ADAPTING TO REALITIES: TRENDS IN HIV PREVENTION RESEARCH FUNDING 2000 TO 2008

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

AMD Alliance for Microbicide Development
AVAC Global Advocacy for HIV Prevention
IAVI International AIDS Vaccine Initiative
UNAIDS Joint United Nations Programme on HIV/AIDS

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Executive Summary

In its fifth annual report, the HIV Vaccines and Microbicides Resource Tracking Working Group[1] (Working Group) documents biomedical HIV prevention research and development (R&D) spending for the calendar year 2008 as well as investment trends spanning almost a decade. This year's report examines a research field altered by changing scientific priorities and likely influenced by the global financial downturn that began in 2008.

2008 saw a range of funding level changes from the prior year both within and among different technologies. Global investment in 2008 for HIV vaccines and microbicides amounted to US$868 million and US$244 million, respectively. As compared to 2007, global HIV vaccine funding declined by US$93 million (10%), while microbicide funding increased by US$17 million (8%). Pre-exposure prophylaxis (PrEP) funding was US$4.3 million (13%) greater in 2008.[2] At the same time, funding for other experimental HIV prevention interventions, such as herpes simplex virus type 2 (HSV-2) suppression through acyclovir treatment and cervical barriers as HIV prevention, received little new funding in 2008.

Several trials released results in 2007 and 2008 that spurred important redirections for the HIV prevention field. The outcomes of the halted Step and Phambili vaccine trials in 2007 accelerated an earlier shift by the US National Institutes of Health (NIH) in its HIV vaccine research priorities toward basic research. These trial outcomes also appear to have significantly reduced commercial investment in HIV vaccines. As cervical barriers and suppressive therapy for HSV-2 infection failed to provide evidence of HIV prevention benefit in efficacy trials, new investments in those approaches fell. Disappointing results from the trials of candidate microbicides cellulose sulfate and Carraguard provoked rethinking in the microbicide field as well. Outcomes in 2008 from the phase IIb trial of PRO 2000, the last non-ARV based microbicide to complete efficacy trials, suggest that the product might have reduced women's risk of HIV acquisition (although these results did not reach statistical significance). Results from a large phase III trial of this candidate will be released in late 2009 and will further contribute to strategic redirections for this field, already expressed in more funding for pre-clinical research and development of ARV-based candidates. Seen in this light, the adjustments in 2008 for vaccines, microbicides, HSV-2 suppression and cervical barriers may be based upon scientific recalibrations in the field reflecting results from recent trials.

Still, the overall trend over the past three years has been of increasing investment for all experimental biomedical prevention strategies. Although vaccine funding decreased in 2008, allocations for vaccines increased by US$109 million (14%) from 2005 to 2008. During the same time period, investment in microbicides and PrEP also increased by US$75 million (45%) and US$32 million (255%), respectively.

1. Working Group members include AVAC, AMD, IAVI and UNAIDS.
2. The increase of US$11 million in PrEP funding from 2007 to 2008 shown in this Report is largely due to a reallocation of US$6.5 million in funds of the USAID FEM-PrEP trial from microbicide research to PrEP research. The US$4.3 million in funding that did not result from the reallocation represents a 13% increase in funding from 2007 to 2008.

2008 Investments and Recent Trends

Funding for HIV Vaccine R&D

- **In 2008, total global investment in preventive HIV vaccine R&D was an estimated US$868 million, a 10% decrease from 2007.**

- **In 2008, public-sector funders provided 84% (US$731 million) of the funds allocated to preventive HIV vaccine R&D. The philanthropic sector provided around 12% (US$104 million), and the commercial sector (pharmaceutical and biotechnology companies) accounted for the remaining 4% (US$33 million).**

- **In 2008, European funders reduced their investments in HIV vaccine R&D by 13% relative to 2007.**

- **Investments from non-US and non-European countries such as Brazil, Canada, India, South Africa and Thailand also decreased from 2007 to 2008, by 16% (from US$49 million to US$41 million).**

- **Funding for HIV vaccines in 2008 was US$93 million less than in 2007. The decline in commercial-sector funding accounted for 61% of this decrease, and the decline in NIH investment accounted for almost all of the remaining 42%. Even with this decline, US public-sector funding still accounted for 71% of the total investments.**

- **A subset of investments was analyzed to provide an estimate of global funding allocations by type of HIV vaccine research activity. Basic and pre-clinical research together accounted for approximately 69% of the funds spent. Support for clinical trials accounted for 19%, cohort and site development for 12%, and advocacy and policy development for the remaining 1%. Basic research investment increased 19% from 2007 to 2008, and pre-clinical research investment decreased by 28% over the same period.**

- **For this year's report, the Working Group began tracking investments in R&D for therapeutic HIV vaccines. For fiscal year 2008, the Working Group identified US$23 million in funding. The public-sector accounted for over 90% of this funding. The US contributed 53% of all funding, and Europe, particularly Italy, contributed 40%.**

Funding for Microbicide R&D

- **In 2008, total global investment in microbicide R&D was US$244 million, an 8% increase over 2007.**

- **In 2008, the public-sector provided US$207 million, 85% of the funds allocated to microbicide R&D. The philanthropic sector provided US$35 million (14%), and the commercial sector accounted for US$2.5 million (1%).**

- **From 2007 to 2008, US funding for microbicides increased 8%. In 2008, however, European funding fell 33% to US$40 million.**

- **In 2008, investments in microbicide R&D activities by non-US and non-European sources were US$12 million, or more than double the 2006 and 2007 investment levels, which averaged US$4 million per year. This increase was driven by investments from two countries—Canada and new funder China—that together accounted for US$11 million in investment in 2008.**

- **A subset of investments in microbicide R&D was analyzed to provide a breakdown of global funding allocations by type of activity or product development stage: 5% was devoted to basic mechanisms of mucosal transmission, 33% to pre-clinical research, 9% to product formulation, 38% to clinical trials, 5% to social science research, 5% to infrastructure, and 5% to policy and advocacy. Basic research investment declined 35% from 2007, and pre-clinical research investment increased by 59% over the same period.**

- **R&D toward a rectal microbicide was funded at US$5.0 million in 2008, with almost all of the funding coming from US public-sector sources. Over half of this funding was devoted to pre-clinical research toward development of new products.**

R&D Funding for Other New Prevention Options and Operations Research

- **In 2007, the Working Group began to monitor funding for other experimental HIV prevention options: HSV-2 suppression, cervical barriers for HIV prevention, PrEP, and operations research for adult male circumcision. In 2008, the Working Group began monitoring R&D investment in HSV-2 vaccines, microbicides for HSV prevention and vertical HIV transmission interventions during birth or through breastfeeding.**

- **Seven public-sector funders and two foundations supported US$80 million for R&D and operations research directed toward one or more HIV prevention options in 2008. Public-sector funders provided US$48 million (60%) of the total funds for new prevention options, the philanthropic sector provided US$28 million (38%), and the commercial sector contribution consisted of a $1.25 million in-kind donation of antiretroviral drugs for PrEP research.**

- **Global public-sector and philanthropic investment in R&D and operations research related to adult male circumcision has totaled US$51.6 million over the last eight years. Investment increased almost US$3 million from 2007 to 2008.**

- **Global public-sector and philanthropic investment in pre-exposure prophylaxis (PrEP) over the last seven years totaled US$119 million. In 2008, funding for PrEP was US$4.3 million greater than in 2007.**

- **Global public-sector and philanthropic investment in HSV-2 suppression for HIV prevention using acyclovir totaled US$51 million from 2002 to 2008. In 2008, the NIH provided US$3.7 million for HSV-2 vaccines and US$367 thousand for microbicides to prevent HSV-2 infection.**

- **In its first year of monitoring funding for operations research related to prevention of vertical transmission, the Working Group identified US$21.2 million in funding in 2008.**

HIV Prevention R&D Funding in a Time of Shifting Science, Tight Budgets and Competing Global Health Priorities

HIV prevention research, in an era of shifting science, competing priorities, and declining budgets, has managed to move forward. Although overall investment levels have grown over recent years, global economic trends in 2009 and beyond could severely affect future HIV prevention research funding. To best adapt to this environment, the HIV prevention research community needs to ensure, more than ever, that R&D activities are sharply focused on key scientific priorities, meet specific milestones and are not duplicative. The path toward achieving that focus is through consensus-driven, shared scientific plans that lay out research priorities within, and possibly across, the HIV vaccine, microbicide, and PrEP fields.

Is current funding sufficient to move the HIV prevention field forward at a timely pace? Understanding, documenting and managing HIV prevention research needs in the context of resource tracking estimates will validate and inform future requests to funders as the field moves forward. Yet, estimating investment need remains an unmet goal for the HIV vaccine, microbicide and PrEP fields. These areas require funders, policy-makers, advocates, and researchers to jointly develop an updated, data-driven, comprehensive assessment of investment needs based upon scientific plans with clear milestones. These plans will, in turn, provide funders, policy-makers and researchers with a basis for determining whether current funding is sufficient and allocated in ways that will advance the entire HIV prevention field efficiently and expeditiously. Additional analytic approaches will also be needed to assess investment levels for operations research related to implementation of the roll out of adult male circumcision and prevention of vertical transmission.[3]

A comprehensive plan to combat the epidemic requires investment in a wide range of more effective methods of prevention to complement expanding access to existing HIV treatment and prevention options. As the HIV prevention research field moves forward in times of economic uncertainty and reduced resources, funders will have to balance the promise of future HIV prevention options against many other worthy purposes, both within the AIDS response and more broadly in global health and development. HIV prevention research has long time horizons and a substantial need for continued resources to meet the goals of developing new prevention options. Although research progress has been made, it will still be many years before HIV vaccines and/or microbicides are licensed and widely used. Other approaches, such as PrEP, may have results earlier, but even with positive results it may be years before PrEP can be implemented, given the HIV testing and implementation infrastructure that PrEP roll out will require.

The development, licensure and widespread use of these prevention technologies is many years away. Progress can only be accomplished through sustained R&D spending across a range of prevention options. Resource tracking of investments over time will be critical to measuring future trends and progress.

3. Investment needs for operations research to improve roll out of male circumcision and prevention of vertical transmission will require focus on implementation rather than product development.

1. Introduction

There have been recent gains in preventing new HIV infections, which declined from 3 million annually in 2001 to 2.7 million in 2007.[4] Yet, these hopeful signs cannot obscure the fact that the global community has not solved the ongoing challenge of developing and delivering new HIV prevention options. Validated prevention options such as adult male circumcision,[5] male and female condoms[6] and ARV treatment to prevent vertical transmission[7] are available, but access and coverage rates are inadequate. There also remains an urgent need to validate new biomedical prevention strategies such as HIV vaccines, microbicides and pre-exposure prophylaxis (PrEP). If these show efficacy, any or all of these tools could offer additional options for protection against HIV and drive down HIV incidence.

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 technology to another, and across funding sources.[8] This effort supports the 2001 United Nations General Assembly Special Session (UNGASS) Declaration of Commitment on HIV/AIDS, which called for increased investment in research related to HIV and AIDS and, specifically, for the development of sustainable and affordable prevention technologies, such as HIV vaccines and microbicides.[9] Information collected in previous years has been used by the Working Group and others to monitor levels of effort and investment trends, and to assess the impact of public policies aimed at accelerating scientific progress.

4. UNAIDS 2008 Report on the Global AIDS Epidemic (December 2008).
5. The Clearinghouse on Male Circumcision for HIV Prevention (*www.malecircumcision.org*)
6. Female Condom: A Powerful Tool for Protection (2006) (*http://www.unfpa.org/hiv/female.htm*)
7. Failing Women, Failing Children: HIV, Vertical Transmission, and Women's Health (2009) (*http://www.aidstreatmentaccess.org/mtt7_final.pdf*)
8. The categories used to define research and development (R&D) can be found in the Appendix. R&D is defined to include policy and advocacy work in support of R&D efforts.
9. 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 2008, 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, 2008.)

2. Results

2.1 Global Investments in HIV Vaccine R&D

In 2008, total global investment in HIV vaccine R&D was US$868 million, a US$93million (10%) decrease from the previous year. Public-sector funders provided 85% (US$731 million) of those investments, the philanthropic sector 11% (US$104 million) and the commercial sector 4% (US$33 million).

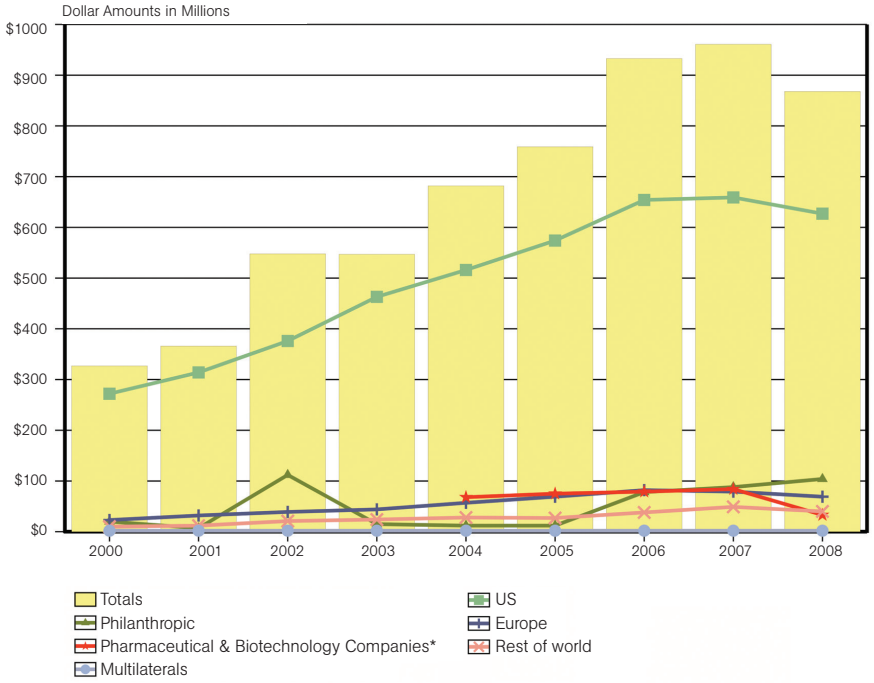
TABLE 1. ANNUAL INVESTMENTS IN HIV VACCINE R&D 2000–2008 (US$mn)

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Public-sector									
US	272	314	376	463	516	574	654	659	620
Europe[A]	23	32	39	44	57	69	82	79	69
Other[B]	10	12	21	24	28	27	38	49	41
Multilaterals	2	2	2	2	2	2	2	2	2
Total public	307	359	436	532	602	672	776	789	731
Philanthropic sector									
Total philanthropic	20	7	112	15	12	12	78	88	104
Total non-commercial investment	327	366	548	547	614	684	854	877	835
Commercial sector									
Pharmaceutical companies					59 (range 47 to 71)	64 (range 52 to 76)	70 (range 52 to 89)	75 (range 52 to 89)	28 (range 18 to 38)
Biotechnology companies					9 (range 7 to 11)	9 (range 6 to 13)	9 (range 6 to 13)	9 (range 6 to 13)	5 (range 4 to 7)
Total commercial					68 (range 54 to 82)	75 (range 61 to 89)	79 (range 65 to 93)	84 (range 61 to 102)	33 (range 22 to 45)
Total global investment	327	366	548	547	682	759	933	961	868

2.1.1 Public Investments in HIV Vaccine R&D

Public agencies and institutions dominate R&D funding for HIV vaccines. Four countries (Canada, the Russian Federation, the United Kingdom and the United States) invested more than US$10 million each of public-sector funds in 2008, and 18 countries invested more than US$1 million each. The European Commission (EC) is the second-largest funder, with US$25 million invested in 2008. Although the US had the largest decline (US$39 million) in funding from 2007 in dollar terms, the percentage decline was smaller for the US (6%) than for Europe (13%) or the remainder of the world (16%).

Annual Investments in HIV Vaccine R&D 2000–2008



*Data on Pharmaceutical and Biotechnology Investments collected only after 2003

2.1.2 Philantrophic Investments in HIV Vaccine R&D

The philanthropic sector accounted for US$104 million or about 12% of the total funds disbursed for HIV Vaccine R&D in 2008. The Bill & Melinda Gates Foundation and the Wellcome Trust together accounted for 91% of all philanthropic investments.

TABLE 2. PHILANTHROPIC INVESTMENT IN VACCINE R&D BY ORGANIZATION IN 2008[10]	
Over US$75mn	• Bill & Melinda Gates Foundation
US$15mn to 20mn	• Wellcome Trust
US$1mn to 2mn	• Elizabeth Glazer Pediatric AIDS Foundation • Esteve Laboratories • Starr Foundation
US$250K to 500K	• Pfizer Inc. • Becton Dickinson & Co.
US$100K to 250K	• amfAR • Broadway Cares • Fundacio La Caixa • James B. Pendleton Trust

2.1.3 Commercial Investments in HIV Vaccine R&D

Total investment by the commercial sector (pharmaceutical and biotechnology companies) in HIV vaccine development in 2008 was estimated at US$33 million (range US$18 million to US$45 million), a decline of 61% from 2007 levels. (These amounts reflect actual investments of the companies' own financial resources. Most of these companies also receive grants and contracts from public-sector agencies, but these investments are attributed to the funding agencies and not to the companies.)

R&D spending decreased significantly after the Step and Phambili vaccine trials ended enrollment and immunizations in late 2007 and the consequent shift of scientific priorities. Merck, the developer of the vaccine in those trials, has substantially reduced its HIV vaccine development activities. Although several major pharmaceutical companies have or have had HIV vaccine programs, Merck's program has been unique in its commitment of staff, resources, and funding to develop an HIV vaccine. No publicly available figures exist to quantify its total investment, which is likely several hundred million dollars. The successful search for an HIV vaccine may be achieved without a major pharmaceutical company, but Merck advanced the field in a way that no pharmaceutical company had done before. The decline in direct commercial investments from 2007 to 2008 may also reflect a contraction in the pharmaceutical/biotech industry as a whole. Eighty-five percent of private-sector investments in HIV vaccine research funding come from large pharmaceutical companies, with the remaining 15% coming from the biotech industry.

10. The contributions by pharmaceutical companies referenced in this table are philanthropic.

In 2007, IAVI launched an Innovation Fund with an initial three-year commitment of US$10 million (half provided by the BMGF). By mid-2009, the Fund had awarded 11 grants to biotechnology companies and other organizations around the world to fund novel immunogen design assay development and any other technologies that might have a significant impact on the pipeline of candidate HIV vaccines. This Fund has the potential to increase commercial involvement in HIV vaccine development.

TABLE 3. COMMERCIAL ENGAGEMENT IN PREVENTIVE HIV VACCINE R&D BY COMPANY IN 2008

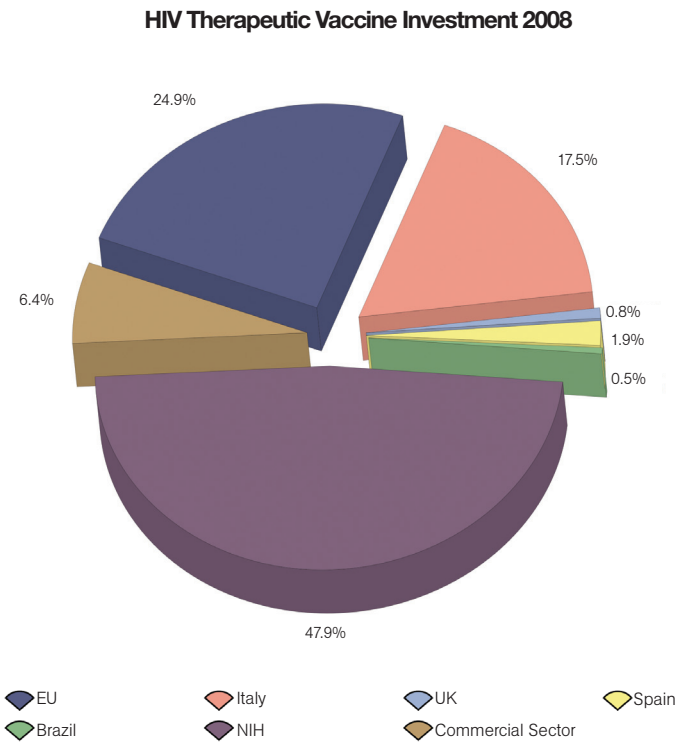
US$5mn to US$10mn	• GlaxoSmithKline • Merck & Co • Novartis International AG • Sanofi Pasteur	
US$1mn to 5mn	• GeoVax, Inc.	
US$100K to 1mn	• Agonomics • Advanced BioScience Laboratories • AlphaVax Human Vaccines • Bavarian Nordic • Crucell N.V. • Pharmexa-Epimmune Inc. • FIT Biotech PLC • GenVec	• ImmunoGenetix • Maxygen • Progenics Pharma • Targeted Genetics Corporation • United Biomedical • Vical • Wyeth-Ayerst Lederle

2.1.4 Funding Allocations for Therapeutic HIV Vaccine R&D

A therapeutic HIV vaccine would be a vaccine used to treat HIV infection. Therapeutic HIV vaccines are designed to enhance immune response to HIV to better control the infection. Therapeutic HIV vaccine research started in the early 1990s, with several trials in the US and Europe. Currently, there are no approved therapeutic HIV vaccines. However, vaccines are being tested in clinical trials with HIV-positive individuals. A number of HIV vaccine candidates are being tested both as preventive in HIV-negative individuals and therapeutic in HIV-positive individuals.

Therapeutic HIV vaccine R&D received an estimated US$23.2 million in 2008, with the US contributing 53% and Europe, in particular the European Commission and Italy, contributing 40%. In 2008, the Italian Istituto Superiore di Sanità (ISS) began recruitment for a new trial of its tat-based HIV vaccine, which has also been under study for several years. European funders provide a greater percentage of the total support for therapeutic HIV vaccines (45%) than for preventive HIV vaccines (8%).

Therapeutic HIV vaccines received modest commercial investment in 2008 from pharmaceutical companies such as GSK and biotech companies such as Bavarian Nordic and Genetic Immunity. In 2008, Genetic Immunity started planning for the trial of its DermaVir patch, using an immunization strategy that targets dendritic cells.



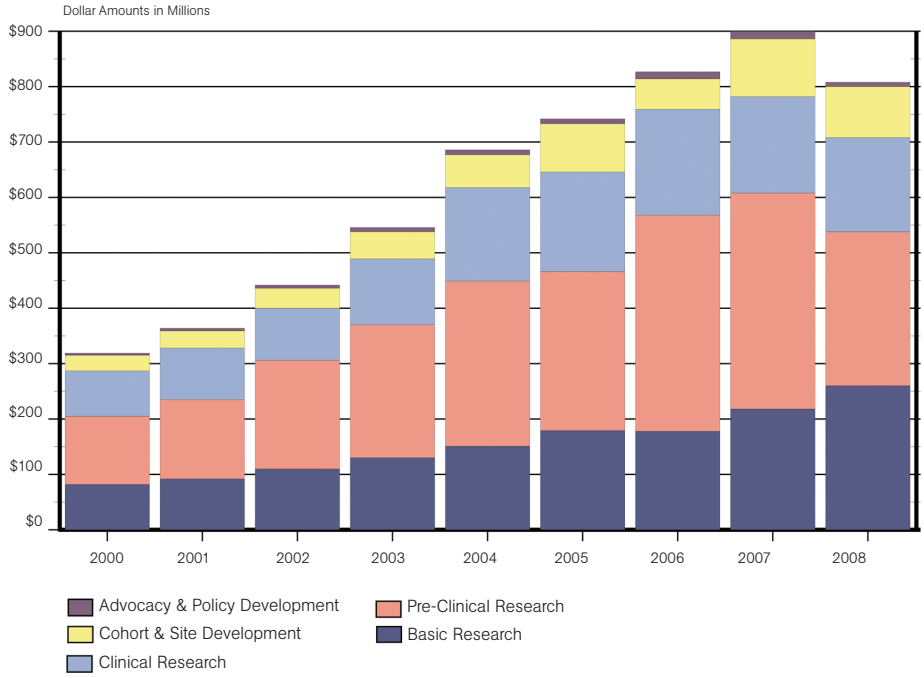
2.1.5 Funding Allocations for HIV Vaccine R&D

For 2008, spending by the public and philanthropic sectors on preventive HIV vaccine R&D was allocated to five categories. The categories with the largest shares were basic research (32%) and pre-clinical research (34%). The others were support for clinical trials (21%), cohort and site development (11%) and advocacy and policy development (<1%). Basic research investment increased 19% from 2007 to 2008, while pre-clinical research investment decreased by 28% over the same period. Further information about the categories used to define R&D can be found in the Appendix.[11]

11. With the exception of policy and advocacy, these categories are those 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 a US$808 million subset that did permit such allocations. These expenditure figures do not include therapeutic vaccines.

TABLE 4. TOP TEN HIV VACCINE FUNDERS IN 2008 (US$mn)	
NIH	556.1
BMGF	81.2
USAID	28.5
WRAIR	26.3
EC/EDCTP	25.3
Russian Federation	16.6
Wellcome Trust	15.6
CIDA	10.6
UK MRC	6.6
DFID	5.8

Vaccine Expenditures* 2000–2008



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

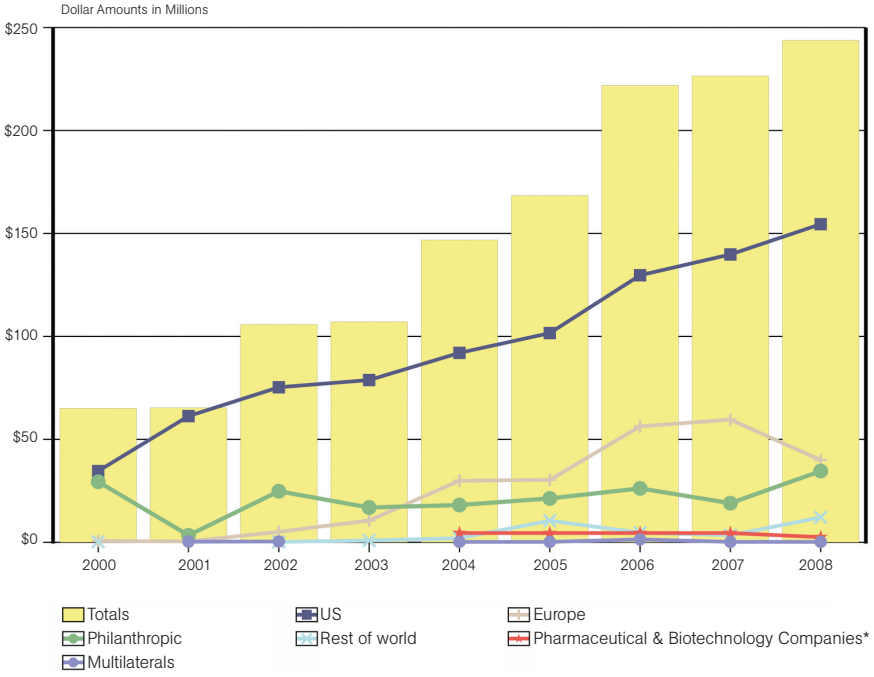
2.2 Global Investments in Microbicide R&D

In 2008, total global investment in microbicide R&D was US$244 million, an 8% increase over 2007. Public-sector funders provided US$207 million (85%), the philanthropic sector US$35 million (14%) and the commercial sector US$2.5 million (1%).

2.2.1 Public Investments in Microbicide R&D

In 2008, public-sector investment in microbicide R&D accounted for 85% of the combined global funding for microbicide research, development and advocacy. The US continues to maintain the largest presence, providing US$155 million (63%) of total investment, an increase of 11% over 2007. European national governments and the European Commission together accounted for US$40 million, a decrease of 33% from 2007.

Annual Investments in Microbicide R&D 2000–2008



*Data on Pharmaceutical and Biotechnology Investments collected only after 2003

TABLE 5. TOP TEN MICROBICIDE FUNDERS IN 2008 (US$mn)	
NIH	115.5
USAID	38.0
BMGF	34.6
DFID	12.7
CIDA	5.8
MOFA	5.6
EC	4.9
Republic of China	4.5
UK MRC	4.2
RMFA	3.6

TABLE 6. ANNUAL INVESTMENTS IN MICROBICIDE R&D 2000–2008 (US$mn)									
	2000	2001	2002	2003	2004	2005	2006	2007	2008
Public-sector									
US	34.6	61.3	75.3	78.8	92	101.6	129.7	139.8	154.4
Europe	0.7	0.4	5.1	10.6	29.9	30.3	56.3	59.6	39.9
Other	0.3	<0.1	0.2	0.9	2.0	10.5	4.7	3.4	12.1
Multilaterals	<0.1	0.3	0.4	<0.1	0.2	0.2	1.4	0.2	0.2
Total public	35.7	62.0	81.0	90.2	124.2	142.6	191.2	203	206.7
Philanthropic sector									
Total philanthropic	29.4	3.4	24.8	16.9	18.1	21.3	26.2	19	34.6
Total non-commercial investment	65.1	65.4	105.8	107.1	142.3	163.9	217.4	221	241.3
Commercial sector									
Biotechnology companies					4.5 (range 3 to 6)	4.5 (range 3 to 6)	4.5 (range 3 to 6)	4.5 (range 3 to 6)	2.5 (range 1.5 to 4)
Total commercial					4.5	4.5	4.5	4.5	2.5
Total global investment	65.1	65.4	105.8	107.1	146.8	168.4	221.9	226.5	243.8

2.2.2 Philanthrophic Investments in Microbicide R&D

In 2008, the philanthropic sector provided US$35 million (15%) of the funds disbursed for microbicide development, an 82% increase from 2007. Virtually all of this funding came from the Bill & Melinda Gates Foundation, with the remainder from amfAR.

2.2.3 Commercial Investments in Microbicide R&D

Total commercial-sector microbicide investment in 2008 was estimated at US$2.5 million, all from the biotechnology subsector. The microbicide field has benefited from pharmaceutical company support chiefly through transfers of intellectual property and technical support.

Early 2009 saw results from a phase IIb trial of PRO 2000, a product developed by Indevus (a biotechnology company recently acquired by Endo Pharmaceuticals). Results are expected later this year from a much larger phase III trial of PRO 2000—known as MDP 301—sponsored by the UK MRC funded Microbicide Development Programme.

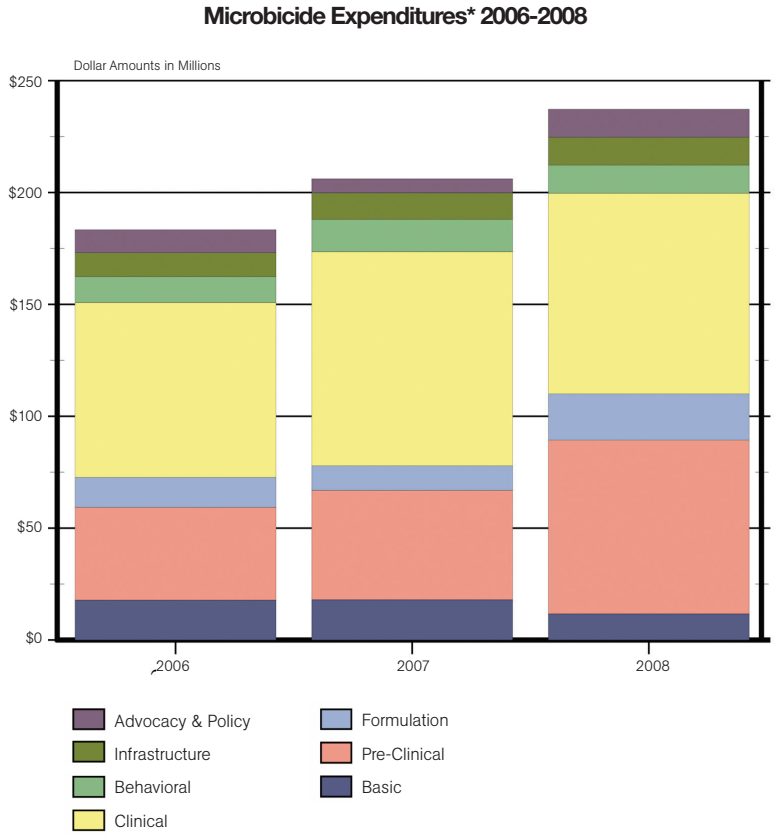
TABLE 7. COMMERCIAL ENGAGEMENT IN MICROBICIDE R&D BY COMPANY 2008

• Ablynx	• Indevus Pharmaceutical (acquired by Endo in early 2009)	• Renaissance Scientific
• Advance Biosciences	• Instead	• Replicor
• Aggenix	• Mapp Biopharmaceutical	• Restrizymes Canada
• Biotech MC	• MGB Pharma	• Starpharma PTY
• CONBA	• Novaflux	• Viriome
• DakoCymation	• Osel	• Vision7 GmbH
• EMD Biosciences	• Paradigm Pharmaceuticals	
• ImQuest		

12. Although this estimate is lower than in previous years, based upon response rates to Working Group data requests in 2008, there are not enough data to establish a trend.

2.2.4 Funding Allocations for Microbicide R&D

In 2008, expenditures on microbicide R&D were allocated across the following seven categories: basic mechanisms of mucosal transmission (5%); discovery, development and pre-clinical testing (33%); formulations and modes of delivery (9%); clinical trials (38%); behavioral and social science research (5%); research infrastructure (5%); and policy and advocacy (5%).[13] Further information on the categories used to define microbicide R&D can be found in the Appendix.



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

13. With the exception of the Policy and Advocacy category, these categories are those used by the NIH to categorize microbicide research. Because not all data from funders permits allocation to these seven categories, these percentages were estimated from the US$235 million subset that did permit such allocations.

2.2.5 Funding Allocations for Rectal Microbicide R&D

In 2008, R&D toward a rectal microbicide was funded at US$5.0 million, with most of the funding coming from US public and philanthropic sources. This amount represents a decrease from US$7 million in 2006.[14] Funders of rectal microbicide research in 2008 included amfAR and the NIH. Approximately half of these funds were used to support pre-clinical development of rectal microbicide candidates. The rest supported basic research, as well as rectal microbicide acceptability and behavioral research.

In February of 2009, results from the first rectal microbicide safety trial—a phase I safety and acceptability study of the UC-781 microbicide gel—were presented at the Conference on Retroviruses and Opportunistic Infections (CROI).

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

Other biomedical prevention strategies, such as PrEP, were explored by the HIV prevention research field in 2008. Funding also went to operations research for implementation of male circumcision for HIV prevention and to refinement and expansion of strategies for preventing vertical infection of infants at birth or during breastfeeding. Two experimental prevention approaches that the Working Group has tracked in the past—HSV-2 suppression through acyclovir treatment and diaphragm use to prevent HIV transmission—received little funding in 2008 as trials wound down.[15] Finally, a modest amount went for HSV-2 vaccines and microbicides for HSV prevention.[16]

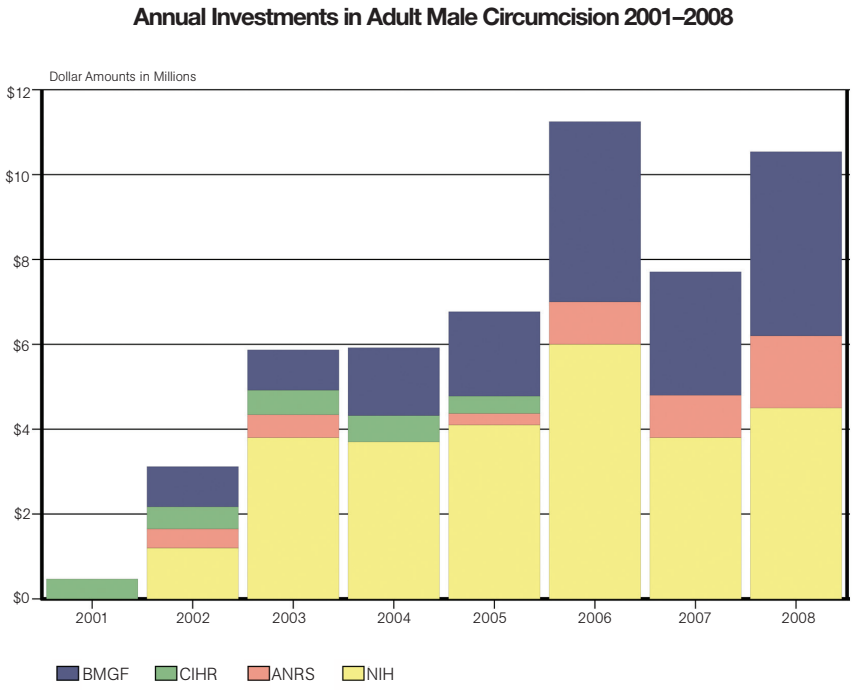
2.3.1 Investments in HIV Prevention R&D Related to Adult Male Circumcision

Global public-sector and philanthropic investment in R&D and operations research related to adult male circumcision has totaled US$51.6 million over the last eight years. Investment in circumcision research slowed after completion of the NIH-funded trials in Rakai, Uganda and Kisumu, Kenya, both in 2006. These trials along with the ANRS-funded study in Orange Farm, South Africa, provided sufficient rationale for investment in introduction of male circumcision as an HIV prevention strategy. As scale-up has proceeded, there has been increased investment by the ANRS, BMGF, and NIH in follow-up studies. A BMGF funded trial looked at the prevention effect of circumcision on the HIV-negative female partners of HIV-positive men. The trial found that circumcision of HIV-positive men did not reduce HIV transmission to female partners. The NIH has supported follow-up of this trial which is scheduled to end September 2009. ANRS funded follow-up research in Orange Farm to determine if circumcision roll out could increase use of existing means of HIV prevention; and decrease the spread of HIV and HSV-2.

14. Rectal Microbicides: Investments and Advocacy (*http://www.rectalmicrobicides.org/docs/rectalreport.pdf*)
15. The Partners in Prevention study continued in 2008 and announced results in 2009. The study received $4.6 million of philanthropic funding in 2008.
16. The efficacy of HSV-2 vaccines and microbicides to possibly prevent HIV infection by preventing HSV infection, which has been associated with higher rates of HIV infection, is not yet being tested. Such follow-up studies to test this hypothesis would be a one likely result of validation of an effective HSV-2 vaccine.

TABLE 8. ANNUAL INVESTMENTS IN ADULT MALE CIRCUMCISION 2001–2008 (US$mn)								
	2001	2002	2003	2004	2005	2006	2007	2008
Public-sector								
ANRS	0	446,349	541,297	0	268,963	1,000,000	1,000,000	1,738,526
CIHR	472,850	516,890	578,606	622,757	414,695	0	0	0
NIH	0	1,205,721	3,806,768	3,654,655	4,118,300	5,984,441	3,817,337	4,487,573
Total public	472,850	2,168,960	4,926,671	4,277,412	4,801,958	6,984,441	4,817,337	6,226,099
Philanthropic sector								
BMGF	0	949,307	949,307	1,596,810	1,988,814	4,246,979	2,905,668	4,344,627
Total philanthropic	0	949,307	949,307	1,596,810	1,988,814	4,246,979	2,905,668	4,344,627
Total	472,900	3,118,300	5,875,978	5,874,200	6,791,800	11,231,400	7,723,000	10,570,726

In addition, PEPFAR began funding roll-out of adult male circumcision programs.[17] WHO and UNAIDS, with support from the BMGF, also invested resources in materials, technical assistance, and policy development to translate the research findings into potential public-health impact.



17. The Working Group has been unable yet to obtain data on investment by the US OGAC in male circumcision roll out.

2.3.2 Investments in HIV Prevention R&D Related to Pre-Exposure Prophylaxis

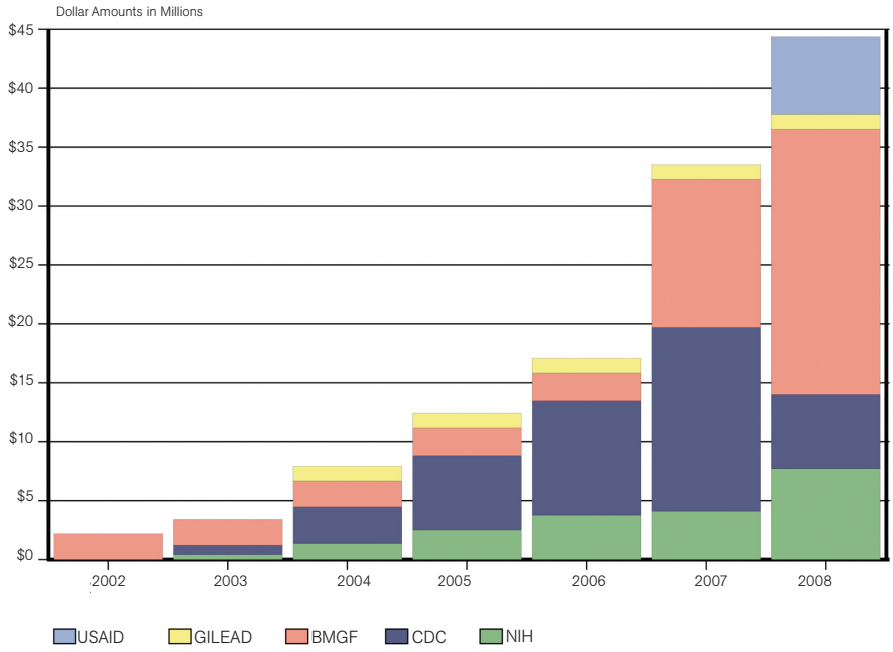
Global public-sector and philanthropic investment in pre-exposure prophylaxis (PrEP) over the last seven years totaled US$119 million. There are currently seven ongoing or planned PrEP trials of tenofovir-disoproxil fumarate (TDF) or of TDF combined with emtricitabine (TDF/FTC). In 2008, funding for PrEP was US$4.3 million greater than in 2007.[18] This total does not include prevention of vertical transmission through ARV treatment, which can be considered PrEP.[19]

TABLE 9. ANNUAL INVESTMENTS IN PRE-EXPOSURE PROPHYLAXIS 2002–2008 (US$mn)

	2002	2003	2004	2005	2006	2007	2008
Public-sector							
CDC	0	798,000	3,104,000	6,339,900	9,700,300	1,561,000	6,339,100
NIH	0	424,300	1,372,528	2,513,400	3,772,800	4,100,900	7,708,800
USAID	0	0	0	0	0	0	6,551,600
Total public	0	1,222,300	4,476,500	8,853,200	13,473,100	19,710,900	20,599,481
Philanthropic sector							
BMGF	2,185,500	2,185,500	2,185,465	2,357,900	2,357,900	12,561,700	22,505,700
Total philanthropic	2,185,465	2,185,465	2,185,465	2,357,900	2,357,900	12,561,700	22,505,700
Commercial sector							
Gilead	0	0	1,250,000	1,250,000	1,250,000	1,250,000	1,250,000
Total commercial	0	0	1,250,000	1,250,000	1,250,000	1,250,000	1,250,000
Total	2,185,500	3,407,800	7,912,00	12,461,100	17,018,000	33,522,600	44,354,700

18. The table above shows a US$10.8 million increase from 2007 to 2008, but most of this increase resulted from the US$6.5 million for the USAID-funded Fem-PrEP trial being reclassified from microbicides to PrEP. Fem-PrEP is a phase III trial investigating the safety and effectiveness of once-daily Truvada in preventing HIV among HIV-uninfected women at risk of becoming infected through sexual intercourse. USAID investment in PrEP began in 2007 with support for the Fem-PrEP study. USAID coded this investment in its microbicide program, and it was not allocated to PrEP in 2007 by the Working Group. In 2008, the Working Group decided to reallocate FEM-PrEP to PrEP investments.
19. The EDCTP trial measuring PrEP to prevent HIV transmission through breast milk using lamivudine has been added to totals for vertical transmission rather than to PrEP.

Annual Investments in Pre-Exposure Prophylaxis 2002–2008



2.3.3 Investments in HIV Prevention R&D Related to HSV-2 Suppression And Prevention

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, the results from the Partners in Prevention trial were released. The Partners trial, conducted at 14 sites in seven African countries, found that on going suppressive acyclovir therapy for HSV-2 in HIV-positive people did not reduce their risk of transmitting HIV to their HIV-negative partners. That study received US$4.6 million in philanthropic funding in 2008 as the trial ended. The trial found that acyclovir treatment does not reduce the risk of acquiring HIV, but trial investigators saw a 0.25 log reduction in plasma HIV level in the acyclovir suppression group. Although this modest reduction in plasma HIV level with acyclovir suppression did not translate to reduced HIV transmission, there was a reduction in CD4 decline and HIV disease progression.[20]

20. Another NIH study conducted in nine countries provided acyclovir treatment to HIV-negative participants with HSV-2 infection. Researchers announced in 2008 that they found no reduction in HIV infection as a result of HSV-2 suppression through acyclovir treatment. Another study of HSV-2 suppression conducted in Tanzania funded by the Wellcome Trust also found no protective effect in results announced in 2007.

Prevention of HSV-2 infection in HIV-negative people who are not already infected with HSV-2 may yet prove to be found to be an effective HIV prevention strategy.[21] In 2008, the NIH provided US$3.7 million for HSV-2 vaccines and US$367 thousand for microbicides to prevent HSV-2 infection. HSV-2 vaccines have received modest commercial investment from pharmaceutical companies such as GSK and biotech companies such as Acambis, GenVec and Vical.

The NIH has funded a phase III trial to assess GSK's HSV vaccine as a preventive for genital herpes in young women who are HSV-1 and -2 seronegative. A previous trial of the vaccine found a significant degree of protection for these women, but not in men.[22] Results are expected to be released in 2010. It is possible that this vaccine, if it prevented HSV-2 infection, could reduce risk of acquiring HIV in HSV sero-negative women, and hence become another HIV prevention tool.

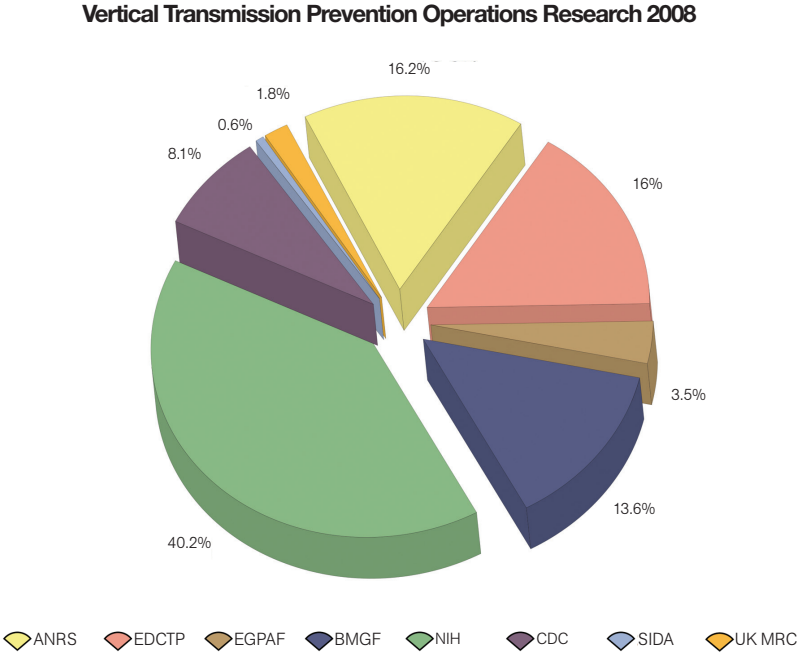
2.3.4 Investments in Operations Research Related to Vertical Transmission

In its first year of monitoring funding for operations research related to prevention of vertical transmission, the Working Group identified US$21.2 million in funding in 2008. The public-sector accounted for over 88% of this funding, with the philanthropic sector providing the remainder.

In 2008, there were nine active clinical trials, funded by the Doris Duke Foundation, NIH, CDC and EDCTP. These studies focused on prevention of vertical transmission at birth or through breastfeeding and on ARV resistance in HIV-positive women taking ARV regimens designed to prevent vertical transmission.[23]

The Doris Duke Operations Research on AIDS Care and Treatment in Africa (ORACTA) program funds research related to vertical transmission and other work to improve outcomes of the rollout and scale-up of ART in Africa. Since 2005, 30 teams of researchers working in Africa received ORACTA grants totaling US$6 million. In 2008, an EDCTP-funded trial began, to measure the efficacy of pre-exposure prophylaxis with lamivudine (3TC) to prevent HIV-1 transmission through breast milk.

21. Abu-Raddad, LJ, Magaret, A, Celum, C, Wald, A, Longini, I, Self, S, Corey, L. Genital Herpes Has Played a More Important Role than Any Other Sexually Transmitted Infection in Driving HIV Prevalence in Africa. PLoS ONE. 2008; 3(5).
22. Stanberry, L.R, Spruance, SL, Cunningham, AL, Bernstein, DI, Mindel, A, Sacks, S, Tyring, S, Aoki, FY, Slaoui, M, Denis, M, Vandepapeliere, P, and Dubin, G. Glycoprotein D adjuvant vaccine to prevent genital herpes. N. Engl. J. Med. 21:1652-1661 2002.
23. These estimates are incomplete because the Working Group was unable to obtain information on operations research funded by the US Office of the Global AIDS Coordinator or by the Global Fund to Fight AIDS, Tuberculosis and Malaria. These agencies are likely to be significant funders of operations research in this area, and further efforts will be made to track their investments in the future.



2.3.5 Investments in HIV Prevention R&D Related to Cervical Barriers

Global investment in cervical barriers as a method of HIV prevention totaled US$621 thousand from the philanthropic sector in 2008. In 2007, the MIRA trial testing a latex diaphragm in 4,500 at-risk HIV-uninfected women in South Africa and Zimbabwe was completed. The scientific premise for the trial was that using a diaphragm would physically block HIV access to the cervix and thus potentially reduce the risk of HIV transmission. The trial results did not show that use of a diaphragm prevented HIV acquisition among women and may explain the reduced investment in this approach in 2008.

3. Discussion

Since 2000, Investments in HIV vaccines, microbicides and PrEP have increased steadily. In 2008, funding trends as compared to 2007 varied by prevention strategy. Vaccines showed a US$93 million (10%) decrease. Microbicides showed a US$17 million (8%) increase and PrEP had US$4.3 million (13%) more funding. Funding for cervical barriers for HIV prevention and HSV-2 suppression fell as trials of those approaches came to an end.[25]

Decreases in funding from 2007 to 2008 may reflect adjustments in scientific priorities away from certain approaches, the beginnings of an escalating economic downturn, cyclical funding for projects, or even shifting of funding away from HIV/AIDS. Increases in funding may reflect enthusiasm for new scientific approaches, peaks in cyclical funding, or up-front funding for larger projects such as clinical trial support.

Several trials released results in 2007 and 2008 that spurred important redirections for the HIV prevention field. The outcomes of the halted Step and Phambili vaccine trials in 2007 accelerated an earlier shift by the US National Institutes of Health (NIH) in its HIV vaccine research priorities toward basic research. These trial outcomes also appear to have significantly reduced commercial investment in HIV vaccines. As cervical barriers and suppressive therapy for HSV-2 infection failed to provide evidence of HIV-prevention benefit in efficacy trials, new investments in those approaches fell. Disappointing results from the trials of candidate micro-bicides cellulose sulfate and Carraguard provoked rethinking in the microbicide field as well. Outcomes in 2009 from the phase IIb trial of PRO 2000, the most recent non ARV-based microbicide to complete efficacy trials, suggest that that product might have reduced women's risk of HIV acquisition (although these results did not reach statistical significance). Results from a large phase III trial of this candidate will be released in late 2009 and will further contribute to strategic redirections for this field, already expressed in more funding for pre-clinical research and development of ARV-based candidates. Seen in this light, the adjustments in 2008 for vaccines, microbicides, HSV-2 suppression and cervical barriers may be based upon scientific recalibrations in the field reflecting results from recent trials.

The most significant change over 2007 was in HIV vaccine funding which saw a decrease across all sectors other than philanthropic investment. From 2006 to 2008, funding for basic research into HIV vaccines increased, while pre-clinical research decreased and clinical-trial investment remained essentially flat. These changes suggest that funds were reallocated to basic research from pre-clinical research. A further reassessment of scientific priorities may also occur when the results from the US Army sponsored phase III trial in Thailand testing the ALVAC/AIDSVAX B/E vaccine regimen are announced September 2009, depending upon the different possible outcomes of that trial.

25. There are currently no major initiatives on HSV-2 suppressive therapy for HIV prevention but ongoing pilot studies and pathogenesis studies will inform next steps.

Support for operations research related to male circumcision rollout and follow-up for the circumcision trials increased by US$3 million from 2007 to 2008. The Working Group also identified US$21 million in funding for operations research related to prevention of vertical transmission. Operations research improving upon, or developing new delivery systems for validated prevention options are being funded at lower levels than for experimental approaches such as HIV vaccines, microbicides and PrEP. This may be appropriate given the difference between the cost of product development and operations research. Nevertheless, researchers and implementers working in the circumcision and prevention of vertical transmission fields should continue to identify gaps to guide funding priorities.

Despite recent declines in HIV vaccine funding, the overall trend since 2000, or even 2005, has been a significant increase in funding from virtually all donors involved in biomedical HIV prevention research and new funders have joined the effort. So perspective is important. The trend over even the past few years has been of increasing investment for all experimental biomedical prevention strategies. HIV prevention research, in an era of shifting science and declining budgets, has managed to maintain momentum.

In last year's report, the Working Group identified the key goal of projecting future investment needs for HIV vaccines, microbicides, and other new prevention options. This goal remains unmet. In claiming that investment in HIV prevention research should be sustained, it will be important to identify specific funding needs for the field. The most recent estimates of resource needs prepared in 2004 for HIV vaccines and microbicides do not reflect current costs and research priorities.[26] Funding levels need to match the requirements for achieving specific scientific goals. Development of agreed-upon scientific plans for each field will be necessary for estimating future investment needs. Funding can then be linked more effectively to scientific priorities, and resource needs for future HIV prevention R&D can be assessed systematically. The HIV vaccine and microbicide fields have developed or are revising scientific plans, which is an important part of this process. The sustainability, flexibility and predictability of funding can also impact HIV prevention R&D, where projects have long timelines.

Developing validated estimates of investment tied to accepted scientific plans will be a challenge for the field. Such planning will equip researchers, product developers, civil society, advocates and other stakeholders to better address questions about the need for HIV prevention research and its direction as we enter a time of reduced resources and competing priorities.

The time to the development, licensure and widespread use of these prevention technologies will be long. Progress can only be accomplished through sustained R&D spending across a range of prevention options. Resource tracking of investment over time will be critical to measuring trends and progress.

26. In 2004, the Global HIV Vaccine Enterprise estimated that between US$1.1 billion and US$1.2 billion is needed annually to speed the search for a safe, effective HIV vaccine. In 2004, the Alliance for Microbicide Development, the International Partnership for Microbicides, and the Global Campaign for Microbicides estimated that US$280 million per year would be required over the next five years to accelerate development of a safe and effective microbicide.

4. Appendix

Methodology

This report was prepared by Cindra Feuer (AVAC), Kevin Fisher (AVAC), Polly Harrison (AMD), Wilson Lee (IAVI), Lucas Romero (AVAC), Shilpa Vuthoori (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 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 10 and 11 for HIV vaccines and microbicides, respectively.

TABLE 10. CATEGORIES USED TO CLASSIFY 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.
Pre-clinical 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 and/or political barriers to their rapid development and use.

TABLE 11. 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, and Pre-clinical Testing	Discovery, development, and pre-clinical evaluation of topical microbicides alone and/or in combination.
Formulations and 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 and 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	Work to educate and mobilize public and political support for microbicides and to address potential regulatory, financial, infrastructure, or political barriers to their rapid development and use.

Entities Referenced in The Report

PUBLIC-SECTOR–COUNTRIES

- Australia; National Health and Medical Research Council (NHRRC)
- Canada; Canadian International Development Agency (CIDA), Canadian Institute of Health Research (CIHR)
- European Commission (EC), European & Developing Countries Clinical Trials Partnership (EDCTP)
- France; Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS)
- India; Indian Council of Medical Research (ICMR)
- Ireland; Development Cooperation Ireland (DCI)
- Italy; Istituto Superiore di Sanità (ISS)
- Netherlands; Ministry of Foreign Affairs (MoFA)
- Norway; Royal Ministry of Foreign Affairs (RMFA)
- Russia Federation
- South Africa; Department of Science and Technology (DST), ESKOM, National Department of Health (NDOH), Medical Research Council (RSA MRC)
- Sweden; Swedish International Development Agency (SIDA)
- United Kingdom; Medical Research Council (UK MRC), Department for International Development (DFID), Microbicide Development Programme(MDP)
- United States; Centers for Disease Control (CDC), National Institute of Health (NIH), Office of Global AIDS Coordinator (OGAC), US Agency for International Development (USAID), Walter Reed Army Institute of Research (WRAIR).

PUBLIC-SECTOR–MULTILATERALS

- The Global Fund to Fight AIDS, Tuberculosis and Malaria
- Joint United Nations Programme on HIV/AIDS (UNAIDS)
- The World Bank
- World Health Organization (WHO)

PHILANTHROPIC SECTOR–FOUNDATIONS, TRUSTS AND NGOS

- amfAR, the Foundation AIDS Research
- Broadway Cares/Equity Fights AIDS
- Esteve Laboratories
- Ford Foundation
- Fundació de la Caixa
- Bill & Melinda Gates Foundation (BMGF)
- Elizabeth Glaser Pediatric AIDS Foundation (EGPAF)
- NY Community Trust
- Impala Platinum Holdings
- James B. Pendleton Trust
- Rockefeller Foundation
- Starr Foundation
- Until There's A Cure Foundation
- Wellcome Trust (Wellcome)

PHILANTHROPIC SECTOR–CORPORATE DONORS

- Becton, Dickinson and Co.
- Gilead Sciences, Inc. (Gilead)
- Pfizer

COMMERCIAL SECTOR–PHARMACEUTICAL COMPANIES

- GlaxoSmithKline (GSK)
- Novartis International AG
- Merck & Co. Inc. (Merck)
- Sanofi Pasteur
- Wyeth-Ayerst Lederle

INTERMEDIARY AGENCIES

- Alliance for Microbicide Development (AMD)
- CONRAD
- Global Campaign for Microbicides
- International AIDS Vaccine Initiative (IAVI)
- International Partnership for Microbicides (IPM)
- International Rectal Microbicide Advocates (IRMA)
- Microbicides Development Programme (MDP)
- Population Council
- South African AIDS Vaccine Initiative (SAAVI)

Acknowledgments

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The full text of this report is available online at the
HIV Vaccines and MIcrobicides Resource Tracking Working Group's website:
www.hivresourcetracking.org

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Notes

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AVAC Global Advocacy for HIV Prevention, www.avac.org
IAVI International AIDS Vaccine Initiative, www.iavi.org
UNAIDS Joint United Nations Programme on HIV/AIDS, www.unaids.org

More information on the Working Group's activities and reports
is available at: www.hivresourcetracking.org

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For more information on microbicides,
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For more information on UNAIDS resource tracking activities,
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ALLIANCE FOR MICROBICIDE DEVELOPMENT
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