ADDING IT ALL UP:

Funding for HIV Vaccine and Microbicide Development, 2000 to 2005

August 2006

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

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

This report was prepared on behalf of the HIV Vaccines and Microbicides Resource Tracking Working Group by Kevin Fisher (AVAC), Gabrielle Lamourelle (IAVI), Polly Harrison (AMD), Mitchell Warren (AVAC), Betsy Finley (AMD), Gian Gandhi (IAVI) and Lisa Regis (UNAIDS).

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In 2002, UNAIDS established a Global Resource Tracking Consortium for AIDS composed of international experts, and in October 2004, an HIV Vaccines and Microbicides Resource Tracking Working Group was formed. This working group was tasked with generating better information on investments in research and development for vaccines and microbicides.

The Working Group would like to thank the many individuals from the public, philanthropic and commercial sectors who provided us with information and whose participation was invaluable to the completion of this project. Support for this project was provided by the Alliance for Microbicide Development (AMD), the AIDS Vaccine Advocacy Coalition (AVAC), the International AIDS Vaccine Initiative (IAVI) and the Joint United Nations Programme on HIV/AIDS (UNAIDS).

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EXECUTIVE SUMMARY

- More than 25 years since the identification of HIV as the cause of AIDS, the HIV pandemic has grown to be the greatest public health threat facing the world. According to UNAIDS global estimates for 2005, about 38.6 million people were living with HIV and another 4.1 million became infected. As HIV affects the lives of millions more people, world leaders have recognized the urgent need to develop and implement a long-term, sustainable approach that includes near-universal access to appropriate HIV prevention, treatment and care.
- A comprehensive plan to combat the epidemic requires investment in new, sustainable methods of prevention to complement investments to expand access to existing HIV treatment and prevention options. Preventive HIV vaccines and microbicides are two technologies currently under development that would provide people with new options for protecting themselves from HIV and buttress other prevention efforts.
- The 2001 United Nations Declaration of Commitment on HIV/AIDS called for mobilizing massive new resources to mount an effective, comprehensive response to the epidemic. In particular, it called for increased investment in research related to HIV and AIDS and, more specifically, for the development of sustainable and affordable prevention technologies, such as vaccines and microbicides.
- The HIV Vaccines and Microbicides Resource Tracking Working Group developed a systematic approach to data collection and collation in order to generate investment estimates of research and development (R&D) investment that can be compared from year-to-year, from one technology to another, and across funders.[1]
- Over the six-year period from 2000 to 2005, funding from the public and the philanthropic sectors for R&D efforts directed at developing preventive HIV vaccines and microbicides more than doubled.
    - For HIV vaccines, non-commercial funding increased from US$327 million to US$684 million;
    - For microbicides, non-commercial funding grew from US$65 million to US$164 million.
- This increase in funding represents both greater contributions from current public and philanthropic donors as well as a growth in the total number and geographical distribution of funders supporting R&D for both new prevention technologies.
- Public sector funders continue to provide the overwhelming majority of the funds allocated to preventive HIV vaccine and microbicide R&D, with the United States and several European countries leading the way.
- Support for HIV vaccine and microbicide R&D also continues to grow outside the US and Europe, with significant financial investments by countries such as Brazil, Canada, China, India, South Africa and Thailand. The public sector, particularly in developing countries where trials are planned or are underway, also provides considerable non-financial support through staff and facilities as increasing numbers of research sites are readied for or initiate clinical trials. These non-cash contributions are not trivial and have grown considerably over the last six years.
- While significant, the levels of investment described above fall short of the estimated resources required to optimally accelerate the development of and assured access to these technologies.
    - For vaccines, 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.
    - For microbicides, the Alliance for Microbicide Development and the International Partnership for Microbicides estimated that US$280 million per year will be required over the next five years to accelerate development of a safe and effective microbicide.

[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.

HIV VACCINE R&D

- In 2005, total global investment in preventive HIV vaccine R&D was approximately US$759 million, an 11.3% increase over 2004 funding levels.
- In 2005, public sector funders provided 88% (US$672 million) of the funds allocated to preventive HIV vaccine R&D. The philanthropic sector provided 2% (US$12 million) and the commercial sector accounted for the remaining 10% (US$75 million) of investment made in 2005.
- During the last six years, European funders increased their commitment to preventive HIV vaccine R&D three-fold, from US$23 million to US$69 million. In 2005, R&D activities outside of the US and Europe continued to grow. Financial investments from countries such as Brazil, Canada, India, South Africa and Thailand totaled US$27 million, in addition to considerable non-financial support provided through staff and facilities in countries where trials are planned or are underway.
- A breakdown of global funding allocations by type of activity or stage of product development was estimated from a subset of investments in preventive HIV vaccine R&D, totaling US$668 million in 2005. Funds predominantly supported basic research and pre-clinical research, which accounted for approximately 64% of the funds spent. In comparison, support for clinical trials accounted for 22%, cohort and site development for 13% and advocacy and policy development for 1%.
- As of July 31, 2006, a preliminary estimate of non-commercial (public sector and philanthropic) commitments and disbursements for 2006 equaled US$781 million; representing a 14% combined increase for these sectors as compared to 2005.

MICROBICIDE R&D

- In 2005, total global investment in microbicide R&D was approximately US$168 million, a 15.1% increase over 2004 funding levels.
- In 2005, public sector funders provided 85% (US$143 million) of the funds allocated to microbicide R&D. The philanthropic sector provided 13% (US$21 million) and the commercial sector accounted for about 3% (US$4.5 million) (range US$3 million to US$6 million) of investment made in 2005.
- During the last six years, European funders increased their commitment to microbicide R&D forty-fold, from US$0.7 million to US$30 million. In 2005, R&D activities outside of the US and Europe from countries such as Brazil, Canada and South Africa continued to grow, totaling US$10.5 million, in addition to considerable non-financial support provided through staff and facilities in countries where trials are planned or are underway.
- A breakdown of global funding allocations by type of activity or stage of product development was estimated from a subset of investments on microbicide R&D totaling US$163 million in 2005. Funds supported basic research and pre-clinical research, which accounted for approximately 42% of the funds expended. In comparison, support for clinical trials accounted for 45%, cohort and site development for 8% and advocacy and policy development for 5%.
- As of July 31, 2006, a preliminary estimate of non-commercial public sector and philanthropic) commitments and disbursements for 2006 equaled US$169 million.

1. INTRODUCTION

More than 25 years since the identification of HIV as the cause of AIDS, the HIV pandemic has grown to be one of the greatest public health threats facing the world. According to Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates, globally about 38.6 million people were living with HIV in 2005 and another 4.1 million became infected in that year.[2] As HIV affects the lives of millions more people, world leaders have recognized the urgent need to develop and implement a long-term, sustainable approach that strives for universal access to appropriate HIV prevention, treatment and care.[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 treatment and prevention options and to enhance the sustainability of commitments to universal access. Preventive HIV vaccines and microbicides are two technologies currently under development that would provide people – particularly women, who are increasingly affected by the epidemic – with new options for protecting themselves from HIV, and buttress other prevention efforts.

Scientists are increasingly confident that it is possible to develop safe and effective vaccines and microbicides. There are still many scientific challenges ahead, though, and ensuring that both of these much needed technologies are developed as quickly, safely and ethically as possible will require even greater global collaboration and coordination. The investment of significantly more resources will also be required, and should be built into a comprehensive and balanced portfolio approach to HIV/AIDS research that incorporates both increased access to currently available tools and services and greater investment to develop new interventions. Accelerating the development and widespread use of vaccines and microbicides will require the active engagement of governments, international agencies, the private sector and community-based organizations.

While significant research progress has been made, it will still be a number of years before these two technologies are licensed and widely used. However, the time to their development, licensure and widespread use could be significantly reduced with increased and more efficient research and development (R&D) spending, accompanied by greater and sustained political commitment and action. Areas for increased attention include support for: conducting basic and applied research; designing and implementing ethical clinical trials; developing and sustaining clinical trial infrastructure; strengthening the capacity of national regulatory agencies; assuring capacity for manufacturing candidate products for trials; conducting process development to ensure that any licensed product can be manufactured at scale at a reasonable price; establishing large-scale manufacturing capacity; and undertaking policy and advocacy activities directed at accelerating vaccine and microbicide development and use.

In 2004, the AIDS Vaccine Advocacy Coalition (AVAC), the Alliance for Microbicide Development (AMD), the International AIDS Vaccine Initiative (IAVI) and UNAIDS initiated a collaborative project to track funding for preventive HIV vaccine and microbicide R&D. The organizations established the HIV Vaccines and Microbicides Resource Tracking Working Group (the "Working Group") to generate and disseminate detailed, comparable data on annual funding levels for preventive HIV vaccine and microbicide research, development and advocacy activities and on how these funds are being spent. This research is being used in part to monitor implementation of the Global Commitment and Action Indicators adopted by the United Nations in 2001 in conjunction with the issuing of the Declaration of Commitment on HIV/AIDS, the goals of which were reaffirmed at the 2006 United Nations General Assembly Special Session (UNGASS) on HIV/AIDS. The Political Declaration adopted at the UNGASS 2006 meeting again called on the world to commit to "intensifying investment in and efforts towards the research and development of new, safe and affordable HIV/AIDS-related medicines, products and technologies, such as vaccines, female-controlled methods and microbicides."[4]

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[2] UNAIDS *Report on the Global AIDS Epidemic* (2006). http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp.

[3] Resolution adopted by the General Assembly of the United Nations. 60th Session, *World Summit Outcome 2005*. http://unpan1.un.org/intradoc/groups/public/documents/UN/UNPAN021752.pdf.

[4] Resolution adopted by General Assembly, 60th Session, *Political Declaration on HIV/AIDS*. http://data.unaids.org/pub/Report/2006/20060615_HLM_PoliticalDeclaration_ARES60262_en.pdf.

The Invaluable Contribution of Clinical Trial Participants

In considering total investment and expenditure on HIV vaccine and microbicide research and development, the enormous contribution of trial participants cannot be overlooked. Globally, the target enrollment for ongoing preventive HIV vaccine and microbicide trials is approximately 47,000 people. These volunteers are essential to the progress of preventive HIV vaccine and microbicide development. Trial participation requires significant time commitments over a period of several years, and involves periodic clinical visits, blood draws, gynecological examinations, and HIV testing and counseling.

No matter how much money is invested, advancing the development of preventive HIV vaccines and microbicides is entirely dependent on the availability, willingness and day-to-day commitment of trial volunteers over a period of years. While volunteers do receive meaningful benefits during a trial, for example, regular medical care, travel expenses and reimbursement for time, they are motivated by the hope that they will have contributed to the discovery of effective new prevention technologies.

Countries Hosting HIV Vaccine Trials in 2005-2006: Australia, Belgium, Botswana, Brazil, Canada, China, Dominican Republic, Finland, France, Germany, Haiti, India, Italy, Jamaica, Kenya, Malawi, Peru, Puerto Rico, Rwanda, South Africa, Sweden, Switzerland, Thailand, Uganda, United Kingdom, United States and Zambia

Countries Hosting Microbicide Trials in 2005-2006: Australia, Belgium, Benin, Brazil, Burkina Faso, Cameroon, India, Madagascar, Malawi, Nigeria, Rwanda, South Africa, Tanzania, Thailand, Uganda, United States, Zambia and Zimbabwe

2. METHODS OF ESTIMATING RESOURCE FLOWS

In order to generate investment estimates that can be compared from year to year, from one technology to another and across funders, the Working Group developed a systematic approach to data collection and collation during the first iteration of this collaborative project in 2005. The same methods were employed to generate the estimates of funding for R&D presented here (see Appendix I for a detailed description).

A broad definition of R&D was used for the analysis, so data were collated on support for product development; clinical trial preparations; community education; and advocacy and policy efforts directed at accelerating HIV vaccine and microbicide development and future use. However, we excluded R&D for vaccines with primarily therapeutic applications (also known as immune-based therapy) and research that may offer benefits or links to preventive HIV vaccines or microbicides (e.g., platform technologies), but that was not directed primarily at their development.

Two different types of resource flows were tracked: investments, defined as annual disbursements by funders; and, when available, expenditures, defined as the level of resources directly spent on R&D activities by funding recipients in a particular year. The main reasons for differentiating between these two resource flows were: (1) some funders may forward fund (i.e., disburse funding in one year to be expended over multiple years); (2) research projects may be delayed and (3) the growing importance of product development public-private partnerships (PDPs) who often receive funds in one year but expend them over a period of time or may hold funds to sustain multi-year contracts.

Investment figures were based on estimates of the level of funds disbursed each year and generated from the perspective of the funder.[5] That is, funds were allocated to the year in which they were disbursed by the donor, irrespective of whether the funds were spent by the recipient in that year or in future years. In order to minimize double-counting, we distinguished between primary funders and intermediary organizations. "Intermediary" organizations receive resources from multiple funders and use these resources to fund their own work as well as the work of others. For example, CONRAD, the International Partnership for Microbicides (IPM), IAVI and the South African AIDS Vaccine Initiative (SAAVI) were classified as intermediary organizations. All identified primary funders were categorized as public (such as government research bodies, international development agencies and multilaterals), philanthropic (such as foundations, charities and corporate donors), or commercial (pharmaceutical and biotechnology companies) sector funders.

There is no agreed method for breaking down funding allocations by type of activity or stage of product development. For this exercise, we have allocated resources identified into five categories (see Table 1). The first four categories are based on the US National Institutes of Health definitions.[6] (See Appendix 3 for examples of the types of activities included in each category). The allocation of funding across these categories was based on the information provided by the intermediaries and/or funders. When this information was not available, we reviewed the descriptions of the projects funded and, based on the description of each project, allocated the funds across the five expenditure categories.

Overhead Costs

When reviewing the different levels of funding between public investment in the United States and that in the European Union, it is necessary to consider differing policies regarding the reimbursement of institutional expenses, often referred to as overhead costs. An organization that funds research through grants is often funding both direct and indirect overhead costs. The direct costs comprise expenses expressly related to R&D, while indirect overhead costs include expenditures that support research, such as administration, security or laboratory maintenance.

In the United States, there is an accepted system of paying research overhead costs with each funded institution negotiating its own level of overhead. These overhead costs, entitled facilities and administration, vary from 40% to 65% of direct costs.[7] A grant of US$1.65 million for HIV vaccine research would therefore render only US$1.0 million in direct funding to researchers.

In contrast, European public funding agencies either do not pay overhead costs, or do so at lower levels. In the EC, for example, for those research institutions which cannot calculate actual costs, the overhead rate is set at 20%. These different funding structures should be taken into account in making dollar for dollar comparisons between U.S. investment levels with those of European funders.

In allocating funding by category, we distinguished between funding provided by primary funders to universities, not-for-profit organizations, companies or for their own R&D activities and funding they provided to "intermediary" organizations like IAVI and IPM. In order to avoid double-counting, grants made to intermediary organizations were subtracted from primary funders' investment figures. Sufficient data to allocate commercial sector funding allocations were not available.

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[5] Organizations were asked to provide data based on the calendar year if possible and, if not, by their fiscal year. For organizations for which the fiscal year and the calendar year did not match we treated the fiscal year as equivalent to the calendar year in which it predominantly occurs. For example, the fiscal year April 1, 2005 to March 31, 2006 was treated as 2005 and the fiscal year July 1, 2005 to June 30, 2006 was treated as 2006.

[6] National Institutes of Health (2000). *National Institutes of Health Fiscal Year 2002 Plan for HIV-Related Research*. Washington, DC. The categories used by the NIH are: Basic, Pre-Clinical, Pediatric, Clinical Trials and Vaccine Preparedness. For the purposes of our estimates we have accepted the NIH breakdown of their expenditures by category. Auditing and reclassifying the NIH data would have been a major exercise and was beyond the scope of this project.

[7] *Report of the Group on Research Overheads*, July 2003, Irish Government Publication.

Financial resources for HIV vaccine and microbicide R&D are only one component of the significant contributions made by the public sector. The public sector provides considerable non-financial support, particularly in countries in the developing world where trials are planned or are underway. Government-salaried collaborators, government-sponsored hospitals and clinics, and government staff on trial review boards play crucial roles in the safe and ethical conduct of clinical trials, as do national regulatory authorities and ethics committees. In addition, governments such as the United Kingdom provide tax credits to companies undertaking R&D activities directly associated with AIDS vaccines. For example, HM Revenue & Customs estimated that the cost of these tax credits over the two-year period 2003-2005 was around US$1.7 million (£1 million). These public sector revenues forgone are not incorporated into the Working Group's estimates although they are nonetheless important 'contributions' that support the funding of new preventive technology R&D.

Table 1: Categories Used to Classify Preventive HIV Vaccine and Microbicide R&D Funding	
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 preventive HIV vaccine and microbicide design. This includes vaccine and microbicide design, development and animal testing.
Clinical Trials	Support for Phase I, II and III trials testing the safety, immunogenicity and efficacy of suitable preventive HIV vaccine and microbicide candidates or concepts in domestic and international settings (including the costs of producing candidate product lots for clinical trials).
Cohort & Site Development	Support to develop the strategies, infrastructure and collaborations with researchers, communities, government agencies, regulatory agencies, NGOs and industry necessary to identify trial sites, build capacity, ensure adequate performance of trials and address the prevention needs of at-risk populations in trial communities.
Advocacy & Policy Development	Efforts directed at educating and mobilizing public and political support for preventive HIV vaccines and microbicides and at addressing potential regulatory, financial, infrastructure and/or political barriers to their rapid development and use.

3. RESULTS

3.1 GLOBAL INVESTMENTS IN HIV VACCINE R&D

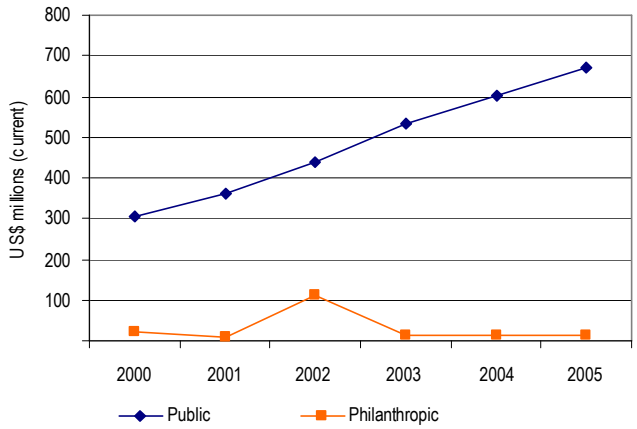
Over the last six years, there has been a marked increase in the level of investment in the development of preventive HIV vaccines. In 2005, total global investment in preventive HIV vaccine R&D was an estimated US$759 million (see Table 2).

Table 2. Annual Investments in Preventive HIV Vaccine R&D between 2000 and 2005 (current US$ millions).
*The 2006 estimates represent actual disbursements and firm commitments made as of July 31, 2006.

	2000	2001	2002	2003	2004	2005	2006*
Public sector							
- US	272	314	376	463	516	574	663
- Europe[A]	23	32	39	44	57	69	26
- Other[B]	10	12	21	24	28	27	10
- Multilaterals	2	2	2	2	2	2	2
Total public	307	359	436	532	602	672	704
Philanthropic sector							
Total philanthropic	20	7	112	15	12	12	77
Total non-commercial investment	**327**	**366**	**548**	**547**	**614**	**684**	**781**
Commercial sector							
- Pharmaceutical companies	-	-	-	-	59 (range 47 to 71)	64 (range 52 to 76)	-
- Biotechnology companies	-	-	-	-	9 (range 7 to 11)	9 (range 9 to 13)	-
Total commercial	-	-	-	-	68 (range 54 to 82)	75 (range 61 to 89)	-
Total global investment[C]					**682**	**759**	

[A]. This figure includes funding from the European Commission
[B]. Other includes all national public sector funding apart from funding from the US and Europe
[C]. Commercial sector investments were estimated for selected years in the series

Figure 1. Annual Public and Philanthropic Investments in Preventive HIV Vaccine R&D between 2000 and 2005.



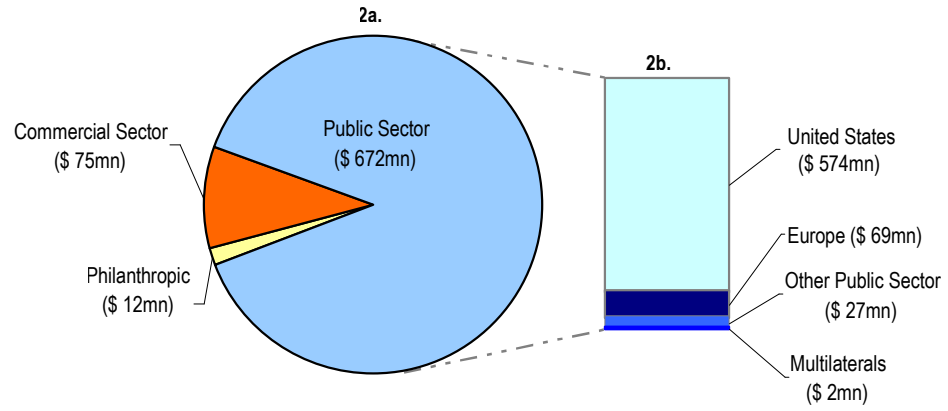
Between 2000 and 2005, non-commercial (public and philanthropic) sector funding more than doubled, increasing from US$327 million to US$684 million (see Figure 1). As of July 31, 2006, commitments from the public and philanthropic sectors for 2006 were approximately US$781 million. A discussion of funding trends specifically between 2000 and 2005 can be found in the Working Group's previous reports.[8]

[8] Available at www.hivresourcetracking.org.

3.1.1 PUBLIC INVESTMENTS IN HIV VACCINE R&D

Of the three sectors, public agencies and institutions dominated funding for HIV vaccine R&D, accounting for 88.5% of total investment in 2005. In contrast, the commercial sector accounted for 9.9% and the philanthropic sector for 1.6% of funding in that year (see Figure 2a).

Figure 2. Sources of Global Funding for HIV Vaccine R&D in 2005.



The United States provided the single largest portion of public funds, and in 2005 it accounted for 85% (US$574 million) of the total funds invested by that sector. For the same year, European national governments and the European Commission together accounted for 10% (US$69 million) of the total funds invested, while national governments from the rest of the world accounted for 4% (US$27 million). Multilateral organizations such as WHO, UNAIDS and the World Bank combined accounted for less than 1% (US$2 million) (see Figures 2b and 3).

Funding for preventive HIV vaccines appears poised to increase in 2006 as it has since 2000. In the public sector, the NIH expects to increase funding for preventive HIV vaccine research by almost $100 million over 2005 levels. Estimates at this time also indicate increases for Canada, Ireland and the United Kingdom.

Figure 3. Annual Public Investments in Preventive HIV Vaccine R&D by Region between 2000 and 2005.

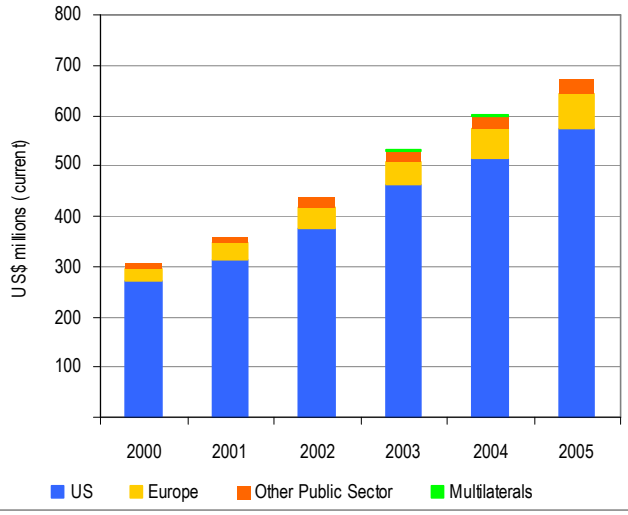


Table 3. National Public Sector Investments in Preventive HIV Vaccine R&D by Country in 2005. [A]	
Over US$25 million	United Kingdom, United States
US$10 to 25 million	Canada
US$5 to 10 million	Italy, Netherlands
US$1 to 5 million	China, Denmark, France, Germany, Japan, South Africa, Sweden
US$500k to 1 million	Brazil, Finland, India, Ireland, Russian Federation
US$50k to 500k	Australia, Cuba, Thailand

[A]. This study reviewed national, not sub-national or provincial, public sector data.

Table 4. National Public Sector Investments in Preventive HIV Vaccine R&D Relative to National Wealth in 2005.[B]	
% of GDP (x 10^{-3})	**Country**
4.0 to 5.0	United States
3.0 to 4.0	(none)
2.0 to 3.0	South Africa
1.0 to 2.0	Canada, Sweden, United Kingdom
0.5 to 1.0	Denmark, Netherlands
<0.5	Australia, Brazil, China, Finland, France, Germany, India, Ireland, Italy, Japan, Norway, Russia, Thailand

[B]GDP estimates are for the year 2004. Source: 2006 World Development Indicators. The World Bank. Washington, DC. Note: no GDP data were available for Cuba for 2004.

Three countries (Canada, the United Kingdom and the United States) invested more than US$10 million in public sector funds in 2005; 12 countries invested more than US$1 million (see Table 3). In addition, the European Commission (EC) invested approximately US$18 million. In terms of total funds disbursed for HIV vaccine R&D between 2000 and 2005, the top five countries (excluding the EC) in descending order are: the United States, the United Kingdom, Canada, the Netherlands and France.

Five countries (Canada, South Africa, Sweden, the United Kingdom and the United States) invested greater than 0.001% of their gross domestic product (GDP) in HIV vaccine research (see Table 4). South Africa contributed a significant portion of GDP to vaccine research, following only the United States as the second largest public sector investor in 2005 as a percentage of GDP.

The proportion of HIV vaccine funding originating in health and research agencies versus international development agencies varies widely across countries. The National Institutes of Health (NIH) alone accounted for 90% (about US$511 million) of total US public sector funding – about 76% of global public sector investment. In many other countries reviewed, international development funding agencies (as opposed to research funding agencies) were equally important sources of funds for HIV vaccine R&D. The three multilateral agencies (UNAIDS, WHO and the World Bank) provided primarily development funding.

Country Profile: Brazil

Brazil has become a model of the increasing global commitment to HIV vaccine development. In 2005, the Brazilian Ministry of Health (MoH) and the United Nations Educational Scientific and Cultural Organization (UNESCO) joined forces in organizing the largest ever Brazilian call for proposals on HIV vaccine research. From 2005 to 2006, MoH annual funding of HIV vaccine-related projects increased five-fold from US$734,000 to US$3,734,000. "The Brazilian National STD-AIDS Program is giving top priority to strengthening research and technological development in HIV vaccine and microbicide research," says Christina Possas, Head of the Research and Development Unit of the Brazilian Ministry of Health. The call solicits proposals under 14 thematic lines of research on a broad range of topics including: mucosal immunity; central memory cells and phenotypes induced by HIV vaccines; correlates of immunity; chimeric antigens of HIV; molecular adjuvants for activation of dendritic cells; and studies supporting the development of preventive and therapeutic vaccines. This US$4 million call for proposals also aims to develop trial capacity for Phase I and II trials and to encourage collaboration among research institutions. In November 2005, for the first time Brazil also invested in a competitive process to fund microbicide projects, and to support sites for future microbicide research.

Country Profile: United States

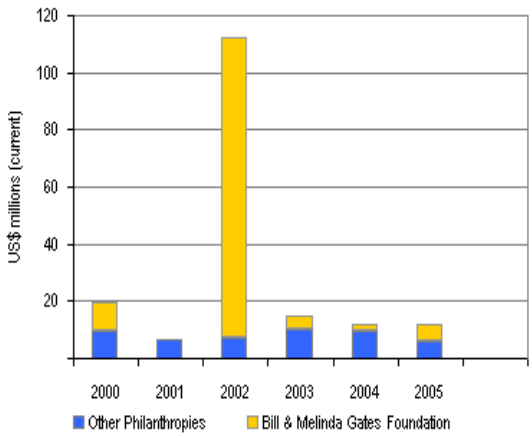
Although public sector agencies and institutions outside the United States increased their investment in preventive HIV vaccine and microbicide R&D, the largest share of public sector funds continued to come from US sources. Of US public agencies funding research in new prevention technologies, the National Institutes of Health (NIH) provides the largest share. Between 2000 and 2005, the NIH has each year funded approximately three-fourths of the global public sector investment in preventive HIV vaccines. The NIH concentrates its funding on basic and preclinical research, which comprised 68% of its funding in 2005 as compared to 19% for clinical trials and 13% for cohort and clinical trial site development in that same year. The United States government's contribution to global public sector funding through all of its agencies is proportionately even greater, comprising more than 85% of global funding in the years 2000 to 2005. While the majority of US funding come from research agencies, the US Agency for International Development (USAID) is also an important source of new prevention technology R&D funding. USAID provided US$27 million for HIV vaccine R&D in 2005.

Similarly, the United States government's share of global public sector funding for microbicides through all of its agencies comprised greater than 70% of global public sector funding in the years 2000 to 2005. The NIH has funded a smaller percentage of United States government resources for microbicides over time, accounting for 84% (US$30.5 million) of the global public sector investment in microbicides in 2000, and 47% (US$66.7 million) of such investment in 2005. The US Agency for International Development has accounted for an increasing percentage of US government funding for microbicides from 2000 to 2005 (US$39 million in 2005).

3.1.2 Philanthropic Investments in HIV Vaccine R&D

The philanthropic sector accounted for US$12 million or about 2% of the total funds disbursed for HIV vaccine R&D in 2005. As seen in Table 2 and Figure 4, levels of total philanthropic funding have varied considerably over the last five years. This variability reflects the funding practices of the philanthropic field, which can involve strategic one-time funding of specific projects, as well as forward funding of multiple year grants (i.e., disbursing funding in one year to be expended by recipients over multiple years).

Figure 4. Annual Philanthropic Investments in Preventive HIV Vaccine R&D between 2000 and 2005.



In 2005, eight philanthropic organizations provided funding of more than US$ 100,000 for HIV vaccine R&D. In addition, two companies also provided direct financial donations of US$ 100,000 or more (see Table 5).

The 2005 philanthropic investment figure does not include HIV vaccine-related grants by the Gates Foundation as part of the Grand Challenges in Global Health (see box below).

Table 5. Philanthropic Investments in HIV Vaccine R&D by Organization in 2005.

Over US$1 million	Bill & Melinda Gates Foundation, Eskom*, Wellcome Trust
US$500k to 1mn	Elizabeth Glaser Pediatric AIDS Foundation
US$250k to 500k	American Foundation for AIDS Research, New York Community Trust, Rockefeller Foundation, Until There's A Cure Foundation
US$100k to250k	Becton Dickinson and Company*, Ford Foundation

*Company donation rather than philanthropic organization

Philanthropic funding will rise significantly in 2006 with the award of $287 million in 16 five-year grants by the Bill & Melinda Gates Foundation to support collaborative HIV vaccine research as part of the Global HIV Vaccine Enterprise.

Grand Challenges

The philanthropic funding estimates for 2005 do not include portions of the Grand Challenge in Global Health Initiative grants from the Bill & Melinda Gates Foundation, the Wellcome Trust and the Canadian Institutes of Health Research. These grants provide funding for critical basic research to address major global health challenges, and include vaccine related funding totaling US$110 million over five years, resulting in approximately US$22 million in research funding for these basic science questions during 2005. Because the Challenge grants are aimed at resolving scientific questions that pose key road blocks to vaccine development generally and not HIV vaccines specifically, these funds are not included in the investment estimates. These scientific questions include finding new mouse models for vaccine candidates; improving vaccine efficacy via dendritic cells and exploring mucosal protection.

3.1.3 COMMERCIAL INVESTMENTS IN HIV VACCINE R&D

Total investment by the commercial sector (pharmaceutical and biotechnology companies) in HIV vaccine development in 2005 was estimated to be US$75 million (range US$61 million to US$89 million). The majority of this funding – over 80% – comes from large pharmaceutical companies.

This estimate reflects what the biopharmaceutical sector invests from internal resources. Most of the pharmaceutical and biotechnology companies active in HIV vaccine R&D also receive extensive program funding from external sources such as public sector agencies [e.g., National Institutes of Health (US) and Agence Nationale de Recherches sur le Sida (France)] or public-private partnerships (e.g., IAVI and SAAVI). Therefore, total spending by the commercial sector is much greater than the estimated US$75 million in funds invested from their own internal sources.

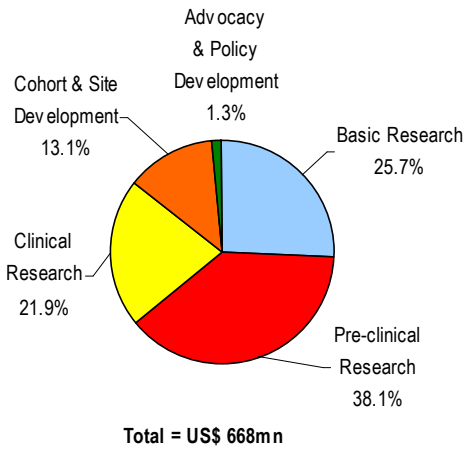
In total, it is estimated that there were almost thirty companies actively engaged in HIV vaccine R&D in 2005 (see Table 6). Three of these companies – all among the large pharmaceutical companies – were estimated to have invested more than US$5 million of their own funds in preventive HIV vaccine R&D in 2005.

Table 6. Commercial Engagement in Preventive HIV Vaccine R&D by Company in 2005.

Over US$10 million	• Merck & Co, Inc.
US$5 million to 10 million	• Sanofi Pasteur • Novartis International AG (after acquisition of Chiron Corporation)
US$1 million to 5 million	• Wyeth-Ayerst Lederle, Inc. • GlaxoSmithKline plc
US$25k to 1 million	• Advanced BioScience Laboratories • AlphaVax Human Vaccines Inc. • AVANT Immunotherapeutics, Inc. • Bavarian Nordic • Bioption AB • Bioqual Inc. • Cobra Biomanufacturing plc • Crucell N.V. • Epimmune Inc. • FIT Biotech PLC • EpiVax, Inc. • GenVec, Inc. • GeoVax, Inc. • Globeimmune, Inc. • Immune Response • Impfstoffwerk Dessau Tornau GmbH • Maxygen, Inc. • Mymetics. • Progenics Pharmaceuticals, Inc. • Targeted Genetics Corporation • Therion Biologics Corporation • Transgene • Vical Inc.

3.1.4 FUNDING ALLOCATIONS FOR HIV VACCINE R&D

Figure 5. Non-commercial Funding Allocations for Preventive HIV Vaccine R&D by Category in 2005.

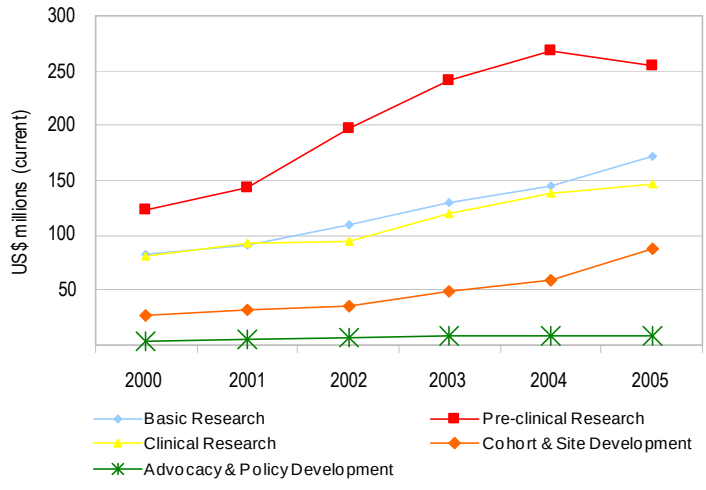


Total = US$ 668mn

In 2005, spending by the public and philanthropic sectors on HIV vaccine R&D predominately supported basic and pre-clinical research activities. Of the five categories across which funding was allocated, basic research and pre-clinical research accounted for 25.7% and 38.1% of funds respectively. In comparison, support for clinical trials accounted for 21.9%, cohort and site development for 13.1% and advocacy and policy development less than 2% of total 2005 funding (see Figure 6). These allocations are estimated from a subset of investments for preventive HIV vaccine R&D totaling US$668 million in 2005.

The allocation of funding across the five categories has remained fairly constant over the past six years (see Figure 6).

Figure 6. Non-commercial Funding Allocations for Preventive HIV Vaccine R&D by Category between 2000 and 2005.



The last six years have seen a rise in the importance of intermediary organizations, and in particular product development public-private partnerships (PDPs) such as IAVI and SAAVI, in the development of new public health technologies. IAVI is the largest of the PDPs working on the development of HIV vaccines, and in 2005 accounted for 8.5% of global investment, or about US$63 million. As the role of PDPs increases, there is a need to consider the impact of donor-restricted funding on their ability to operate in a swift and flexible manner. In particular, PDPs require long term funding commitments to be assured that research can be completed and products can ultimately be brought to market.

3.2 Global Investments in Microbicide R&D

Total global investment amounted to US$168 million (range US$166.9 to US$169.9 million) in microbicide R&D reflecting a marked increase in the level of investment over the last six years (see Table 7). Between 2000 and 2005, investments from the public and philanthropic sectors more than doubled, from an estimated US$65 million to approximately US$163.9 million (see Table 7 and Figure 7).

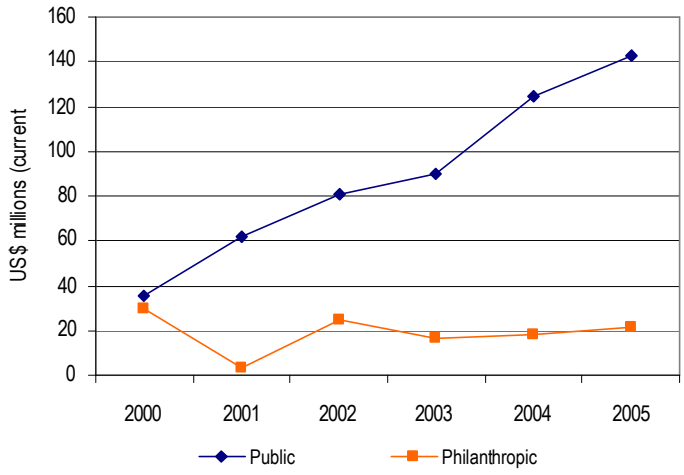
Table 7. Annual Investments in Microbicide R&D between 2000 and 2006 (current US$ millions).
*The 2006 estimates represent actual disbursements and firm commitments made as of July 31, 2006.

	2000	2001	2002	2003	2004	2005	2006*
Public sector							
- US	34.6	61.3	75.3	78.8	92	101.6	110.9
- Europe[A]	0.7	0.4	5.1	10.6	29.9	30.3	31.7
- Other[B]	0.3	<0.1	0.2	0.9	2.0	10.5	0
- Multilaterals	<0.1	0.3	0.4	<0.1	0.2	0.2	0.2
Total public	35.7	62.0	81.0	90.2	124.2	142.6	142.8
Philanthropic sector							
Total philanthropic	29.4	3.4	24.8	16.9	18.1	21.3	26
Total non-commercial investment	**65.1**	**65.4**	**105.8**	**107.1**	**142.3**	**163.9**	**168.8**
Commercial sector							
- Pharmaceutical companies	-	-	-	-	-	-	-
- Biotechnology companies	-	-	-	-	4.5 (range 3 to 6)	4.5 (range 3 to 6)	-
Total commercial	-	-	-	-	4.5 (range 3 to 6)	4.5 (range 3 to 6)	-
Total global investment[C]					**146.8**	**168.4**	

A. This figure includes funding from the European Commission
B. Other includes all national public sector funding apart from funding from the US and Europe
c. Commercial sector investments were estimated for selected years in the series

Public agencies and institutions dominated funding for microbicides R&D, accounting for 84.7% (US$142.6 million) of total investment in 2005. In contrast, the philanthropic sector accounted for 12.6% (US$21.3 million) and the commercial sector for 2.7% (US$4.5 million) of funding in that year (see Figure 8). As of July 31, 2006, commitments from the public and philanthropic sectors for microbicide R&D for 2006 had reached approximately US$168.4 million.

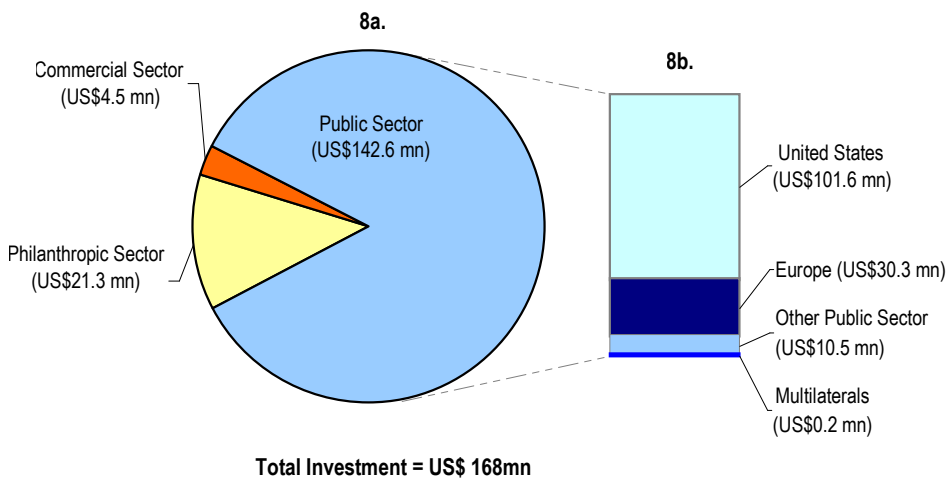
Figure 7. Annual Public and Philanthropic Investments in Microbicide between 2000 and 2005.



A number of philanthropic, public sector and commercial sector funders provided support for the Microbicides 2006 Conference, held in Cape Town, South Africa. These funds totaling approximately US$2.0 million in 2006. In addition, the Rockefeller Foundation is expected to provide another US$4.0 million in support for microbicide development in 2006.

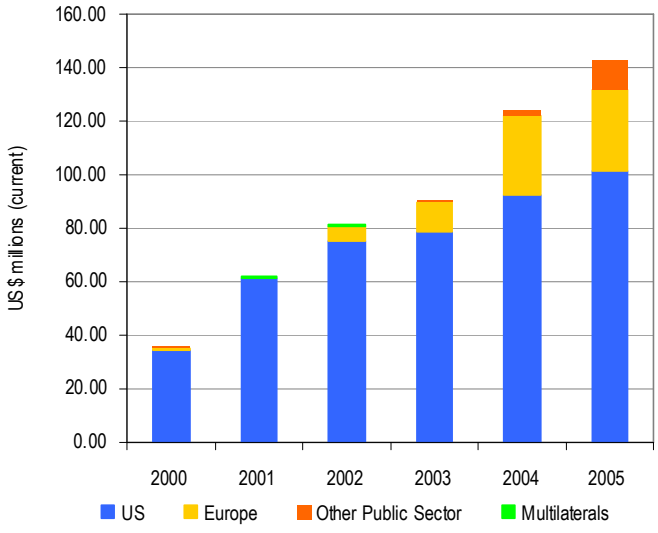
3.2.1 PUBLIC INVESTMENTS IN MICROBICIDE R&D

Figure 8. Sources of Funding for Microbicide R&D in 2005.



In 2005, public sector investment in microbicide R&D amounted to approximately 85% of the combined global funding for microbicide research, development and advocacy. Of the US$649.6 million from non-commercial sources invested in the development of microbicides between 2000 and 2005, 25.2% was invested in 2005.

Figure 9. Annual Public Investments in Microbicide R&D by Region between 2000 and 2005.



The United States dominates public sector funding for microbicides, providing 71%(US$ 101.6 million) of the total funds made available by the public sector in 2005. European national governments and the European Commission together accounted for 21% (US$30.3 million) (see Figure 8).

National governments from the rest of the world accounted for 7%(US$10.5 million) of public sector funding and the multilateral organizations reviewed (WHO, UNAIDS and the World Bank) together accounted for less than 1% (US$ 0.2 million) of total public sector investment (see Figure 8).

Three countries (Canada, the United Kingdom and the United States) invested more than US$10 million of public sector funds microbicide development in 2005; eight countries invested more than US$1 million that year (see Table 8).

Table 8. National Public Sector Investment in Microbicide R&D by Country in 2005.

Over US$10 million	Canada, United Kingdom, United States
US$5 to 10 million	*(none)*
US$1 to 5 million	Denmark, Ireland, Norway, Sweden
US$500k to 1 million	*(none)*
US$50k to 500k	Australia, Belgium, Brazil, China, France, South Africa

While the United States, and, in particular, the NIH, continues to dominate public sector funding for microbicides, the proportion of resources from European funders has increased. Between 2000 and 2005, the share of funding from European public sector sources (including the EC) grew from less than 1% to 21% (US$7 million in 2005).

In terms of cumulative funds disbursed for microbicide R&D between 2000 and 2005, the top five countries (excluding the EC) in descending order were: the United States, the United Kingdom, Canada, the Netherlands and Ireland. Over the same period, the proportion of public funding originating from non-US sources increased from 3% to 29%.

Table 9. National Public Sector Investment in Microbicide R&D Relative to National Wealth in 2005.[A] (Countries are listed alphabetically within each category.)

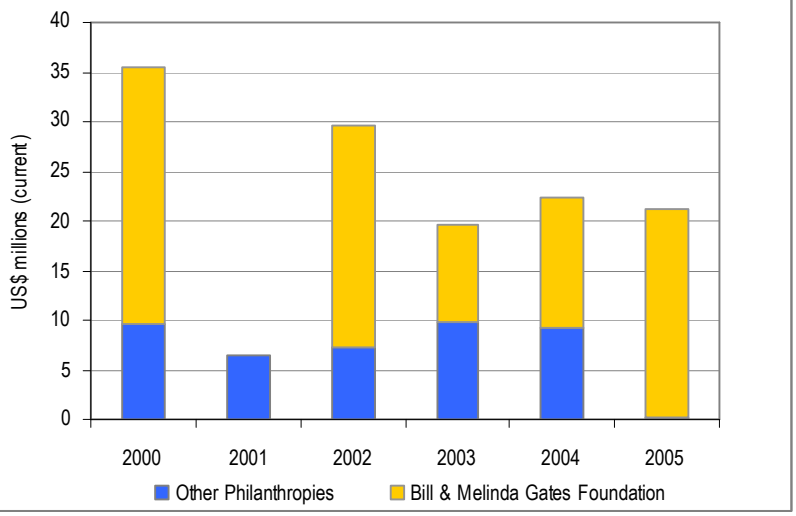
% of GDP (x 10^{-5})	Country
>1.5	Ireland
1.0 to 1.5	Canada, Norway, Sweden
0.5 to 1.0	Denmark, United Kingdom, United States
0.0. to 0.5	Australia, Belgium, Brazil, France

[A] GDP estimates are for the year 2004. Source: 2006 World Development Indicators. The World Bank. Washington, DC.

The sources of public sector funding for microbicide R&D vary widely from country to country. In some countries the majority of funding comes from health and research agencies, while in other countries, international development agencies provide most or all of the public funding available for microbicide development. The United States is unusual in having significant funding invested by both types of agencies. The NIH, primarily a health and research funding agency, accounted for 66% of US public sector funding in 2005, while the US Agency for International Development (USAID) provided about 29% of US public resources for microbicide R&D. Together, US public sector agencies accounted for approximately 60% of total global investment in microbicide R&D.

3.2.2 PHILANTHROPIC INVESTMENTS IN MICROBICIDE R&D

Figure 10. Annual Philanthropic Investments in Microbicide R&D between 2000 and 2005.



In 2005, funding from the philanthropic sector totaled US$21.3 million, or 13% of the total funds disbursed for microbicide development from public and philanthropic sources. Philanthropic funding levels have fluctuated considerably over the six-year period studied – from a low of US$3.4 million in 2001 to a high of US$29.4 million in 2000 (see figure 10). This variability reflects the funding practices of the philanthropic field, which can involve strategic one-time funding of specific projects, as well as forward funding of multiple year grants (i.e., disbursing funding in one year to be expended by recipients over multiple years).

Table 10. Philanthropic Investment in Microbicide R&D by Organization in 2005. Organizations are listed alphabetically within each category.

Over US$1 million	Bill & Melinda Gates Foundation
US$500k to 1mn	(none)
US$100k to 500k	(none)
US$50k to 100k	American Foundation for AIDS Research, Wellcome Trust

In 2005, the Bill & Melinda Gates Foundation provided funding of more than US$1 million for microbicide R&D. Two additional organizations (the American Foundation for AIDS Research and the Wellcome Trust) provided funding in the US$50,000 to US$100,000 range.

Table 11. Commercial Engagement in Microbicide R&D in 2005.

• Biofem, Inc. • Cellegy/Biosyn, Inc. • Dow Pharmaceutical Sciences • Gilead Sciences • Idenix Pharmaceuticals • ImQuest BioSciences • Indevus Pharmaceuticals, Inc.	• Mapp Biopharmaceutical Inc. • Novaflux Technologies • Osel, Inc. • Polydex Pharmaceuticals Ltd. • ReProtect LLC • Starpharma Ltd. • Tibotec Pharmaceuticals Ltd.

3.2.3 COMMERCIAL INVESTMENTS IN MICROBICIDE R&D

Total commercial sector microbicide investment in 2005, excluding funding from external sources, was estimated to be US$4.5 million (range US$3 million to US$6 million).

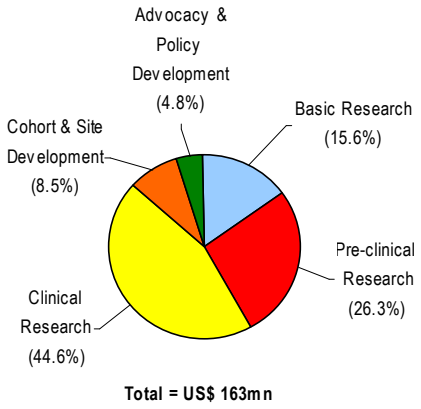
Fourteen biotechnology or biopharmaceutical companies participated in some aspect of microbicide R&D

in 2005. Virtually all of these companies received support for their work on microbicide R&D through public sector granting mechanisms, predominantly from the NIH, and/or through intermediary organizations such as CONRAD and IPM. Although investments from companies' own financial resources are generally small and supplementary to any external funding they receive, small – sometimes 'virtual' – private companies have played crucial roles in the development of a number of current microbicide candidates. Of the five candidates currently in late-stage clinical trials, four were developed by biopharmaceutical companies (ImQuest BioSciences, ReProtect, Indevus Pharmaceuticals and Polydex Pharmaceuticals).

3.2.4 Funding Allocations For Microbicide R&D

In 2005, total funding allocations by the public, philanthropic and commercial sectors on microbicide R&D were concentrated on basic and pre-clinical research activities. Of the five categories across which funding was allocated, basic research and pre-clinical research accounted for approximately 16% and 26% respectively of the funds spent. Support for clinical trials accounted for 45%, cohort and site development for 8% and advocacy and policy development for 5% (see Figure 11). These allocations are estimated from a subset of investments on microbicide R&D, totaling US$163 million in 2005.

Figure 11. Funding Allocations for Microbicide R&D by Category in 2005.



Non-financial (In-kind) Contributions at the Trial Site and Community

Direct funding of HIV vaccine and microbicide R&D is only one component of the significant contributions made from public sources which. The public sector provides considerable non-financial support, particularly in countries in the developing world where trials are planned or are underway. Government-salaried collaborators, government-sponsored hospitals and clinics, and government staff on trial review boards play crucial roles in the safe and ethical conduct of clinical trials, as do national regulatory authorities and ethics committees. These and other non-cash contributions are not trivial and have grown considerably over the last five years, as increasing numbers of research sites are readied for or initiate clinical trials.

Non-financial (In-kind) Contributions in Product Development

The commercial sector contributes to the development of preventive HIV vaccines and microbicides in a number of ways. Some companies invest their own resources; under the Working Group's methodology, these funds were accounted for in the commercial sector investments estimate (with the exception of corporate donations, which were included as philanthropic funding). Most companies engaged in this R&D receive financial support from public sector agencies, either directly or through intermediary entities. These funds were accounted for in the public or philanthropic sector investment estimates, depending on the origin of the funds.

In addition, some companies contribute proprietary intellectual property to wider research and development efforts. It would be quite difficult, if not impossible, to place a financial value on these contributions. Like other in-kind contributions such as anti-retroviral drugs (ARVs) donated for use in clinical trials, these contributions have not been valued by the Working Group are not included in the resource estimates presented here. Nevertheless, these are important contributions. To date, several companies have transferred intellectual property under various arrangements for development as microbicides. For example, Bristol-Myers Squibb and Merck have both donated royalty-free licenses for selected compounds to IPM, and Cellegy/Biosyn has transferred intellectual property for several compounds to CONRAD for further development.

4. DISCUSSION

An estimated 38.6 million (range: 33.4 million – 46.0 million) people worldwide were living with HIV in 2005. An estimated 4.1 million (range: 3.4 million – 6.2 million) became newly infected with HIV and an estimated 2.8 million (range: 2.4 million – 3.3 million) lost their lives to AIDS.[9] Safe, effective and globally accessible vaccines and microbicides are the best hope to bring the devastating AIDS pandemic under control. A comprehensive response needs equally to deliver the interventions and programs we have today while working to develop for better tools for tomorrow. Better prevention tools will be critical to ensuring the financial sustainability of commitments to universal access to treatment and care.

Over the last six years, public sector funding for preventive HIV vaccines and microbicides has increased substantially, and preliminary investment estimates suggest that funding levels for HIV vaccines will be still higher in 2006. The significant increase in funding over the last six years has coincided with a dramatic increase in the overall financial commitment to the HIV/AIDS field in general. While the Working Group has not collected data on overall financial commitments to HIV/AIDS, evidence suggests that funders have increased funding for the development vaccines and microbicides in conjunction with their commitments to expanding access to the prevention and treatment tools already available.

The growing funding for HIV vaccine and microbicide R&D reflects a number of factors including: increased scientific confidence that it is possible to develop safe and effective preventive HIV vaccines [10] and microbicides;[11] increased recognition of the potential role of new technologies in controlling the spread of HIV[12] and the need to invest in a comprehensive response; and, for microbicides, the entry of five products into late-stage clinical trials. There are still many scientific challenges ahead and ensuring that both of these technologies are developed in a timely fashion will require even greater global collaboration and coordination. The investment of significantly more resources will also be required, and should be built into a balanced portfolio approach to AIDS that incorporates both increased access to currently available interventions and services and greater investment in new interventions.

As promising as the commitments foreseen for 2006 appear, there are indications that HIV prevention research may not continue to experience the increases observed over the past six years. Firstly, appropriations to the National Institutes of Health – which accounts for 67% of HIV vaccine and 39% of microbicide research funding – have leveled off in the last fiscal year.[13] Funding from the NIH in 2007 may decline to 2005 or earlier levels. In 2006, philanthropic funding will rise significantly with the award of $287 million in 16 five-year grants by the Bill & Melinda Gates Foundation to support collaborative HIV vaccine research. And while the additional resources committed by the Foundation are a critical part of the global effort, philanthropic funding is unlikely to supplant the public sector's funding of this important research, to fully engage industry or to provide the long term sustained support the field needs to develop and deliver these new prevention tools.

Nevertheless, there is some cause for optimism as continued increases are observed in investments from some European countries and from developing countries such as Brazil, China, India, South Africa and Thailand. Moreover, greater collaboration in both fields, through the Global HIV Vaccine Enterprise, the Center for HIV Vaccine Immunology (CHAVI), the Neutralizing Antibody Consortium, the Live Attenuated

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[9] UNAIDS *Report on the Global AIDS Epidemic* – A UNAIDS 10th anniversary special edition. (2006).

[10] *The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise*, Public Library of Science 2:2 (February 2005)

[11] PF Harrison, TL Lamphear (2005). *Microbicides.* In *The AIDS Pandemic: Impact on Science and Society*. KH Mayer, HF Pizer, eds. Elsevier Academic Press. San Diego.

[12] C Watts, A Foss, P Vickerman, L Kumaranayake (2004). *Microbicide Awareness, Investment and Demand – Advocacy and Networking to Accelerate Microbicide Development and Availability: Emerging Issues from Epidemiological and Economic Analysis*" London School of Hygiene and Tropical Medicine, Health Policy Unit, Department of Public Health and Policy. London.

[13] James T. Brett. *Setbacks for medical research*. The Boston Globe. July 5, 2006. Although a budget increase is projected for NIH funding for HIV vaccines in 2006, this is the result of the re-allocation of previously allocated funds rather than an influx of new resources.

Consortium, the Europrise Network of Excellence for Vaccines and Microbicides and the working groups under the Microbicide Development Strategy (MDS) Initiative, suggests that by reducing duplication and combining efforts we may be able to optimize investments in research and development. The Europrise Network, established in 2006 with funding from the European Commission, is particularly exciting as it intentionally links together HIV vaccine and microbicide investigators.

Given the many uncertainties in developing new HIV prevention technologies, it is impossible to say exactly how much money ultimately will be required. However, analyses estimating resources needed to accelerate the development of these technologies suggest that increased financial and political commitments are needed, in addition to greater collaboration and commitment to efficiency in resource allocation. The Global HIV Vaccine Enterprise estimates that US$1.1-US$1.2 billion is needed annually to speed the search for a safe, effective HIV vaccine. An analysis supported by the IPM and the AMD suggests that annual funding for microbicide R&D needs to double yet again to US$280 million a year over the next five years. These funds are needed to ensure that key developmental tasks are carried out, such as accelerating basic, applied and clinical science; moving new and existing candidate products into clinical trials; preparing sites and expanding trial capacity in host countries; implementing large-scale clinical trials necessary for regulatory approvals; manufacturing both pilot and bulk lots of product; and undertaking policy and advocacy activities directed at accelerating HIV vaccine and microbicide development and use.

The Working Group reviewed a great deal of information on R&D funding flows committed between 2000 and 2006. The Working Group set as its goal to provide the most complete picture currently available of resources invested in the research and development of preventive HIV vaccines and microbicides. It is, however, important to recognize that in any estimation exercise limitations do exist. The data presented in this paper were generated primarily through direct contact with funding agencies and intermediary organizations. Each organization was asked to provide information on the funds it disbursed over the last five years and to provide details of the specific projects funded. This approach, while time-consuming, provides the detail necessary for ensuring data comparability across funders and over time. Nevertheless there are gaps, reflecting both missing and incomplete information, and we plan to improve the comprehensiveness of the data in the future years.

Information on investment levels, however, reveals only part of the resource flow picture; it is also important to understand what portion of resources committed are spent each year and how. Additional effort is needed to gather detailed information on the breakdown of expenditure and investments by stage of product development, including subdividing some of these categories. For example, the category pre-clinical research subsumes a wide range of activities, from early discovery through translational work. Gathering these detailed data is no small undertaking and, in the case of some funders, may require the individual audit of numerous grants. Still, collection of this type of information, combined with estimates of funding needs and absorptive capacity, is critical to identifying areas where additional resources and effort could be focused to shorten the development timeline or increase the likelihood of success.

The quality of commercial sector data in future estimates would benefit from a stronger collaboration with industry to find creative solutions to track funding from that sector's own resources; funding they receive from public, philanthropic and intermediary agencies; and the flow of non-financial goods between the different agencies (e.g., transfer of intellectual property rights). This sort of information is essential if these figures are to be used for assessing the impact of public policies designed to offer incentives for private sector investment.

Future resource tracking efforts would also benefit from a concerted systemic effort toward collating detailed information on the breakdown of R&D funding allocations by stage of product development. Collection of this type of information, combined with estimates of funding needs and absorptive capacity, should help identify areas where more resources and effort need to be focused.

APPENDIX 1: *Methods of Estimation*

Data collection by the Working Group involved accessing both public information and collecting information through direct appeals to funding agencies (see Box A1). The Working Group: 1) identified key funding agencies; 2) collected publicly available information; 3) contacted the funding agencies identified and 4) reviewed, checked and analyzed the information collated. A list of the organizations contacted as part of data collection for this report is included in Appendix 2.

ESTIMATING INVESTMENTS

Investment figures were based on estimates of the level of funds disbursed each year and generated from the perspective of the funder. In other words, funds were allocated to the year in which they were disbursed by the donor irrespective of whether the funds were expended by the recipient in that year or in future years.

In developing these estimates, we distinguished between primary funders and intermediary organizations. Intermediary organizations are those that receive resources from multiple funders and use these resources to fund their own work as well as others. For example, CONRAD, IPM, the Microbicides Development Programme (MDP) and the Population Council were classified as intermediary organizations. In order to avoid double counting, intermediary organizations were classified as recipients rather than funders. All identified primary funders of microbicide R&D were allocated to one of three categories: public, philanthropic or commercial sector funders (see Table A1).

Table A1. Public, Philanthropic and Commercial Sector Primary Funders

Public sector	• National governments (including government research bodies, international development assistance agencies and other government funding agencies) • European Commission • Multilateral agencies
Philanthropic sector	• Private, not-for-profit organizations (e.g., foundations, trusts and non- governmental organizations) • Charities • Corporate donations • Individual gifts and bequests
Commercial sector	• Pharmaceutical companies • Biotechnology companies

A broad definition of R&D was used and data were collated on: product development efforts; support for clinical trial preparations; community education; and advocacy and policy efforts directed at accelerating HIV vaccine and microbicide development and future use. We did not, however, include research that may have benefits or links (e.g., platform technologies) but that was not directed primarily at these technologies.

A four-step process was followed to estimate annual investment levels for both microbicide and preventive HIV vaccine R&D (see Box A1). All primary funders were asked to provide data on annual disbursements, as this gives a more accurate picture of annual investments than commitments or pledges made.[14]

[14] The Organization for Economic Cooperation and Development (OECD) makes a clear distinction between disbursements and commitments. Disbursements reflect the amount actually spent by a donor and record the actual release or transfer to a recipient of

However, not all organizations were able to provide disbursement data, and for these organizations commitment data were used instead.

It should also be noted that many public sector and philanthropic agencies do not specifically track funding for HIV vaccine and microbicide R&D. In these situations, the information provided was generally from a key word search conducted by the agency of projects funded or was based on the knowledge of the informant contacted. The former can lead to the identification of a number of projects where only a portion of each grant is directly related to HIV vaccine and microbicides development. In these cases, we reviewed the description of the project and estimated the percentage of the overall grant directly related to HIV vaccine and microbicides. In addition, not all organizations were able to provide annual breakdowns of their grants. For these organizations, we allocated the total funds disbursed or committed equally over the duration of the grant.

In the case of the commercial sector, we contacted the main companies engaged in HIV vaccine and microbicide R&D as of mid-2005 and asked them to provide us with information on levels of their own investments, excluding direct or indirect funding that they might receive from the public sector and from intermediary agencies. Many of the companies contacted did not specifically track R&D funding for these technologies or were otherwise reluctant to share sensitive information on funding, citing concerns about proprietary business issues. As a result, industry estimates are presented as a range for selected years,based on data collected and discussions with experts in the field.

All figures in the report are reported in current US dollars and have not been adjusted for inflation. Funding information provided in other currencies was converted into US dollars using the appropriate International Monetary Fund (IMF) annual average exchange rate, except for those funds where we had access to the actual rate received.

There is no agreed method for breaking down funding allocations by type of activity or stage of product development. For this exercise, we have allocated funding into five categories. The first four categories are based on the US National Institutes of Health definitions.[15], (See Appendix 3 for examples of the types of activities included in each category). To prepare these allocations we primarily relied upon investment data, except in the cases where intermediary organizations were able to provide expenditure data. Grants to intermediary organizations were excluded from investment figures of their funders to avoid double counting. The allocation of funding across these categories was based on the information provided by the intermediaries and/or funders. When this information was not available, we reviewed the descriptions of the projects funded and, based on the description of each project, allocated the funds across the five expenditure categories.

financial resources, goods or services valued at the cost to the donor. A commitment, on the other hand, is a firm obligation expressed in writing and backed by the necessary funds to provide a particular level of support.

[15] National Institutes of Health (2000). National Institutes of Health Fiscal Year 2002 Plan for HIV-Related Research. Washington, DC. The NIH categories are: Basic, Pre-Clinical, Pediatric, Clinical Trials and Vaccine Preparedness. For the purposes of our estimates we have accepted the NIH breakdown of their expenditures by category. Funding classified as “pediatric” by NIH was allocated equally between pre-clinical research and clinical trials. Auditing and reclassifying the NIH data would have been a major exercise and was beyond the scope of this project

Box A1: The process followed to estimate annual investments for both HIV vaccines and microbicides

Step 1: Identifying key funding agencies

A list of all organizations involved in funding preventive HIV vaccine and microbicide R&D was drawn up based on funders identified in previous resource tracking efforts and supplemented by discussions with key individuals working in the HIV vaccine and microbicide fields. As new funders were identified, they were added to the list.

Step 2: Collecting publicly available information

For each of the funders identified, the publicly available information was reviewed for data on annual investment levels. Information sources consulted included: government reports, annual reports, US Securities and Exchange Commission (SEC) filings, published studies and articles, 'grey' literature, scientific presentations and website postings.

Step 3: Contacting the funding agencies identified

Public sector:

Letters were written to all of the public sector funders identified asking them for information on funds disbursed since 2000 and future commitments in their local currency. Information requested included:

- Description of the projects or programs funded;
- Duration of grants/ contracts/ awards;
- Total funding committed;
- Funding disbursement by year since 2000; and
- Projected disbursement or future funding commitments by year.

Agencies contacted included national research funding agencies (e.g., Agence Nationale de Recherches sur le Sida (ANRS) in France and the Canadian Institutes of Health Research (CIHR)), overseas development agencies (e.g., the Department for International Development (DFID) in the UK and the Agency for International Development (USAID) in the US)and multilateral organizations (e.g., UNAIDS, the World Bank and the World Health Organization). Each national agency was also asked to suggest other national agencies that should be contacted.

Philanthropic sector:

Letters were written to all of the identified philanthropic funders known to have awarded more than US$100,000 to either technology between 2000 and 2005. The letters were similar to those sent to public sector funders and asked for the same information. For smaller funders, disbursement estimates were based on information collated from intermediaries and internet searches and, where no information was readily available, the organizations were contacted directly.

In the case of corporate donations, data were only collected on cash donations. No attempt was made to include in-kind support such as goods, services, and donated staff time owing to the difficulties in valuing these contributions.

Commercial sector:

Each of the main companies identified was contacted in writing, in person or by phone and asked to provide information on its own internal funding (i.e., they were asked not to include funds received from external sources such as research agencies or intermediary organizations).

Step 4: Reviewing, checking and analyzing the information collated

The financial information received from each funder was reviewed against the project inclusion criteria and cross-checked. Any issues or questions were followed up with the funder. In the case of US agencies that track HIV vaccine or microbicide funding explicitly, we have made use of their self-reported figures rather than examining each grant individually.

For those organizations that did not respond to information requests even after repeated follow-ups, annual disbursements were estimated based on publicly available information, supplemented by discussions with experts working in the field.

The estimates for each sector were then reviewed for consistency to ensure that similar definitions were used and to eliminate double counting.

DATA LIMITATIONS

Every effort was made to obtain a comprehensive set of data that was comparable across organizations and countries. The data presented in this report, however, are subject to a number of caveats.

Missing or incomplete information:
Requests for information were directed to all public, philanthropic and commercial organizations that were identified as providing funding for HIV vaccine or microbicide R&D. However,

- We may have missed key funding organizations or developers.
- Public sector data collection efforts focused on national and international funding; information on sub-national or provincial funding was not included in the estimates.
- Not all organizations provided financial information. For those that did not, annual investment and funding estimates were extrapolated based on information available in the public domain and expert opinions.
- Many private sector companies do not specifically track spending on these technologies and hence do not have the relevant data readily available. In addition, many companies were reluctant to share financial information due to proprietary business concerns.

Differences in definitions:
In our data analysis we tried to make the data collated consistent across funders and over time so that accurate trends and comparisons could be drawn. However,

- Not all funders reported disbursement data on a calendar year, but instead reported funding flows based on their own fiscal year and contracting mechanisms.
- The funding allocation estimates are based on a combination of expenditure data from intermediary organizations and investments by non-intermediary organizations.
- Most funders and intermediary organization do not break down their expenditures and investments by type of activity or stage of product development and, if they do so, use their own definitions.
- Within a particular organization, changes may have occurred in how they classify funds over the six-year period studied.

Sources of information and double counting:
Every attempt was made to reduce the potential for double counting and to distinguish between funders and recipients of funding. However,

- All financial information was “self reported” by organizations and not independently verified.
- A number of the pharmaceutical and biotechnology companies active in HIV vaccine and microbicide R&D receive either direct or indirect support from the public sector (e.g., the NIH, ANRS and the European Community (EC)) and intermediary organizations (e.g., IAVI and SAAVI) to finance their work. The data presented here reflect, to the best of our ability, only the direct investments by the companies of their own resources.

APPENDIX 2: *Funding Institutions and Developers Included in the HIV Vaccine and Microbicide Estimates*

Public sector – Countries

- Australia
- Belgium
- Brazil
- Canada
- China
- Cuba
- Denmark
- European Commission
- Finland
- France
- Germany
- India
- Ireland
- Italy
- Japan
- The Netherlands
- Norway
- Russia
- South Africa
- Sweden
- Thailand
- United Kingdom
- United States

Public sector - Multilaterals

- UNAIDS
- United Nations Population Fund (UNFPA)
- The World Bank
- World Health Organization

Philanthropic sector – Foundations, Trusts and NGOs

- American Foundation for AIDS Research
- Bristol Myers Squibb Foundation
- Broadway Cares/Equity Fights AIDS
- Crusaid
- Deutsche AIDS Stiftung
- Ford Foundation
- Bill & Melinda Gates Foundation
- Elizabeth Glaser Pediatric AIDS Foundation
- Gill Foundation
- John & Marcia Goldman Foundation
- Linda & John Gruber Foundation
- Phoebe W. Haas Charitable Trust B
- Henry M. Jackson Foundation
- John M. Lloyd Foundation
- John D. and Catherine T. MacArthur Foundation
- James S. McDonnell Foundation
- Mercury Phoenix Trust
- Moriah Fund
- NY Community Trust
- Overbrook Foundation
- Parthenon Trust
- James B. Pendleton Trust
- Perls Foundation
- Rockefeller Foundation
- San Francisco AIDS Foundation
- Starr Foundation
- Stichting Aids Fonds
- Tides Foundation/John Lee Fund
- Turner Foundation
- Until There's A Cure Foundation
- Vanderbilt Family Foundation
- Wellcome Trust

Philanthropic sector - Corporate donors

- Becton, Dickinson and Company
- Eskom International Inc.
- Impala Platinum Holdings Limited
- TransNet Corporation

Commercial sector - Pharmaceutical companies

- GlaxoSmithKline plc
- Merck & Co. Inc.
- Sanofi Pasteur (formerly Aventis Pasteur)
- Wyeth-Ayerst Lederle Inc.

Commercial sector - Biotechnology companies

- Advanced BioScience Laboratories
- AlphaVax Human Vaccines Inc.
- AVANT Immunotherapeutics, Inc.
- Bavarian Nordic
- Berna Biotech Ag
- Biofem, Inc.
- Bioption AB
- Bioqual Inc.
- Cellegy/Biosyn, Inc.
- Chiron Corporation
- Cobra Pharmaceuticals Plc
- Crucell N.V.
- Dow Pharmaceutical Sciences
- Epimmune Inc.
- EpiVax, Inc.
- FIT Biotech Oyj Plc.
- GenVec, Inc.
- Gilead Sciences
- GlobeImmune, Inc.
- GeoVax, Inc.
- Idenix Pharmaceuticals
- Impfstoffwerk Dessau Tornau GmbH
- ImQuest BioSciences
- Indevus Pharmaceuticals, Inc.
- Mapp Biopharmaceutical Inc.
- MaxyGen, Inc.
- Novartis International AG
- Novaflux Technologies
- Osel, Inc.
- PAREXEL International Corporation
- Polydex Pharmaceuticals Ltd.
- Progenics Pharmaceuticals, Inc.
- ReProtect LLC
- Starpharma Ltd.
- Targeted Genetics Corporation
- Therion Biologics Corporation
- Tibotec Pharmaceuticals Ltd.
- VaxGen, Inc.
- Vical Inc

Intermediary agencies

- Aaron Diamond AIDS Research Center
- African AIDS Vaccine Programme
- Alliance for Microbicide Development
- Canadian Network for Vaccines and Immunotherapeutics
- CONRAD
- Family Health International
- Global Campaign for Microbicides
- Harvard AIDS Institute
- International AIDS Vaccine Initiative
- International Partnership for Microbicides
- Microbicides Development Programme
- Population Council
- PATH (Program fro Appropriate Technology in Health)
- South African AIDS Vaccine Initiative

APPENDIX 3: *Descriptions of the Five Expenditure Categories*

BASIC RESEARCH	• Defining mechanisms of systemic/mucosal immunity • Seeking correlates of immune protection for HIV-infected/highly exposed but seronegative • Developing *in vitro* tools to analyze vaccine responses • Developing *in vitro/in vivo* tools to study systemic/mucosal mechanisms • Defining entry mechanisms of HIV and other STIs • Determining timing and processes in establishment of infection via sexual transmission of HIV and other STI pathogens • Identifying approaches/timing/new target(s) to successfully block establishment of infection • Defining the interaction of relevant pathogens with target cells/mucosal surfaces • Studies of intercourse physiology and normal cervico-vaginal and rectal ecology • Elucidating mechanism by which inflammation and/or concomitant infections influence HIV transmission • Investigations of effects of endogenous and exogenous hormonal states on susceptibility to infection
PRE-CLINICAL RESEARCH	• Supporting novel vaccine and microbicide design and testing for safety/ immunogenicity • Fostering collaboration between academia, industry, government agencies, and NGOs • Optimizing vaccine characteristics and microbicide formulation for broad international use (cheap, easy to produce/administer, stable) • Improving or modulating immune responses (e.g. development of improved adjuvants and delivery methods, cytokines, chemokines, and other strategies) • Supporting testing in animal models and looking at *in vitro* correlates of *in vivo* protective response and impact on vaccine-induced immunity from: formulation, site of delivery, regimen, nature/timing/phenotype/route of infectious virus challenge, genetic factors, age, viral mutation/variation, mucosal/genital/hormonal co-factors • Discovery, development, and preclinical evaluation of HIV vaccine and microbicide candidates for, or in combination • Developing reagents and standardized methods to assess vaccine-induced immune response in animals and humans • Conducting research on safety and regulatory considerations of HIV vaccines and microbicides in development • Developing strategies for testing candidate microbicides in parallel and/or head-to-head • Addressing lack of well-established correlation between *in vitro* testing, animal models, and clinical testing
CLINICAL TRIALS	• Supporting Phase I and II trials that study immunogenicity and address strain selection to provide data for decisions on proceeding to Phase III • Developing strategies for retention and follow-up of participants to meet pre-defined endpoints • Supporting large-scale efficacy trials of HIV vaccines and microbicides meeting Phase II criteria that are ethical and minimize social and economic harm to volunteers • Conducting behavioral research during clinical trials including but not limited to risk assessment, factors affecting adherence to protocol, and product acceptability • Coordinating trial research with pre-clinical, therapeutics, and other relevant research, including studies designed to permit validation of preclinical assays
COHORT & SITE DEVELOPMENT	• Identifying potential sites and populations for trials (e.g.: assess seroincidence in the population and viral subtypes as well as genetic and other factors that may affect trial results) • Developing and maintaining personnel (including social and behavioral scientists) and laboratory infrastructure in potential trial sites to conduct trials • Developing regional or central laboratory capacity that could serve a group of trial sites and also provide standardized GLP-quality storage of specimens for comparative analyses during and after trials. • Working with host governments, regulatory bodies, local agencies, vaccine manufacturers, multilaterals to plan, prepare and conduct trials • Developing relationships with communities and community organizations in potential sites • Exploring innovative trial designs to minimize time and costs without compromising participant safety (e.g., use of serodiscordant couples; use of secondary endpoints)
PROCESS DEVELOPMENT & MANUFACTURING	• Supporting bioprocess development • Designing, constructing and validating large-scale manufacturing facilities
ADVOCACY & POLICY DEVELOPMENT	• Developing and supporting public education efforts • Developing and supporting policy research and development directed at accelerating the development and rapid use of HIV vaccines and microbicides • Exploring alternative strategies for supporting R&D efforts and the purchase of HIV vaccines and microbicides • Supporting on-going national and international advocacy efforts • Supporting analysis of modeling to anticipate resource needs, potential demand for product, costs of product and distribution, and epidemiological impact

HIV Vaccines and Microbicides Resource Tracking Working Group

AIDS Vaccine Advocacy Coalition (AVAC) www.avac.org
Alliance for Microbicide Development (AMD) www.microbicide.org
International AIDS Vaccine Initiative (IAVI) www.iavi.org
Joint United Nations Programme on HIV/AIDS (UNAIDS) www.unaids.org

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

For more information on HIV vaccines, please contact the AIDS Vaccine Advocacy Coalition (avac@avac.org) or the International AIDS Vaccine Initiative (publicpolicy@iavi.org).

For more information on microbicides, please contact the Alliance for Microbicide Development (info@microbicide.org).

For more information on UNAIDS resource tracking activities, please contact the UNAIDS Resource Tracking Unit (rtdata@unaids.org).