, and research expanding on the 2009 results of the RV 144 trial in Thailand, which showed modest protection against HIV and scientifically demonstrated for the first time that an AIDS vaccine was possible. Despite the onset of a global recession in 2008, funding for HIV vaccines and microbicides remained essentially level in 2009. Global HIV vaccine funding remained stable, and microbicide funding decreased by 3% (US$8 million) from 2008 to 2009. Funding for PrEP increased by US$8 million (18%) in that same period. In addition, funding for operations research aiming to improve delivery and uptake of male circumcision and prevention of vertical HIV transmission continued to improve.

Given the global recession, which has deeply affected economies and the budgets of HIV prevention research funders, level funding for HIV prevention is positive news. Total global HIV prevention research funding for vaccines, microbicides, PrEP and male circumcision has slipped 5% in 2009 from its historical high of US$1.23 billion, reached in 2007. The decline since 2007 has been felt primarily in funding of HIV vaccines, although in 2009 microbicide funding also suffered its first year-to-year decline since 2000.

This stability in funding is encouraging, but it masks some reasons for concern about funding for HIV prevention. These concerns have to do with the structure of funding sources and the implications of level or "flat" funding.

- *Current Funding Levels and Structures Do Not Adequately Anticipate the Costs of Potential Late-Stage Research*. Even when funding does not decline, scientific momentum is imperiled when funding is not available for testing of new prevention approaches in clinical trials. The HIV prevention field is primed to take the important next step in testing new HIV prevention agents in large-scale trials of vaccines, microbicides, and new PrEP agents. Yet, our ability as a field to undertake even the most critical of these large-scale trials is at risk in the current funding environment since such large-scale trials cannot be simply incorporated into existing HIV prevention budgets. As for the future, even when funding does not decline in absolute terms, flat funding constrains future research programs by making it difficult for funders already

committed to long-term projects and funding levels to shift gears as new opportunities arise. For example, challenges have already been encountered in identifying sufficient funding to follow up on the RV 144 trial results, or to respond to the growing need for additional pharmacokinetics (PK) and pharmacodynamics (PD) data for microbicide and PrEP trials. Further, if there are positive results in 2010 research from the CAPRISA 004 microbicide trial or in the iPrEx oral PrEP trial in 2011, or further RV 144 research points to a possible correlate of HIV protection, it may be difficult to build quickly upon such new developments simply because the current financing levels and structures cannot adjust accordingly.

- *Funding Stability is Concentrated in a Few Funders.* Funding stability in 2009 was largely the result of increased or sustained funding by the US and the BMGF. Together, these two funders accounted for 79% of vaccine funding, 59% of microbicide funding and 70% of PrEP funding. [Figures 13, 14 and 15] Both funders face challenges in continuing to fund HIV prevention research at comparable levels. US funding for HIV prevention research could decline once the stimulus funding expires in 2011 and the US government takes steps to reduce its budget deficit. The BMGF also confronts increasing demands from a variety of global health needs.

- *A Diversity of Funders is Needed to Supplement Resources and to Diversify Research Approaches.* Europe (including the EC), with the largest economy in the world as measured by GDP, has provided US$550 million in support for HIV vaccine research and US$280 million for microbicide research in the past decade.[14] Still, European funding for development of both technologies has declined from a peak in 2006–2007 and investment by some European countries as a percentage of their GDP has declined since 2005. [Table 1] In addition, a number of the G20 countries currently do not provide any funding for HIV prevention research. New funders are clearly needed, not just to supplement funding but for their important voices, alternative perspectives, and fresh approaches to global HIV prevention research and development. Diverse funding sources can also contribute to generating diverse research approaches by providing additional funding to research networks in different countries that may pursue alternative approaches and by bringing in new and young investigators who may consider innovative strategies.

- *Flat Funding Does Not Account for Increases in the Costs of Biomedical Research.* With biomedical research costs rising 3–4% annually, the real value of existing funding commitments diminishes even if funding is not reduced. For HIV vaccines, the flat or declining funding since the peak in 2007 has been amplified by the 10% overall increase in the cost of HIV vaccine R&D from 2007 to 2010.

- *Current Funding Levels May Not Be Indicative of Future Commitments*. This report highlights R&D funding investment for the development of HIV prevention products in 2009. Developing such products is costly and typically requires a number of years to complete. As such, a significant portion of the 2009 funding was likely reflective of resources committed when the global economy was far healthier. As current funding commitments come to an end, the concern will be whether donors will renew commitments at existing funding levels or whether cost cutting measures will result in reductions in HIV prevention R&D funding.

FIGURE 13. PRIMARY HIV VACCINE FUNDERS 2000–2009 (US$MILLION)

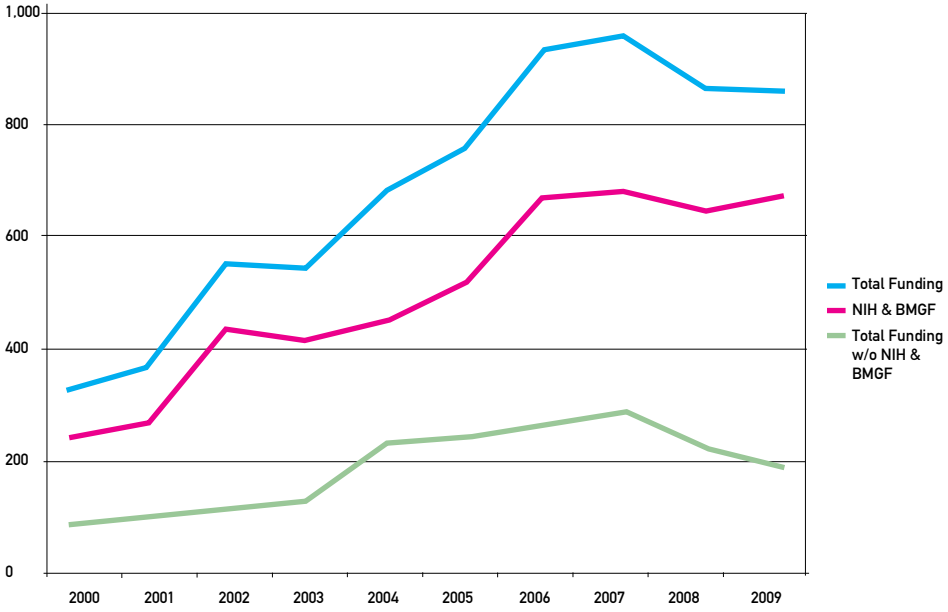


FIGURE 14. PRIMARY MICROBICIDE FUNDERS 2000–2009 (US$MILLION)

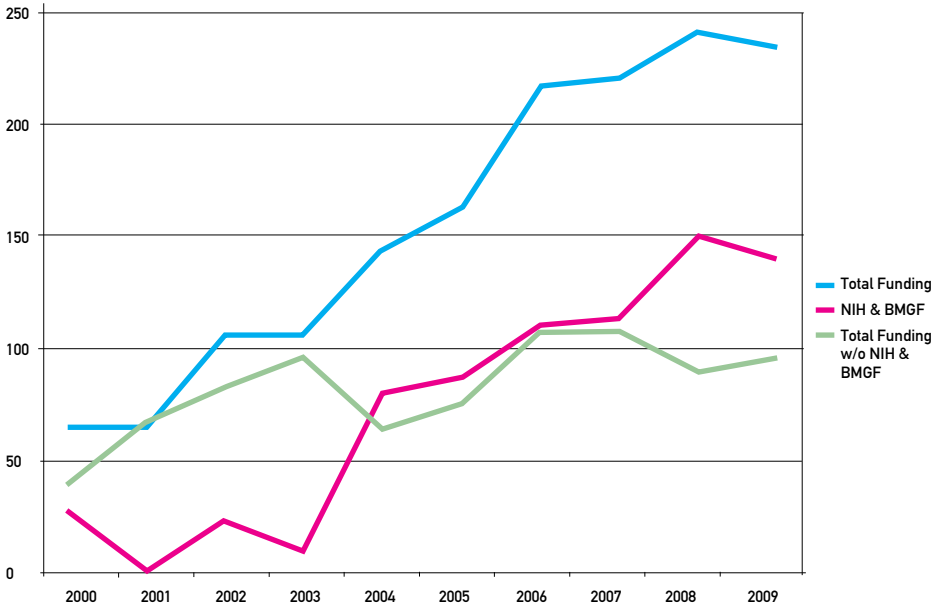
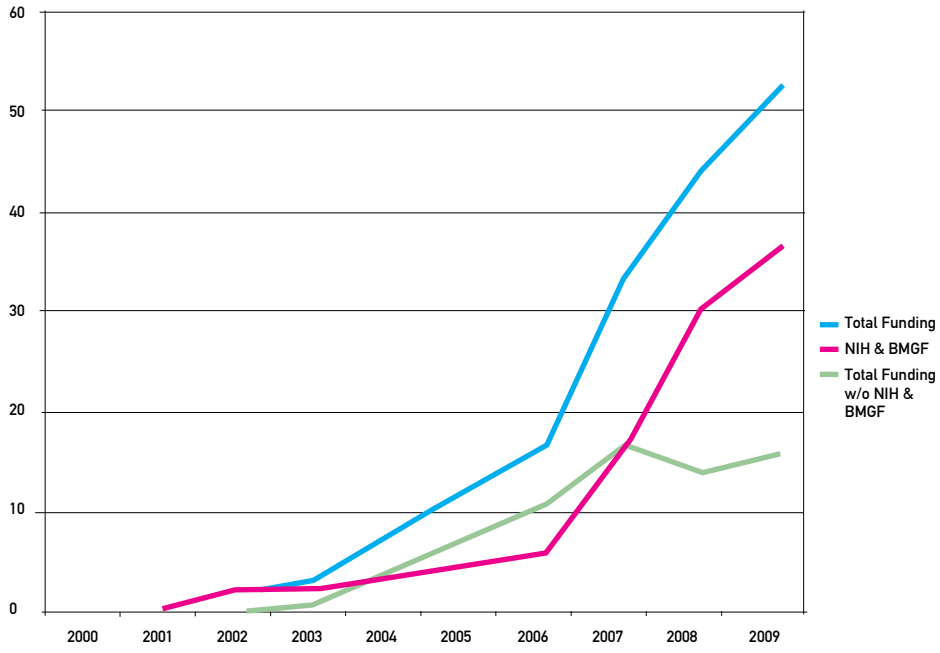


FIGURE 15. PRIMARY PrEP FUNDERS 2000–2009 (US$MILLION)



A number of trials have released or will release results over the 2009–2010 period that, together or separately, could radically change the trajectory of HIV prevention research. The overall trend since 2000, or even the past five years, has been for funding to increase significantly and for new funders to join in the effort to support HIV prevention research. Yet, even at the funding levels that have been achieved, the HIV prevention research field is unlikely to have sufficient resources to respond to all of the opportunities that could arise in the next few years. Now is the time to anticipate that possibility and responsibly ensure the capacity and flexibility to respond when opportunity knocks.

APPENDIX

METHODOLOGY

This report was prepared by Kevin Fisher (AVAC) and Wadzanayi Muchenje (AVAC), with contributions from Abie Alexander (IPM), Thomas Harmon (IAVI), Polly Harrison (AVAC), Wilson Lee (IAVI), Judith Orvos (IPM), 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 8. CATEGORIES USED TO CLASSIFY HIV VACCINE R&D FUNDING

Category	Definition
Basic Research	Studies to increase scientific knowledge of protective immune responses and host defenses against HIV.
Preclinical Research	R&D efforts directed at improving 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 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 HIV vaccines and at addressing potential regulatory, financial, infrastructure, or political barriers to their rapid development and use.

TABLE 9. 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	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	Educate and mobilize public and political support for microbicides and address potential regulatory, financial, infrastructure, or political barriers to their rapid development and use.

NOTES

1. These data are used to monitor the implementation of the UNGASS Global Commitment and Action Indicator 2—the amount of public funds available for HIV vaccine and microbicide research and development. In April 2009, the Report of the Secretary General on global progress toward that commitment reaffirmed the need for investment in new prevention research, acknowledging that the road to successful development of these technologies may be lengthy. (From the *Declaration of Commitment on HIV/AIDS and Political Declaration on HIV/AIDS: Midway to the Millennium Development Goals*, April 1, 2009.)

2. The G8 is composed of Canada, France, Germany, Italy, Japan, Russia, UK and the USA. The G20 comprises the G8, the European Commission, and China, Argentina, Australia, Brazil, India, Indonesia, Korea, Mexico, Saudi Arabia, South Africa and Turkey.

3. The RV 144 trial cost approximately US$105 million. McNeil, D. *For First Time AIDS Vaccine Show Some Success*, NY Times, Sept. 24, 2009. Estimates for a smaller trial in high HIV incidence populations have been US$30-40million.

4. The increase for therapeutic vaccine funding over the US$23.2 million identified by the Working Group in 2008 is likely not an increase but the result of better reporting by industry. Because the Working Group was unable to verify investment by a number of companies engaged in HIV therapeutic vaccine research, US$17.5 million is likely an underestimate of commercial investment.

5. With the exception of the new category of "policy and advocacy" added for these reports, the categories used to describe different R&D activities were derived from those developed by the US NIH and are shown in Tables 8 and 9 for HIV vaccines and microbicides, respectively.

6. Source: IPM; See also Stone A, Harrison PF. *Microbicides—Ways Forward*. Alliance for Microbicide Development: Silver Spring, MD, USA. 2010.

7. From *Promise to Product: Advancing Rectal Microbicide Research and Advocacy*. International Rectal Microbicides Advocates: May, 2010. (Available at www.rectalmicrobicides.com).

8. There are common areas of investigation in rectal and vaginal microbicide research which can make it difficult to clearly allocate R&D between them so that this rectal microbicide figure may include funding allocated to microbicide R&D in this report.

9. With the exception of the new category of "policy and advocacy" added for these reports, the categories used to describe different R&D activities were derived from those developed by the US National Institutes of Health and are shown in Tables 8 and 9 for HIV vaccines and microbicides, respectively.

10. The Partners PrEP study by the University of Washington, for example, is supported by a US$61 million grant by the BMGF. (data available at www.gatesfoundation.org)

11. *Progress in Male Circumcision Scale-up: Country Implementation and Research Update*. World Health Organization and UNAIDS. June 2010

12. The increase shown in this report in research into vertical transmission is the result of more comprehensive reporting in 2009, rather than an increase in funding over 2008.

13 *AIDS Epidemic Update* UNAIDS (Nov. 2009) Estimation of new HIV infections by UNAIDS utilizes indirect mathematical or statistical methods to estimate incidence and laboratory tests that help to measure the rate of new infections combined with modelling that 120 countries worldwide use to generate the epidemiological estimates reported annually by UNAIDS.

14. Nominal 2009 GDP for the World and the European Union. World economic outlook database. International Monetary Fund. April 2010.

ACKNOWLEDGEMENTS

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