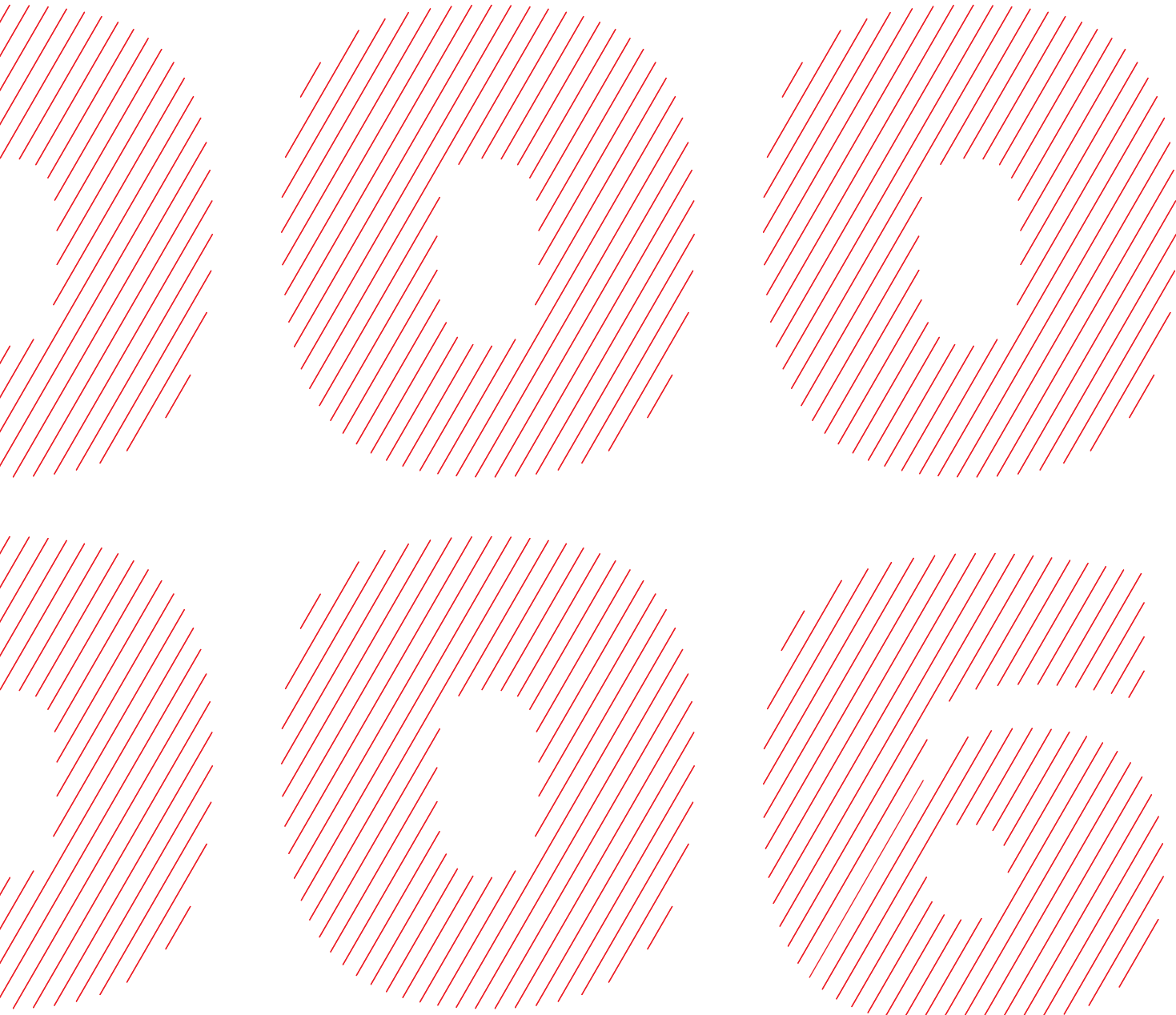


BUILDING A COMPREHENSIVE RESPONSE

**FUNDING FOR HIV VACCINES, MICROBICIDES AND
OTHER NEW PREVENTION OPTIONS: 2000 - 2006**



**HIV VACCINES AND MICROBICIDES
RESOURCE TRACKING WORKING GROUP
WWW.HIVRESOURCETRACKING.ORG**



ALLIANCE FOR
MICROBICIDE
DEVELOPMENT



BUILDING A COMPREHENSIVE RESPONSE:

Funding for HIV Vaccine, Microbicide and
New Prevention Tools Research and Development
2000 to 2006

November 2007

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 (UN-
AIDS)

This report was prepared by the HIV Vaccines and
Microbicides Resource Tracking Working Group by
Betsy Finley (AMD); Kevin Fisher (AVAC), Natanya
Gayle (AVAC); Polly Harrison (AMD), Jose-Antonio
Izazola (UNAIDS); Shilpa Vuthoori (IAVI) and Mitchell
Warren (AVAC)

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EXECUTIVE SUMMARY

According to UNAIDS global estimates, about 40 million people were living with HIV and another 4.3 million became HIV positive in the year 2006¹. These numbers strongly suggest that existing HIV prevention strategies alone are not enough to curb the pandemic and that new interventions are urgently needed. A recent report by the Global HIV Prevention Working Group² calls for a major scale-up of global HIV prevention programs, citing new data which indicate that expanded access to existing prevention methods could avert approximately half of the 60 million HIV infections expected to occur by 2015. The report provides additional support for the view that existing prevention efforts have not kept pace with the epidemic and need to be supplemented by new approaches.

As HIV affects the lives of millions more people each year, public, philanthropic and commercial sectors have recognized the pressing need to develop and implement a comprehensive, effective, sustainable approach toward near-universal access to appropriate HIV prevention, treatment and care. Despite the bio-medical research challenges of creating new HIV prevention tools, the need for additional strategies, such as vaccines, microbicides or adult male circumcision, becomes critical as we continue to fall short of providing the necessary treatment to people living with HIV and AIDS. Scaling up existing strategies and developing new prevention technologies to complement them can provide a range of options that may be used alone or in combination, and may appeal more broadly to various cultural and socio-economic backgrounds.

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. Next year, civil society representatives will meet again for the 2008 UNGASS meeting to assess global progress in the development of new prevention tools.

The HIV Vaccines and Microbicides Resource Tracking Working Group developed a systematic approach to data collection and analysis to generate estimates of research and development (R&D) investment that can be compared across years, technologies and funders³. Over the seven-year period from 2000 to 2006, public and philanthropic funding for preventive HIV vaccine and microbicide R&D almost tripled.

– For HIV vaccines, non-commercial funding increased 161% from US\$327 million to US\$854 million.

– For microbicides, non-commercial funding grew 250% from US\$65 million to US\$217 million.

Public-sector funders continue to provide the overwhelming majority of the funds allocated to R&D for preventive HIV vaccines and microbicides, with the United States, Canada, the European Commission and several European countries leading the way. Countries outside of North America and Europe such as Brazil, India, Japan, South Africa and Thailand provide additional support. The public-sector, particularly in developing countries where trials are planned or are underway, also contributes considerable non-financial support through clinical and laboratory staff and facilities.

This year, the HIV Vaccine and Microbicides Resource Tracking Working Group (the Working Group)⁴

1

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

2

Global HIV Prevention Working Group. Bringing HIV Prevention to Scale: An Urgent Global Priority., (June 2007). <http://www.kff.org/hivaids/hiv061004pkg.cfm>

3

These data are used to monitor the implementation of the UNGASS Global Commitment and Action Indicator 2 – the amount of public funds available for R&D for HIV vaccines and microbicides.

4

The Working Group is comprised of 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).

has expanded its resource tracking to include investments in four additional experimental prevention approaches: adult male circumcision (AMC), herpes simplex virus type 2 (HSV-2) suppression, cervical barriers and pre-exposure prophylaxis using antiretroviral drugs (PrEP). In December of 2006, circumcision of men engaging in vaginal sex was validated as a new prevention approach. This year also saw results from an unsuccessful diaphragm trial testing the utility of cervical barriers as a means of HIV control. These tools are needed to provide a broad and comprehensive range of options in addition to vaccines and microbicides.

While the level of funding in 2006 is significant, there is a critical need to sustain- and even increase- investment to optimally accelerate the development of and ensure eventual access to these technologies. Financing needs for the research and development of HIV vaccines, microbicides, and other new prevention options- whether to explore new R&D approaches, bring novel candidates into the pipeline, or scale up clinical trial capacity- will remain substantial in the coming years.

HIV VACCINE R&D

In 2006, total global investment in preventive HIV vaccine R&D was approximately US\$933 million, a 23% increase over 2005 funding levels. This growth is largely due to new research initiatives funded through the US National Institutes of Health (NIH), the European Commission (EC) and the Bill & Melinda Gates Foundation (Gates Foundation).

In 2006, public-sector funders provided 83% (US\$776 million) of the funds for preventive HIV vaccine R&D. The philanthropic sector provided 8% (US\$78 million) and the commercial sector accounted for the remaining 8% (US\$79 million).

During the last seven years, European funders increased their commitment to preventive HIV vaccine R&D nearly four-fold, from US\$23 million to US\$82 million. This funding accounts for almost 10% of the public-sector total for 2006, up from 7% in 2000. In 2006, R&D activities outside of the US and

Europe continued to grow. Investments from other countries including Brazil, Canada, India, South Africa and Thailand totaled almost US\$38 million. A breakdown of global funding expenditures by activity or stage of product development was estimated from a subset of investments in preventive HIV vaccine R&D, totaling US\$826 million⁵ The two product development categories of Basic Research and Pre-clinical Research together accounted for approximately 69% of the funds spent. In comparison, support for Clinical Trials accounted for 23%, Cohort and Site Development for 7%, and Advocacy and Policy Development for 2%. The most significant change from 2005 was an increased focus on pre-clinical research, which grew from 38% to 47% of expenditures in 2006.

MICROBICIDE R&D

In 2006, total global investment in microbicide R&D was approximately US\$222 million, a 35% increase over 2005 funding levels. This growth was due to increased commitments from the NIH, the US Agency for International Development (USAID) and European funders.

In 2006, the public-sector provided almost 86% (US\$191.2 million) of the funds allocated to microbicide R&D. The philanthropic sector provided 12% (US\$26.2 million) and the commercial sector accounted for 2% (US\$4.5 million).

During the last seven years, European funders increased their commitment to microbicide R&D from US\$0.7 million to almost US\$56.3 million. In 2006, support for R&D activities outside of the US and Europe decreased to about US\$4 million from \$10 million in 2005, but still significantly exceeded investment in each year prior to 2005.

A breakdown of global funding allocations by type of activity or stage of product development was estimated from a subset of investments in microbicide R&D totaling almost US\$183 million in 2006⁶ In 2006, the Working Group began to calculate microbicide expenditures based primarily on categories developed by the NIH to describe microbicide-specific R&D⁷ These categories are Basic Mechanisms of Mucosal Transmission (Basic Mechanisms);

Discovery, Development, and Pre-clinical Testing (Pre-clinical Research); Formulations and Modes of Delivery (Formulation); Clinical Trials; Microbicide Behavioral and Social Science Research (Social Science); Microbicide Research Infrastructure (Infrastructure); and Advocacy and Policy Development (Advocacy) ⁸

Using these categories, 10% of funding was devoted to Basic Mechanisms; 22% to Pre-clinical Research; 7% to Formulation; 42% to Clinical Trials; 6% to Social Science; 6% to Infrastructure; and 6% to Advocacy.

philanthropic sector, through grants from the Gates Foundation, provided 63% (US\$116 million). The Working Group found no commercial involvement in R&D for these other new prevention options apart from the donation by Gilead Sciences Inc. of anti-retroviral drugs for use in the PrEP trials.

NEW PREVENTION TOOLS R&D

Between 2000 and 2006, five public sector funders and two foundations provided US\$183.6 million for research and development activities in support of four other HIV prevention interventions: adult male circumcision, herpes HSV-2 suppression, cervical barriers and PrEP.

Resource tracking of research and development in these areas is significantly different from that for vaccines and microbicides. The spectrum of funders for these trials is smaller, and the research and development activities in support of these potential prevention tools are most typically clinical trials.

In 2006, the public-sector provided 37% (US\$68 million) of the funds allocated to new prevention technology R&D for adult male circumcision, HSV-2 suppression, cervical barriers and PrEP. The

5

A subset of total investments was used because expenditure breakdowns could not be determined or reasonably estimated for approximately \$107 million in HIV vaccine investments.

6

A subset of total investments was used because expenditure breakdowns could not be determined or reasonably estimated for approximately \$37 million in microbicide investments.

7

The Working Group has made the decision to utilize these definitions to categorize R&D because (1) NIH funds constitute a large percentage of resources for microbicide R&D; (2) the definitions more closely accord with the Working Group's understanding of microbicide R&D; and 3) the definitions are generally consistent with the manner in which the Working Group classifies HIV vaccine R&D resources.

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To the NIH categories for microbicide research, the Working Group also added Advocacy and Policy Development.

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1.0 INTRODUCTION

In June of 2007, the annual G8 Summit was held in Heiligendamm, Germany. The G8 nations renewed commitments to provide financing to address HIV treatment and prevention. Despite significant increases in funding for HIV/AIDS, latest data from UNAIDS and the Kaiser Foundation show that these new resources are likely to fall short of the estimated need. The 11 million people projected to need antiretroviral treatment by the year 2010 may be underestimated by up to 50%, based on a better understanding of clinical progression to AIDS and new data that show that starting treatment earlier provides a more effective response⁹

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 care¹⁰ A comprehensive plan to combat the epidemic requires investment in developing and utilizing a wide range of more effective prevention methods to complement the current expansion of access to existing HIV treatment and prevention options. Preventive HIV vaccines and microbicides are two technologies currently under development that would provide people – and in the case of microbicides, particularly women, who are increasingly affected by the epidemic – with new options for protecting themselves from HIV.

This year witnessed the emergence of a new prevention tool – adult male circumcision. In December of 2006, new evidence from clinical trials confirmed male circumcision as the first new biomedical HIV

prevention strategy since the female condom was approved for use 13 years ago¹¹ Male circumcision may be joined by HSV-2 suppression and PrEP as validated prevention technologies, all of which will be tested for effectiveness. These investigative prevention tools have been added to our resource tracking efforts. We have also included information on investment in cervical barriers as prevention options, although they were recently determined in clinical trials not to be effective in preventing HIV infection.

Clinical trials to determine the efficacy of experimental HIV vaccine and microbicide candidates are underway around the world. In 2006, clinical trials of HIV vaccines were being conducted in Thailand by Sanofi Pasteur and in the Americas by Merck & Co.¹² Additionally, there are currently three efficacy or proof-of-concept trials of microbicide products and several closed or completed effectiveness trials under analysis¹³ There are still many scientific and logistical challenges ahead, and ensuring that both of these much needed tools are developed as quickly, safely and ethically as possible will require even greater global collaboration and coordination. Moreover, these tools must be developed in tandem with other prevention options.

The sustained effort and increased innovation needed to achieve these developments will require significantly greater investment, which 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

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Kaiser Family Foundation. Bringing HIV Prevention to Scale: An Urgent Global Priority, Global HIV Prevention Working Group (June 2007). <http://www.kff.org/hiv/aids/hiv061004pkg.cfm>.

10

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>.

11

http://www3.niaid.nih.gov/news/newsreleases/2006/AMC12_06press.htm

12

The Merck trial ended in 2007 as did a South African proof-of-concept trial of the Merck candidate

13

Alliance for Microbicide Development Mapping the Microbicide Effort: A Companion to the Microbicide Development Strategy. (March 2007). <http://www.microbicide.org/microbicideinfo/reference/MappingFinal.pdf>

10 interventions. Accelerating the development and widespread use of preventive HIV vaccines, microbicides and other prevention tools will require the active engagement of national 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 vaccines and microbicides are licensed and widely used. Although male circumcision was found to be effective in preventing HIV infection in the trial results announced in December of 2006, a plan for appropriate global access to this new prevention tool has yet to be developed. This point highlights the critical work necessary to support introduction and use of new HIV prevention strategies. However, the time to the development, licensure and widespread use of

these prevention technologies could be significantly reduced with increased and more efficient and strategic 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 the development and use of new preventive technologies, including HIV vaccines and microbicides¹⁴

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HIV Vaccine Research and Development: Modeling the Path to Speedier Success. (2006)
IAVI Policy Research Working Paper #10.

RESOURCE TRACKING WORKING GROUP - A SHORT HISTORY

In 2003, UNAIDS was faced with the challenge of developing estimates of HIV vaccine and microbicide research and development investment. These estimates were to help 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. At the same time, the International AIDS Vaccine Initiative (IAVI) and the Alliance for Microbicide Development (AMD) were independently developing estimates for HIV vaccine and microbicide research and development. In the interest of coordinating this research, IAVI and AMD were invited to join with UNAIDS in compiling this information, and shortly thereafter, were joined by the AIDS Vaccine Advocacy Coalition (AVAC).

In 2004, AVAC, AMD, 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 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 spent. This research continues as a collaborative effort to advance the following goals: (1) to monitor implementation of the Global Commitment and Action Indicators adopted by United Nations General Assembly Special Session (UNGASS) on HIV/AIDS; (2) to reduce donor fatigue in governments and foundations due to multiple information requests; and (3) to ensure that data collection is equivalent across technologies¹⁵ The Working Group is financially supported by contributions from the four participating members and the International Partnership for Microbicides

(IPM). The Working Group is not itself an advocacy group, although all of its members are advocates for HIV prevention research and development.

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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 Political Declaration adopted at the UNGASS meeting called again 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."

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2.0

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 2004. The same methods were employed to generate the estimates of funding for R&D presented here (see Appendix 1 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, microbicide and other new prevention technology 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 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.¹⁶ 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 subsequent 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, Family Health International, the International Partnership for Microbicides (IPM),

IN-KIND CONTRIBUTIONS FROM COMMERCIAL SOURCES

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. Assigning a monetary value to such contributions is at best challenging; thus, they have not been included in financial estimates in this report. However, this should not underplay their potential importance to driving research forward. A number of companies have been active, particularly in recent years, in providing ARV compounds for development as potential microbicides, in doing so contributing significantly to the next-generation candidates.

Industry Contributions to Microbicide Development: The Case of the International Partnership for Microbicides (IPM)

Between 2004 and 2006, IPM obtained the non-exclusive royalty-free licenses to develop the following antiviral compounds as microbicides: Dapivirine (TMC120), a non-nucleoside reverse transcriptase inhibitor (NNRTI) from Tibotec Therapeutics; Merck L 167, a CCR5 antagonist (and two related back-ups) from Merck & Co.; BMS-793, an entry inhibitor from Bristol-Myers Squibb; and Tenofovir (PMPA), a nucleoside reverse transcriptase inhibitor (NRTI) from Gilead Sciences (which license is also shared with CONRAD). In 2007, IPM also signed Material Transfer Agreements with two additional pharmaceutical companies for early evaluation of several CCR5 blockers, with the hope that full licensing agreements can be negotiated for development of these compounds.

IAVI and the South African AIDS Vaccine Initiative (SAAVI) were classified as intermediary organizations. All identified primary funders were categorized by sector 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).

There are also funding differences between public investment in the United States and in Europe due to differing policies in reimbursement of institutional expense often referred to as overhead cost. For example, in the United States, there is

negotiated level of reimbursement of overhead cost in public-sector funding that varies between 40% and 65%. In comparison, overhead cost in the European Union is sometimes not covered in grant awards, or covered at a lower level or covered at a set rate of 20% for institutions who are unable to calculate actual cost¹⁷

There is no standardized method for breaking down funding allocations by type of activity or stage of product development. For vaccines in this exercise, we have allocated resources into five categories (Table 1). The first four categories are based on NIH definitions.¹⁸ For microbicides, we have allocated resources into seven categories based upon the NIH

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Organizations were asked to provide data based on the calendar year if possible or, 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 would be treated as 2005 and the fiscal year November 1, 2005 to October 31, 2006 would be treated as 2006.

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A detailed discussion on overhead cost can be found in the Working Group's 2006 report. Adding it All Up: Funding for HIV Vaccine and Microbicide Development, August 2006. www.hivresourcetracking.org

18

National Institutes of Health (2007). National Institutes of Health Trans-NIH Plan for HIV-Related Research for Fiscal Year 2008. Washington, DC. 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.

CANADIAN HIV VACCINE INITIATIVE

In February 2007, Canada added to its significant investment in the fight against HIV/AIDS with the establishment of the Canadian HIV Vaccine Initiative (CHVI), a collaboration between Canada and the Bill & Melinda Gates Foundation. CHVI was created as Canada's contribution to the Global HIV Vaccine Enterprise as part of a global commitment to create a safe, effective, affordable and globally accessible HIV vaccine. To assist in this global effort a combined US\$139 million has been pledged by the Canadian Government (US\$111 million) and the Gates Foundation (US\$28 million). The initiative will focus on six key areas: discovery and social research, clinical trial capacity and networks, pilot-scale manufacturing capacity for clinical trials, policy and regulatory issues,

community and social dimensions and planning, and coordination and evaluation. Dr. Frank Plummer, Director of the Public Health Agency of Canada (PHAC), the agency that will house CHVI, described it as a unique collaboration among a number of Canadian health agencies working in HIV/AIDS including PHCA, the Canadian Institute of Health Research (CIHR), the Canadian International Development Agency and Health Canada. Between 2000 and 2006, Canadian agencies have contributed US\$78 million to HIV vaccine research and development. Plummer noted that CHVI would act as a national infrastructure to coordinate Canadian vaccine science. Plummer highlighted the pilot vaccine manufacturing facility that would be created under the CIHR. This facility, Plummer noted,

would not just be available for Canadian vaccine candidates. Instead, it could be used for HIV vaccine candidates developed outside Canada. The impetus for creating this facility was the Global HIV/AIDS Vaccine Enterprise, which identified the lack of manufacturing capacity as a potential "bottleneck," said Plummer. Sanofi Pasteur, a vaccine company with offices in Toronto, Canada, is currently testing its canary pox vaccine with HIV Env protein boost in Thailand and is one of the groups that will be working with CHVI as an advisor.

definitions applicable to microbicide research (Table 2). The allocation of funding across these two sets of categories was based on the information provided by the intermediaries and/or funders. Where this information was not available, the descriptions of the projects funded were reviewed and, based on the description of each project, funds were allocated across the expenditure categories. See Appendix 3 for examples of the types of activities included in each category.

Resource tracking for new prevention tools (male circumcision, HSV-2 suppression, PrEP and cervical barriers) examined research activities and clinical trials to test the effectiveness of these interventions. Research and development in this area is almost exclusively devoted to clinical trials, rather than basic research or pre-clinical development, so expenditures were not broken down into categories as they were for vaccines and microbicides.

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 developing countries 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 HIV vaccines. These foregone public-sector resources 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 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 design. This includes vaccine design, development and animal testing.

CLINICAL TRIALS

Support for Phase I, II and III trials testing the safety, immunogenicity and efficacy of suitable preventive HIV vaccine candidates or concepts in domestic and international settings (including the costs of producing candidate-product lots for clinical trials).

COHORT & SITE DEVELOPMENT

Support to develop the strategies, infrastructure and collaborations with researchers, communities, government agencies, regulatory agencies, NGOs and industry necessary to identify trial sites, build capacity, ensure adequate performance of trials and address the prevention needs of at-risk populations in trial communities.

ADVOCACY & POLICY DEVELOPMENT

Efforts directed at educating and mobilizing public and political support for preventive HIV vaccines and at addressing potential regulatory, financial, infrastructure or political barriers to their rapid development and use.

In past years, the Working Group has analyzed microbicide research and development using the categories listed in Table 1. This system permitted a comparison between vaccine and microbicide research.

TABLE 2: CATEGORIES USED TO CLASSIFY MICROBICIDE R&D FUNDING

BASIC MECHANISMS OF MUCOSAL TRANSMISSION

Elucidate basic mechanisms of HIV transmission at mucosal/epithelial surfaces that are important for microbicide research and development in diverse populations.

DISCOVERY, DEVELOPMENT, AND PRECLINICAL TESTING

Target R&D efforts at the 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 BEHAVIORAL AND SOCIAL SCIENCE RESEARCH

Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide research domestically and internationally.

MICROBICIDE RESEARCH INFRASTRUCTURE

Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide research domestically and internationally.

ADVOCACY & POLICY DEVELOPMENT

Efforts directed at educating and mobilizing public and political support for microbicides and at addressing potential regulatory, financial, infrastructure or political barriers to their rapid development and use.

In 2006, for the first time, the Office of AIDS Research (OAR) within NIH began to subdivide its investment into specific categories¹⁹, reflecting the particular research priorities of microbicide development. These priorities include understanding mucosal transmission, microbicide formulation and delivery, and the behavioral research necessary to understand microbicide use and acceptance. These categories, set forth in Table 2, were used by the Working Group to categorize expenditures in 2006. These NIH categories were supplemented by a category for Advocacy and Policy Development. Use of these microbicide-specific categories represents a change from previous years and so precludes ready comparison with microbicide expenditures prior to 2006 for this report.

THE OFFICE OF AIDS RESEARCH

The NIH Office of AIDS Research (OAR) is located within the Office of the Director of the US National Institutes of Health (NIH) and is responsible for the scientific, budgetary, legislative and policy elements of the NIH AIDS research program. The United States

Congress has provided broad authority to the OAR to plan, coordinate, evaluate and fund all NIH AIDS research. The OAR is responsible for the development of an annual comprehensive plan and budget for all NIH AIDS research, including vaccines and microbicides.

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National Institutes of Health, Office of AIDS Research. OAR Plan 2008, Prevention Research: Microbicide Vaccines Behavioral and Social Science. <http://www.oar.nih.gov/public/pubs/fy2008/Chapter2.pdf>.

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3.0 RESULTS

TABLE 3. ANNUAL INVESTMENTS IN PREVENTIVE HIV VACCINE R&D BETWEEN 2000 AND 2006 (CURRENT US\$ MILLIONS).

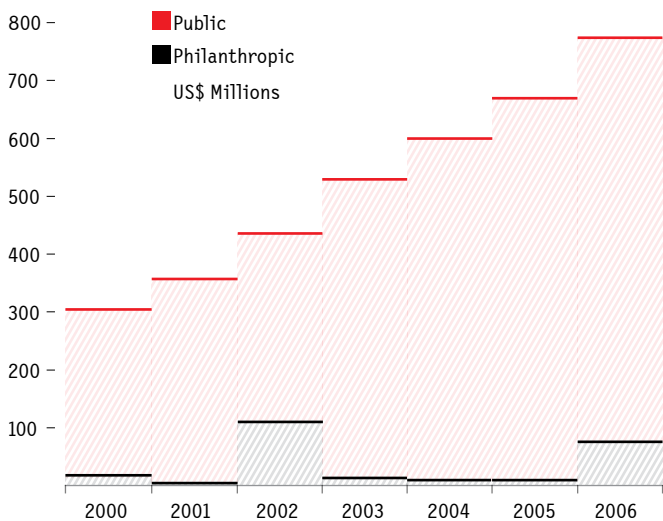
	2000	2001	2002	2003	2004	2005	2006*	
PUBLIC SECTOR								A. This figure includes funding from the European Commission
- US	272	314	376	463	516	574	654	
- Europe (A)	23	32	39	44	57	69	82	
- Other (B)	10	12	21	24	28	27	38	
- Multilaterals	2	2	2	2	2	2	2	B. Other includes all national public sector funding apart from funding from the US and Europe
TOTAL PUBLIC	307	359	436	532	602	672	776	
PHILANTHROPIC SECTOR								C. Commercial sector investments were estimated for selected years in the series
TOTAL PHILANTHROPIC	20	7	112	15	12	12	78	
TOTAL NON-COMMERCIAL INVESTMENT	327	366	548	547	614	684	854	
COMMERCIAL SECTOR								
- Pharmaceutical companies	-	-	-	-	59 (range 47 to 71)	64 (range 52 to 76)	70 (range 58 to 82)	
- Biotechnology companies	-	-	-	-	9 (range 7 to 11)	9 (range 9 to 13)	9 (range 9 to 13)	
TOTAL COMMERCIAL	-	-	-	-	68 (range 54 to 82)	75 (range 61 to 89)	79 (range 65 to 93)	
TOTAL GLOBAL INVESTMENT (C)					682	759	933	

18 **3.1**
**GLOBAL INVESTMENTS
 IN HIV VACCINE R&D**

Over the last seven years, there has been a marked increase in the level of investment toward the development of preventive HIV vaccines. In 2006, total global investment in preventive HIV vaccine R&D was an estimated US\$933 million (Table 3). As will be described in further detail, the increase in investment from 2005 is largely attributed to increased support from key funders in the non-commercial (public and philanthropic) sectors.

Between 2000 and 2006, funding by the non-commercial sectors more than doubled, increasing from US\$327 million to US\$854 million (Figure 1). Philanthropic funding increased to almost US\$80 million in 2006, largely reflecting the initiation of the Gates Foundation grant to support the Collaboration for AIDS Vaccine Discovery (CAVD). CAVD is an international network of vaccine discovery consortia and service facilities funded to apply "new technologies, concepts and approaches to the design of safe and effective preventive vaccines against HIV/AIDS."²⁰

FIGURE 1. ANNUAL PUBLIC AND PHILANTHROPIC INVESTMENTS IN PREVENTIVE HIV VACCINE R&D BETWEEN 2000 AND 2006



RUSSIAN VACCINE CENTER

In 2007, Dr. Gennady Onishchenko, the Russian Federation's chief medical officer, announced the inception of a Russian center aimed at coordinating regional HIV vaccine research. Creation of the facility, expected to cost approximately US\$50 million, will be funded over three years. According to Onishchenko, seven research institutions in Russia have been investigating HIV/AIDS, one of which will become the primary research center. That

center will act as the regional body coordinating HIV vaccine research in Eastern Europe and Central Asia. The Russian Vaccine Center was created in part as the Federation's contribution to the Global HIV Vaccine Enterprise.

FIGURE 2. PUBLIC, PHILANTHROPIC AND COMMERCIAL FUNDING FOR HIV VACCINES IN 2006

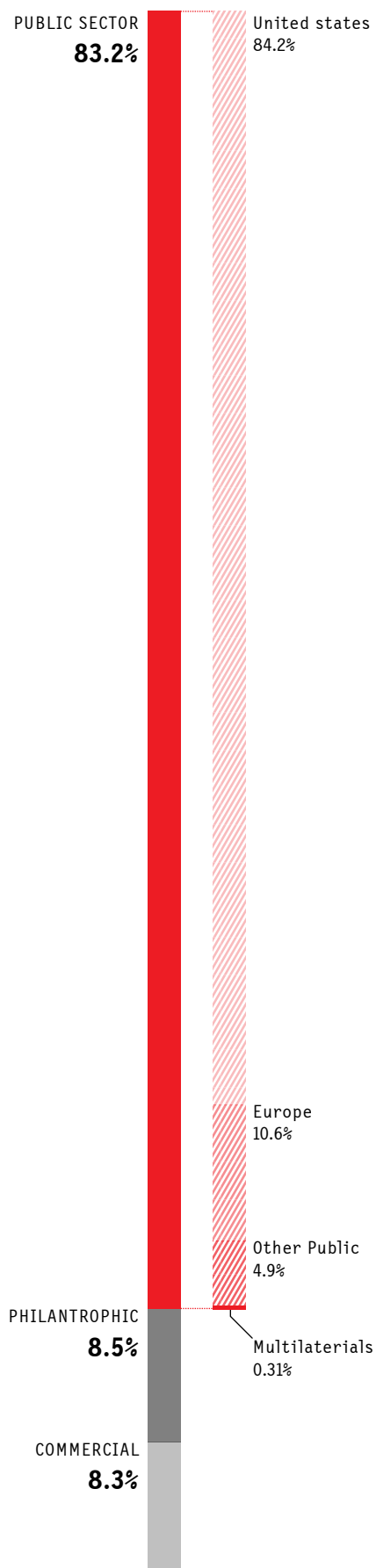
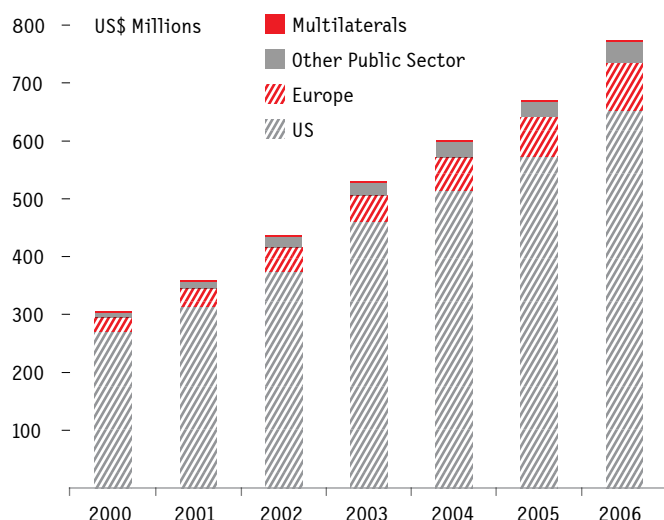


FIGURE 3. ANNUAL PUBLIC INVESTMENT IN PREVENTIVE HIV VACCINE R&D BY REGION BETWEEN 2000 AND 2006.



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 in 2006, accounting for 83% of total investment. In comparison, the commercial and philanthropic sector each accounted for about 8% of funding in that year (Figure 2).

The United States provided the single largest portion of public funds in 2006, accounting for 84% (US\$654 million) of the total funds invested by that sector. For the same year, European national governments and the European Commission together accounted for 11% (US\$82 million) of the total funds invested, while national governments from the rest of the world accounted for 5% (US\$38million). Multilateral organizations such as the World Health Organization (WHO), UNAIDS and the World Bank accounted for less than 1% (US\$2 million) (Figures 2 and 3).

Four countries (Canada, the Netherlands, the United Kingdom and the United States) invested more than US\$10 million in public-sector funds in 2006, and 15 countries invested more than US\$1 million (Table 4). In addition, the European Commission (EC) invested approximately US\$23 million. In total funds disbursed for HIV vaccine R&D between 2000 and 2006, the top five individual countries in descending order are the United States, the United Kingdom, Canada, the Netherlands and France.

FIGURE 4. ANNUAL PHILANTHROPIC INVESTMENTS IN PREVENTIVE HIV VACCINE R&D BETWEEN 2000 AND 2006

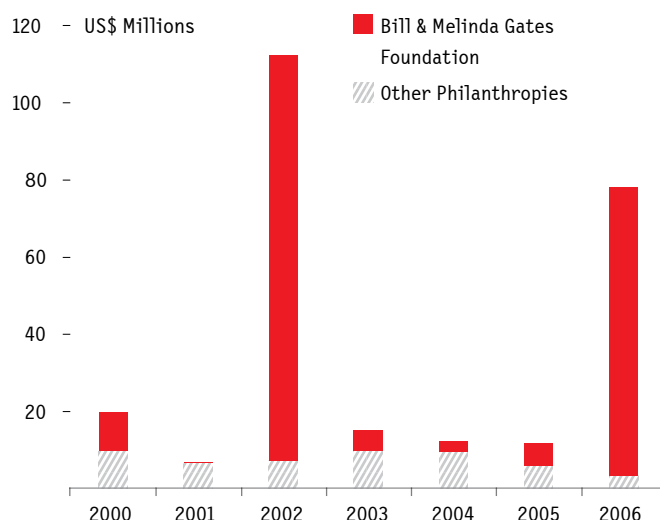


TABLE 4. NATIONAL PUBLIC SECTOR INVESTMENTS IN PREVENTIVE HIV VACCINE R&D BY COUNTRY IN 2006.

OVER US\$25 MILLION: United States **US\$10 TO 25 MILLION:** Canada, Netherlands, United Kingdom **US\$5 TO 10 MILLION:** Ireland, South Africa **US\$1 TO 5 MILLION:** Australia, China, Denmark, France, Germany, Italy, Japan, Norway, Sweden **US\$500K TO 1 MILLION:** Brazil, Russian Federation **US\$50K TO 500K:** Cuba, Finland, Thailand

The proportion of HIV vaccine funding originating in health and research agencies versus international development agencies varies widely across countries. The NIH alone accounted for 91% (about US\$593 million) of total US public-sector funding - representing about 76% of global public-sector investment. In many of the other countries reviewed, international development funding agencies (as opposed to research funding agencies) were equally important sources of funds for HIV vaccine R&D, particularly in Europe. The three multilateral agencies (UNAIDS, WHO and the World Bank) provided primarily international development funding.

3.1.2 PHILANTHROPIC INVESTMENTS IN HIV VACCINE R&D

The philanthropic sector accounted for US\$78 million or about 8% of the total funds disbursed for HIV vaccine R&D in 2006. As seen in Figure 4 and Table 5, levels of total philanthropic funding have varied considerably over the last seven years. This variability reflects the funding practices of the philanthropic field, which can involve both 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). For example, the Gate Foundation funded CAVD was established in July 2006 with 16 grants totaling US\$287 million over five years.

In 2006, seven philanthropic organizations provided funding of more than US\$100,000 for HIV vaccine R&D. In addition, two companies provided direct financial donations of US\$100,000 or more (Table 5).

TABLE 5. PHILANTHROPIC INVESTMENTS IN HIV VACCINE R&D BY ORGANIZATION IN 2006.

OVER US\$1 MILLION Bill & Melinda Gates Foundation, Eskom*, Wellcome Trust **US\$500 THOUSAND TO 1 MILLION** Elizabeth Glaser Pediatric AIDS Foundation **US\$250 THOUSAND TO 500 THOUSAND** American Foundation for AIDS Research, Bloomberg-Global Health / Governors Island; Klingenstein Fund, Until There's a Cure **US\$100 THOUSAND TO 250 THOUSAND** Becton Dickinson and Company*, Ford Foundation, Rockefeller Foundation

*Charitable contribution by private company.

In 2006, seven philanthropic organizations provided funding of more than US\$100,000 for HIV vaccine R&D. In addition, two companies provided direct financial donations of US\$100,000 or more (Table 5).

3.1.3

COMMERCIAL INVESTMENTS IN HIV VACCINE R&D

TABLE 6 COMMERCIAL ENGAGEMENT IN PREVENTIVE HIV VACCINE R&D BY COMPANY IN 2006.

OVER US\$10 MILLION: Merck & Co, Inc. **US\$5 MILLION TO US\$10 MILLION:** Sanofi Pasteur, Novartis International AG (after acquisition of Chiron Corporation), GlaxoSmithKline **US\$1 MILLION TO 5 MILLION** Wyeth-Ayerst Lederle, Inc. **US\$25 THOUSAND TO 1 MILLION:** Advanced BioScience Laboratories

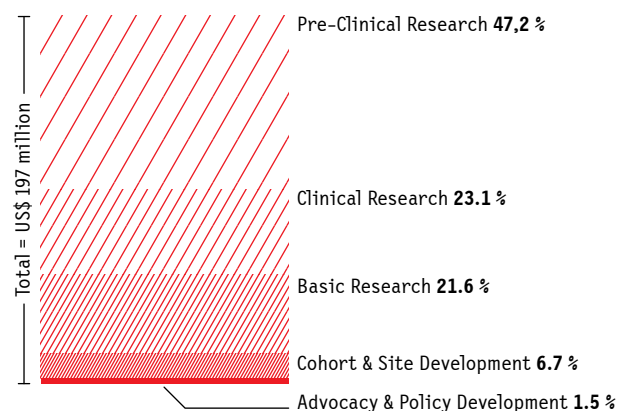
AlphaVax Human Vaccines Inc. / AVANT Immunotherapeutics, Inc. / Bavarian Nordic / Bioption AB / Crucell N.V. / Epimmune Inc. / FIT Biotech PLC / EpiVax / GenVec, Inc. / GeoVax, Inc. / Globeimmune, Inc. / Impfstoffwerk Desau Tornau GmbH / Juvartis Bio-Therapeutics / Maxygen, Inc. / Novavax, Inc. / Progenics Pharmaceuticals, Inc. / Targeted Genetics Corporation / Therion Biologics Corporation / United BioMedical / Transgene / Vical Inc.

Total investment by the commercial sector (pharmaceutical and biotechnology companies) in HIV vaccine development in 2006 was estimated to be US\$79 million. The majority of this funding - almost 90% - comes from large pharmaceutical companies.²¹

It is important to note that this estimate reflects only 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., the NIH and Agence Nationale de Recherches sur le Sida [ANRS, France]) or public-private partnerships (e.g., IAVI and SAAVI). Therefore, estimated total spending by the commercial sector is much greater than the estimated US\$79 million in funds invested from their own internal sources.

In total, there were over 20 companies actively engaged in HIV vaccine R&D in 2006 (Table 6). Four of these companies - all categorized as large pharmaceutical companies - were estimated to have invested more than US\$5 million of their own funds.

FIGURE 5. NON-COMMERCIAL FUNDING ALLOCATIONS FOR PREVENTIVE HIV VACCINE R&D BY CATEGORY IN 2006

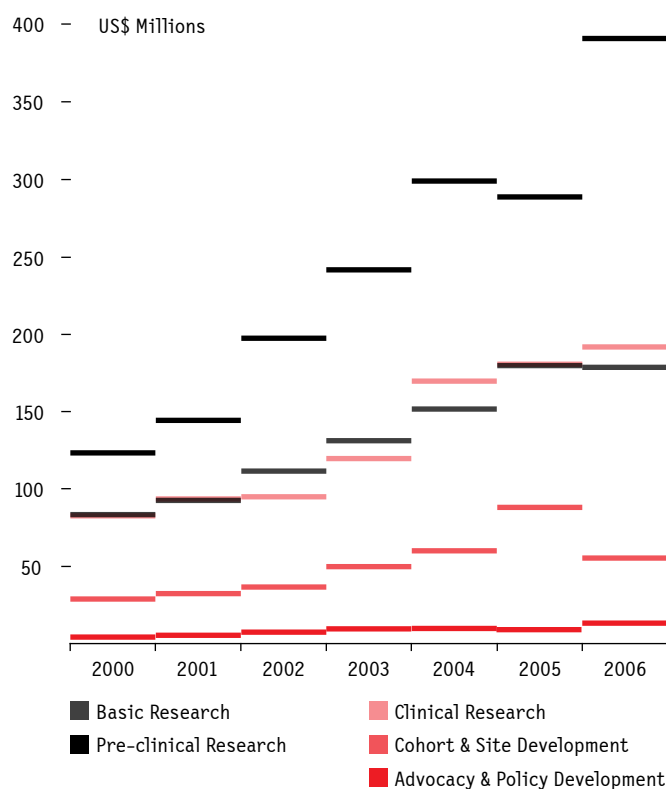


3.1.4 FUNDING ALLOCATIONS FOR HIV VACCINE R&D

In 2006, 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 were allocated, basic research and pre-clinical research accounted for 21.4% and 47.2% of funds, respectively. In comparison, support for clinical trials accounted for 23.1%, cohort and site development for 6.7%, and advocacy and policy development for 1.5% (Figure 5). These allocations are estimated from a subset of investments for preventive HIV vaccine R&D totaling US\$826 million in 2006.

The allocation of funding across the five categories has remained fairly constant over the past years (Figure 6). However, 2006 saw an increase in pre-clinical and clinical research, with a corresponding decrease in basic research and cohort and site development. The increase in pre-clinical development may reflect a desire to devote greater resources to developing new, innovative HIV vaccine candidates with different vectors, and to identify vaccine candidates capable of inducing neutralizing antibodies. The reduction in spending for cohort and clinical site development may reflect a shifting of resources into clinical trial sites as several efficacy trials began or were announced in 2006.

FIGURE 6. NON-COMMERCIAL FUNDING ALLOCATIONS FOR PREVENTIVE HIV VACCINE R&D BY CATEGORY IN 2000 - 2006



3.2 GLOBAL INVESTMENTS IN MICROBICIDE R&D

Total global investment in microbicide R&D amounted to US\$222 million, reflecting a marked increase in the level of investment over the last seven years (Table 7). From 2000 to 2006, investments from the public and philanthropic sectors more than tripled, from an estimated US\$65 million to approximately US\$217 million (Table 7 and Figure 7).

Public agencies and institutions dominated funding for microbicide R&D, accounting for almost 86% (US\$191.2million) of total investment in 2006. In comparison, the philanthropic sector accounted for 12% (US\$26.2 million) and the commercial sector for 2% (US\$4.5 million) (Figure 8).

3.2.1 PUBLIC INVESTMENTS IN MICROBICIDE R&D

In 2006, public-sector investment in microbicide R&D amounted to approximately 86% of the combined global funding for microbicide research, development and advocacy. The United States dominates public-sector funding for microbicides, providing 68% (US\$129.7 million) of the total in 2006. European national governments and the European Commission together accounted for 29% (US\$56.3 million) (Figure 8).

National governments from the rest of the world accounted for less than 2% (US\$3.8 million) of global public-sector funding, and the multilateral organizations reviewed (WHO, UNAIDS and the World Bank) together accounted for less than 1% (US\$1.4 million) (see Figure 8).

TABLE 8. NATIONAL PUBLIC SECTOR INVESTMENT IN MICROBICIDE R&D BY COUNTRY IN 2006.

OVER US\$10 MILLION United Kingdom, United States **US\$5 TO 10 MILLION** Ireland, Netherlands **US\$1 TO 5 MILLION** Canada, Denmark, Norway, Sweden **US\$500 THOUSAND TO 1 MILLION** (none in this range) **US\$50 THOUSAND TO 500 THOUSAND** Belgium, Brazil, China, France, Germany, South Africa

Two countries (the United Kingdom and the United States) invested more than US\$10 million of public-sector funds in microbicide development in 2006, and eight countries invested more than US\$1 million that year (Table 8). While the United States, particularly the NIH and USAID, continues to dominate

TABLE 7.
ANNUAL INVESTMENTS IN
MICROBICIDE R&D BETWEEN
2000 AND 2006 (US\$ MIL-
LIONS).

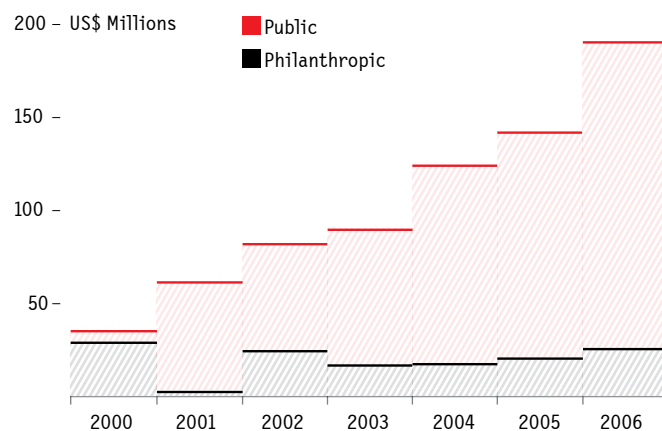
	2000	2001	2002	2003	2004	2005	2006
PUBLIC SECTOR							
- US	34.6	61.3	75.3	78.8	92	101.6	129.7
- Europe (A)	0.7	0.4	5.1	10.6	29.9	30.3	56.3
- Other (B)	0.3	<0.1	0.2	0.9	2.0	10.5	3.8
- Multilaterals	<0.1	0.3	0.4	<0.1	0.2	0.2	1.4
TOTAL PUBLIC	35.7	62.0	81.0	90.2	124.2	142.6	191.2
PHILANTHROPIC SECTOR							
TOTAL PHILANTHROPIC	29.4	3.4	24.8	16.9	18.1	21.3	26.2
TOTAL NON-COMMERCIAL INVESTMENT							
	65.1	65.4	105.8	107.1	142.3	163.9	217.4
COMMERCIAL SECTOR							
- Pharmaceutical companies	-	-	-	-	-	-	-
- Biotechnology companies	-	-	-	-	4.5 (range 3 to 6)	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)	4.5 (range 3 to 6)
TOTAL GLOBAL INVESTMENT (C)					146.8	168.4	221.9

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 7. ANNUAL PUBLIC AND PHILANTHROPIC INVESTMENTS IN MICROBICIDES BETWEEN 2000 AND 2006



public-sector funding for microbicides, the proportion of resources from European funders has significantly increased. Between 2000 and 2006, the share of funding from European public-sector sources (including the European Commission) grew from less than 1% to 29% (US\$56.3 million in 2006).

In cumulative funds disbursed for microbicide R&D between 2000 and 2006, the top five countries in descending order were the United States, the United Kingdom, Canada, the Netherlands and Ireland.

The sources of public-sector funding for microbicide R&D vary widely. In some countries, the majority of funding comes from health and research agencies, while in other countries most or all is provided by international development agencies. 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 68% of US public-sector microbicide funding in 2006, while USAID, an international development agency, provided about 30%.

3.2.2 PHILANTHROPIC INVESTMENTS IN MICROBICIDE R&D

In 2006, funding from the philanthropic sector totaled US\$26.2 million, or 12% of the total funds disbursed for microbicide development from non-commercial 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 9). 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.

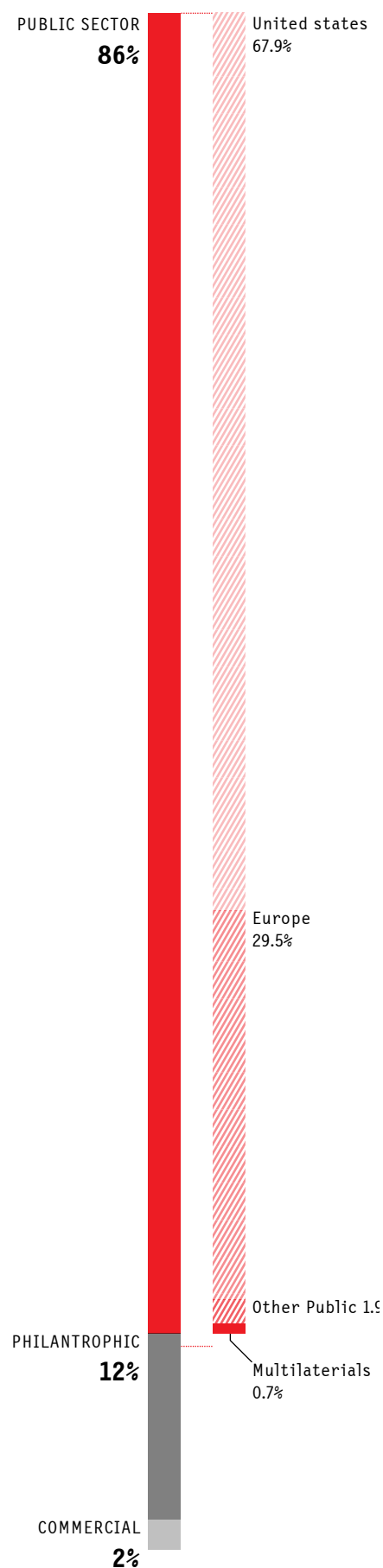
TABLE 9. PHILANTHROPIC INVESTMENT IN MICROBICIDE R&D BY ORGANIZATION IN 2006.

Organizations are listed alphabetically within each category

OVER US\$1 MILLION Bill & Melinda Gates Foundation, Rockefeller Foundation
US\$500 THOUSAND TO 1MN Wellcome Trust
US\$100 THOUSAND TO 500 THOUSAND American Foundation for AIDS Research

In 2006, the Gates Foundation provided more than US\$20 million for microbicide R&D, and the Rockefeller Foundation provided US\$4 million. Two additional organizations (the American Foundation for AIDS Research and the Wellcome Trust) each provided funding in excess of US\$100,000.

FIGURE 8. SOURCES OF FUNDING FOR MICROBICIDE R&D IN 2006



COMMERCIAL INVESTMENTS IN MICROBICIDE R&D

Total commercial-sector microbicide investment in 2006, excluding funding from external sources such as government sources, was estimated to be US\$4.5 million. This estimate is based upon interviews with a number of companies and remains at the same level as in past years.

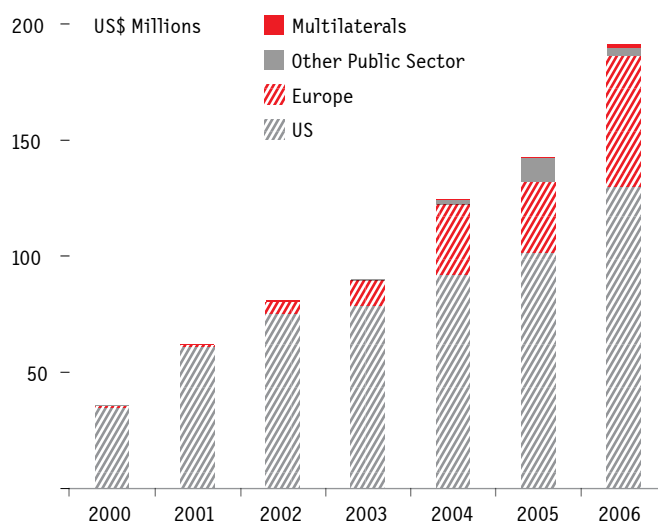
Some 40 biotechnology and biopharmaceutical companies participated in some aspect of microbicide R&D in 2006.²² Virtually all the work of these companies on microbicide R&D was supported through public-sector granting mechanisms, predominantly from the NIH, the EC and/or through intermediary organizations such as CONRAD and IPM. Although investments from companies' own financial resources are generally small and supplementary to any external funding they receive, private companies have played crucial roles in the development of a number of current microbicide candidates.

TABLE 10. COMMERCIAL INVOLVEMENT IN MICROBICIDE R&D BY COMPANY IN 2006.

Ablynx / Advanced BioSciences Laboratories / Bio-Stat Solutions, Inc. (BSS) / Carbohydrate Synthesis Ltd. / DakoCytomation / EMD Biosciences / Farmov-Parexel / Fisher BioServices Corporation / Gilead Life Sciences, Inc. / Glycores 2000 / HLSP / HTI Plastics / Idenix Pharmaceuticals / ImQuest BioSciences / Indevus Pharmaceuticals, Inc. / Instead, Inc. / I.T.I., Inc. / Lekoko PMC / LIFElab / Lionex

Diagnostics and Therapeutics / Mapp Biopharmaceutical / MatTek Corporation / Medivir / Novaflex Technologies / Novartis (Siena) / Osel, Inc. / Paradigm Pharmaceuticals / Pepsican Systems / Polydex Pharmaceuticals Ltd. / Progenics / Renaissance Scientific, LLC / RNA-TEC / ReProtect, Inc. / SGS Biopharma / Social & Scientific Systems, Inc. / Starpharma Holdings Ltd. / Tibotec BVBA / Vision7 GmbH / VivoMetrics / Voxiva

FIGURE 9. ANNUAL PUBLIC INVESTMENT IN MICROBICIDE R&D BY REGION BETWEEN 2000 AND 2006



EUROPEAN COMMITMENT TO NEW PREVENTION TECHNOLOGIES

The European Commission's (EC) funding commitments and expenditures with respect to Product Development Public-Private Partnerships (PDPs) and public-sector funding of R&D play important roles in the search for new health technologies to prevent and treat the major poverty-related diseases, AIDS, tuberculosis and malaria.

The EC has demonstrated a sustained commitment to funding PDPs concerned with HIV/AIDS through its development aid and assistance. Directorate General for Development (DG Development) grants totalling €12.52 million have been committed to HIV vaccines (€6 million) and microbicides (€6.52 million). These grants will build local capacity and ownership in the development of HIV vaccines in East and Southern Africa and for

microbicide advocacy and networking to accelerate microbicide development and availability. In addition, the EC has also committed funds for HIV/AIDS-related R&D projects via the Directorate General for Research's (DG Research) Sixth Framework Programme (FP6) and the European and Developing Countries Clinical Trials Partnership (EDCTP). On December 18, 2006, the EC established the Seventh Framework Programme (FP7) for research and technological development for the period 2007 to 2013. Excluding the EDCTP, EC commitments for HIV/AIDS-related R&D have been distributed among roughly 27 HIV/AIDS projects with a total funding allocation of €74.25 million. 43% of this (€31.72 million) pertains to HIV vaccine R&D, while 21% (€15.95 million) is related to microbicide research. The remaining 37%

(€26.45 million) is related to treatment and general HIV/AIDS disease research. Of the €8.26 million that has been committed to clinical trials via the EDCTP, 18% (€1.5 million) has been awarded to HIV/AIDS-related clinical trials.

Part of the EC commitment is the research consortium, EUROPRISE, which was founded in January of 2007 with a €15.5 million grant from the EC. It brings together HIV/AIDS researchers at 32 European institutions and includes two major pharmaceutical companies (Novartis and GlaxoSmith Kline). EUROPRISE is funded principally to facilitate coordination. EUROPRISE's focus is on the intersection between vaccine and microbicide research, and it seeks to engender coordination between researchers from these respective fields.

3.2.4 FUNDING ALLOCATIONS FOR MICROBICIDE R&D

In 2006, expenditures on microbicide R&D were concentrated on pre-clinical testing and clinical trial activities. We allocated expenditures across seven NIH categories (described in Table 2): Basic Mechanisms of Mucosal Transmission (9.7%); Discovery, Development and Preclinical Testing (22.6%); Formulations and Modes of Delivery (7.3%); Clinical Trials (42.6%); Microbicide Behavioral and Social Science Research (6.3%); Microbicide Research Infrastructure (5.9%); and Policy and Advocacy (5.6%) (Figure 10). These allocations are estimated from a subset of investments in microbicide R&D, totaling US\$183 million in 2006.²³

3.3 GLOBAL INVESTMENTS IN NEW PREVENTION TECHNOLOGIES R&D

In addition to investments in experimental HIV vaccines and microbicides, there have been investments in a number of new experimental biomedical interventions. These interventions include adult male circumcision as a method of preventing sexual transmission of HIV, use of the drug acyclovir to reduce HIV transmission to HSV-2 infected individuals, use of diaphragms as cervical barriers to prevent HIV infection and the use of antiretroviral drugs as a prophylactic measure to prevent HIV infection. Of these interventions, only male circumcision has been proven effective - and then only protective for men engaged in vaginal intercourse.

However, the results from clinical trials of several of these other potential interventions are expected in the next few years, and wider implications of adult male circumcision are also under further examination.

In each of these cases, the research and development devoted to these tools was primarily or exclusively related to clinical trials of the effectiveness of these interventions in preventing HIV transmission, as the tools themselves already exist. Circumcision, for example, is a long-practiced procedure in many countries, religions and cultures, and Tenofovir and Tenofovir-3TC, the drugs used in the PrEP trials, had been previously tested and licensed as treatment drugs. Similarly, acyclovir is a tested and

FIGURE 10. ANNUAL PHILANTHROPIC INVESTMENTS IN MICROBICIDE R&D BETWEEN 2000 AND 2006

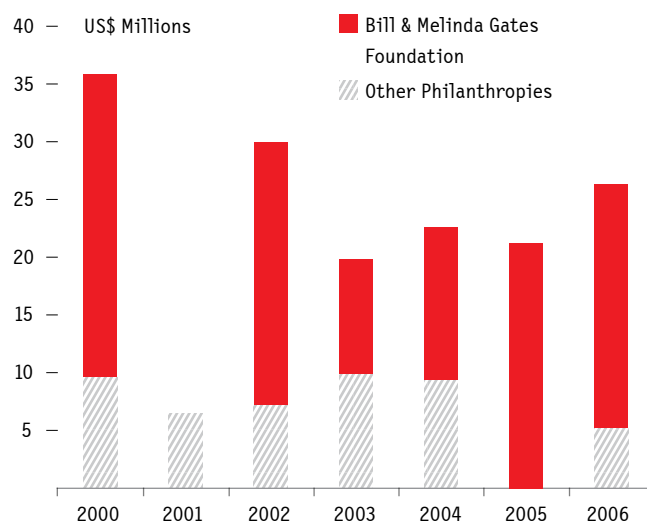
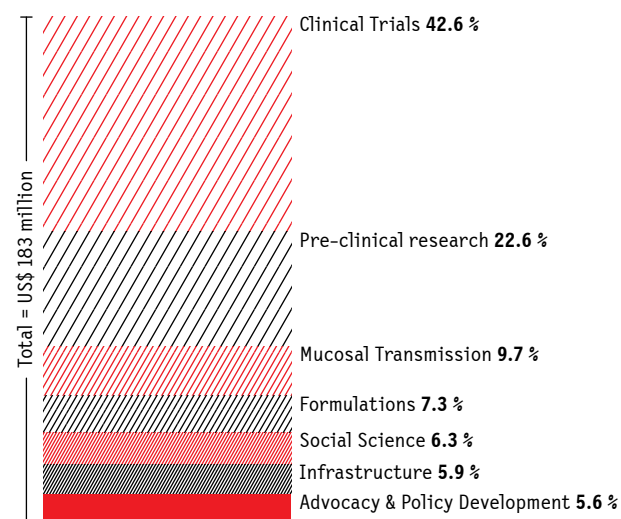


FIGURE 11. FUNDING ALLOCATIONS FOR MICROBICIDE R&D BY CATEGORY IN 2006



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Alliance for Microbicide Development. Mapping the Microbicide Effort: A Companion to the Microbicide Development Strategy. Silver Spring, MD, USA. (2007) <http://www.microbicide.org/microbicideinfo/reference/MappingFinal.pdf>

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A subset of total investments was used because expenditure breakdowns could not be determined or reasonably estimated for approximately \$40 million in microbicide investments

TABLE 11		2001	2002	2003	2004	2005	2006	2001-2006	
ANNUAL INVESTMENT IN OTHER NEW PREVENTION TECHNOLOGIES, 2001 THROUGH 2006 (US\$)	PUBLIC SECTOR								
	US	0	3,777,653	7,086,535	8,835,590	18,180,362	24,821,396	62,701,536	
	ARNS [1]	0	446,439	541,297	0	268,963	0	1,256,699	
	1 Agence Nationale de Recherches sur le Sida (ANRS).	CIHR [2]	472,850	516,890	578,606	622,757	414,965	0	2,606,068
		DFID UK [3]		60,514	60,515	0	0	0	121,029
	2 Canadian Institutes of Health Research (CIHR).	UKMRC [4]					302,400	306,300	608,700
		TOTAL PUBLIC	472,850	4,740,982	8,266,953	9,458,347	19,166,690	25,127,696	67,294,032
		PHILANTHROPIC SECTOR							
	3 Department of International Development UK (DFID).	GATES FOUNDATION	0	10,137,267	25,049,388	25,696,891	25,439,990	28,118,457	114,441,993
	4 UK Medical Research Council (UK MRC).	WELLCOME TRUST	0	337,674	337,674	337,674	337,675	337,675	1,688,372
		TOTAL PHILANTHROPIC	0	10,552,615	25,427,062	26,074,565	25,817,665	28,496,132	116,130,365
		TOTAL	472,850	15,316,437	33,694,015	35,532,912	44,984,355	53,623,828	183,424,397

TABLE 12		2001	2002	2003	2004	2005	2006	2001-2006	
ANNUAL INVESTMENT IN ADULT MALE CIRCUMCISION, 2001 THROUGH 2006 (US\$)	PUBLIC SECTOR								
	NIH	0	1,205,721	3,806,768	3,654,655	4,118,300	5,984,441	18,769,885	
	ANRS [1]5	0	446,439	541,297	0	268,963	0	1,256,699	
	CIHR [2]	472,850	516,890	578,606	622,757	414,965	0	2,606,068	
	TOTAL PUBLIC	472,850	2,169,050	4,926,671	4,277,412	4,802,228	5,984,441	22,632,652	
		PHILANTHROPIC SECTOR							
	GATES FOUNDATION	0	949,307	949,307	1,596,810	1,988,814	4,246,979	9,731,217	
	TOTAL	472,850	3,118,357	5,875,978	5,874,222	6,791,420	10,231,420	32,363,869	

licensed drug treatment for HSV-2 and the diaphragm is a widely accepted and understood method of birth control. In each case these trials examined – whether these interventions were capable of preventing HIV infection, a purpose for which they were not originally designed.

Total global public-sector and philanthropic investment in these four new prevention tools has amounted to US\$183.6 million over the last six years (Table 11). Between 2000 and 2006, investments from the non-commercial sectors were increasing annually.

3.3.1 INVESTMENTS IN HIV PREVENTION RESEARCH AND DEVELOPMENT RELATED TO MALE CIRCUMCISION

In 2006, clinical studies showed that aseptic adult male circumcision performed by trained personnel can reduce male risk of HIV infection via vaginal intercourse. The scientific basis for these trials is that the inner lining of the foreskin is rich in HIV target cells which are highly susceptible to HIV infection. The studies completed to date do not address the safety and efficacy of circumcision in HIV-infected men, or the protective effect – if any – for the male or female partners of circumcised men. Further research is needed to address these questions, along with operations research to determine how male circumcision can be best implemented in a variety of cultural, economic and epidemiological settings. Total global public-sector and philanthropic investment in male circumcision amounted to US\$78.6 million over the last six years (Table 12).

3.3.2

INVESTMENTS IN HIV PREVENTION RESEARCH AND DEVELOPMENT RELATED TO HSV-2 SUPPRESSION

An ongoing clinical trial is currently studying the use of acyclovir for the reduction of HIV acquisition among high-risk HSV-2-seropositive, HIV seronegative individuals. The scientific basis for this research is that the presence of genital ulcers caused by HSV-2 has been identified as a possible risk factor for becoming infected with HIV. A total of 2,820 women and men who have sex with men are part of this study in the U.S., Africa and Latin America. Another study is looking at HSV-2 suppression as a way to prevent HIV transmission among HIV serodiscordant couples in Botswana. If these trials establish that HSV-2 suppression is an effective strategy to reduce HIV transmission, further operations research will be needed to determine how this strategy can be implemented. Total global public-sector and philanthropic investment in HSV-2 suppression has amounted to US\$78.2 million over the last five years (Table 13).

3.3.3

INVESTMENTS IN HIV PREVENTION RESEARCH AND DEVELOPMENT RELATED TO VAGINAL BARRIERS

The Methods for Improving Reproductive Health in Africa (MIRA) trial recently announced the findings from a study of the use of the latex diaphragm in combination with non-contraceptive lubricant gel to prevent HIV acquisition among women.²⁴ The findings that women who used diaphragms and condoms as an HIV prevention method had the same HIV incidence as women who used only condoms led the investigators to not recommend diaphragms as an HIV prevention method at this time.

	2002	2003	2004	2005	2006	2002-2006
TABLE 13 ANNUAL INVEST- MENT IN HERPES SUPPRESSION, 2002 THROUGH 2006 (US\$) ²⁵	PUBLIC-SECTOR					
NIH	2,571,932	2,481,754	1,625,723	5,208,813	4,838,673	16,726,895
DFID	60,514	60,515	0	0	0	121,029
UK MRC	0	0	0	302,400	306,300	608,700
TOTAL PUBLIC	2,632,446	2,542,269	1,625,723	5,511,213	5,144,973	17,456,624
PHILANTHROPIC SECTOR						
GATES FOUNDATION	0	14,912,121	14,912,121	14,912,120	14,912,120	59,648,482
WELLCOME TRUST	0	377,674	377,674	377,674	377,675	377,675
TOTAL PHILANTHROPIC	0	15,289,795	15,289,795	15,289,794	15,289,795	61,159,179
TOTAL	2,571,932	17,771,549	16,915,518	20,801,007	20,434,768	78,615,803

	2002	2003	2004	2005	2006	2002-2006
TABLE 14 ANNUAL INVEST- MENTS IN CERVICAL BARRIERS 2002 THROUGH 2006 (US\$)	PUBLIC-SECTOR					
USAID	0	0	0	0	525,200	525,200
TOTAL PUBLIC	0	0	0	0	525,200	525,200
PHILANTHROPIC SECTOR						
GATES FOUNDATION	7,021,294	7,021,294	7,021,294	7,021,294	7,441,596	35,526,772
TOTAL	7,021,294	7,021,294	7,021,294	7,021,294	7,966,796	36,051,972

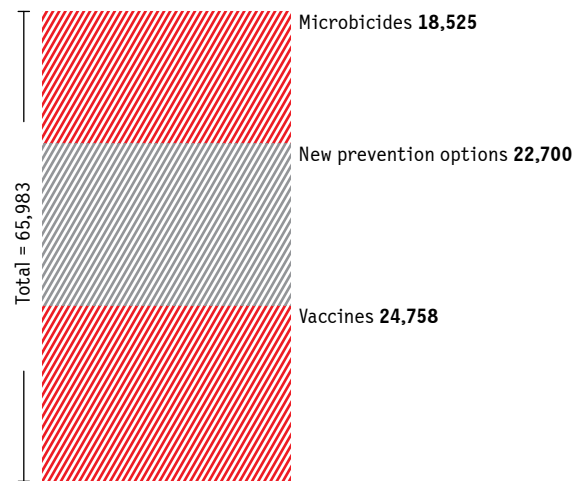
	2002	2003	2004	2005	2006	2002-2006
TABLE 15 ANNUAL INVEST- MENTS PRE-EXPO- SURE PROPHYLAXIS 2002 AND 2007	PUBLIC-SECTOR					
NIH			451,212	2,513,398	3,772,807	6,737,417
CDC	0	798,013	3,104,000	6,339,851	9,700,275	19,942,139
TOTAL PUBLIC	0	798,013	3,555,212	8853249	13,473,082	26,679,556
PHILANTHROPIC SECTOR						
GATES FOUNDATION	2,166,666	2,166,666	2,166,666	1,517,762	1,517,762	9,535,522
TOTAL	2,166,666	2,964,679	5,721,878	10,371,011	14,990,844	36,215,078

The scientific basis for this trial was that cell types found in the cervix (the opening to the uterus) are highly susceptible to HIV infection. The MIRA trial tested the hypothesis that covering the cervix (in this study, with the contraceptive diaphragm) would reduce the risk of HIV infection in women during vaginal sex. The study examined diaphragm use in 4,500 at-risk HIV uninfected women in South Africa and Zimbabwe. Total global public-sector and philanthropic investment in cervical barriers amounted to US\$36 million over the last five years (Table 14).

3.3.4 INVESTMENTS IN HIV PREVENTION RESEARCH AND DEVELOPMENT RELATED TO PRE-EXPOSURE PROPHYLAXIS.

There are four trials underway involving the use of two antiretroviral (ARV) drugs as a pre-exposure prophylaxis (PrEP) against HIV infection.²⁶ The scientific rationale is that antiretrovirals may prevent HIV infection in uninfected individuals by disabling or interfering with HIV during the initial period after exposure to the virus. One study is looking at a daily dose of Tenofovir-Disoproxil Fumarate (TDF) to prevent HIV infection in injection drug users in Bangkok, Thailand. Another PrEP study is looking at a daily regimen of tenofovir-3TC for the prevention of HIV infection in 1,200 heterosexually active adults in Botswana. A third PrEP study is looking at the safety and effectiveness of daily tenofovir-3TC in preventing HIV transmission in HIV uninfected men who have sex with men (MSM) in Peru and Ecuador. Finally, a fourth study is testing TDF in 400 HIV uninfected MSM in the U.S. If these trials establish that PrEP is an effective HIV prevention strategy, further operations research will be needed to determine how this strategy can be implemented. Total global public-sector and philanthropic investment in PrEP amounted to US\$36.2 million over the last five years (Table 15).

FIGURE 12. NUMBER OF TRIAL VOLUNTEERS - 2007



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Where grants are disbursements for individual years of multi-year grants are known, actual disbursements are used for each year. Where a multi-year grant is awarded, and information on year-to-year disbursement is not known, funds are allocated for each year of the grant by dividing the total amount of the grant by the time period of the grant.

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A number of microbicide researchers have received funding to study the use of antiretroviral drugs as microbicide formulations as an HIV prevention approach. This research was allocated to microbicide R&D. Studies in the PrEP estimates, in contrast, research oral-antiretroviral use as a prevention tool.

4.0

DISCUSSION

The rising tide of HIV infections in the face of current prevention efforts has drawn increased attention to the need for expanding existing prevention efforts as well as developing new prevention options. An effective strategy to reduce HIV infections must be truly comprehensive, affording individuals and communities a range of options to use either alone or in combination. Currently, there are a number of new prevention options being researched and studied in clinical trials throughout the world.

The growth in 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 vaccines²⁷ and microbicides,^{28 29} increased recognition of the potential role of new technologies in controlling the spread of HIV and the need to invest in a comprehensive response. The role of the G8, and commitments by the European Commission and the NIH have also helped in increasing global investment. The announcement of new vaccine laboratories to be created in Canada and the Russian Federation are examples of increased global attention to HIV vaccine research.

However, there are still many scientific challenges, so that developing appropriate biomedical tools for HIV prevention in a timely fashion essentially demands greater global collaboration and coordination. While the current levels of funding described here are significant, there will be an inevitable need to sustain - and even increase - investment in preventive HIV vaccine, microbicide, and other new prevention technology R&D to optimally accelerate the development of and assure eventual access to these technologies. Under almost any R&D scenario, financing requirements are likely to remain substantial in the coming years as new, large clinical trials become necessary and trial sites must be both maintained and, in some case, developed and strengthened. In the case of microbicides, HIV vaccines, and STD prevention, there will also be a need to assure a steady inflow of candidates with different mechanisms of action into the early part of the R&D pipeline, since the typical pattern in

pharmaceutical development in general is substantial attrition of candidates as they move through both the preclinical and clinical stages of development. In the microbicide field, the key players, including AMD and IPM, are currently engaged in the very challenging task of calculating the projected financial and infrastructure needs for microbicide research and development, particularly future clinical trials, as well as the incentive levels that could more rapidly augment early pipeline. The purpose of all this work is to responsibly inform evidence-based advocacy for expanding the financial base for microbicide R&D.

As just one example of future funding requirements for prevention technologies, if any of the current HIV vaccine or microbicide candidates in Phase 2b or Phase 3 trials were to show efficacy in the next few years, the HIV prevention field would have to find support for manufacturing and service delivery scale-up, while still sustaining development of improved next-generation candidates. Alternatively, negative trial results would also necessitate innovation to replenish the candidate pipeline and would push the vaccine or microbicide fields to intensify upstream research and early product development activities, again requiring significant funding.

As promising as the investment levels for 2006 appear, there are indications that HIV prevention research resources may not continue to grow at the pace observed over the past seven years. Total appropriations to NIH, the largest funder of the new prevention technologies' research and development, have been leveling off since 2004³⁰, and may not even keep pace with inflation by FY 2008.³¹ Downward trends in NIH funding are a particular cause for concern since the US agency accounts for about two-thirds of the global investment in HIV vaccine research and 38% of the global investment in microbicide research. In 2006, philanthropic funding for vaccine research rose significantly, largely due to the award of US\$287 million in 16 five-year grants by the Bill & Melinda Gates Foundation to support collaborative HIV vaccine research.

However, it is uncertain if this type and magnitude of funding will be sustained beyond this timeframe.

Nevertheless, there is some cause for optimism as continued increases are observed in investment from Canada, Europe and from countries such as Brazil, China, India, South Africa and Thailand. Moreover, the investment in other investigative prevention options such as adult male circumcision, PrEP and HSV-2 suppression represent positive developments and have resulted in confirming at least one new HIV prevention option in the past year.

Given the many uncertainties in developing new biomedical methods to prevent HIV, it is impossible to say exactly how much more money ultimately will be required. The increasing costs of all clinical trials suggest that current investment levels will fall short of what is needed to carry out key developmental tasks, such as accelerating and increasing innovation in basic, applied and clinical science; moving new and existing candidate products into clinical trials; preparing sites and expanding and sustaining 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.

While the financial resources needed for vaccine, microbicide and other new prevention technology R&D are likely to be large and must be sustained over the long term, the potential benefits of effective and accessible products make these investments worthwhile. More effective prevention technologies are needed to avert millions of new HIV infections in the coming years and provide a comprehensive response to fight the epidemic.

No single new prevention tool will to end the pandemic. Men, women, adolescents and infants in different countries and settings are likely to need a tool box of different options to address their specific risks and lives. Our experience with roll-out and acceptance of established HIV prevention tools shows that no single approach is in itself sufficient. If the goal is to substantially curb an epidemic, only by developing a variety of prevention tools through robust research and development funding will we develop the truly comprehensive effort that is undeniably required.

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30

Fiscal 2008 Appropriations for NIH and CDC, <http://www.familiesusa.org/assets/pdfs/nih-and-cdc-funding-chart.pdf>

31

National Institutes of Health., President's Budget Summary FY 2008. <http://officeofbudget.od.nih.gov/PDF/Press%20info-2008.pdf>

APPENDIX 1

METHODS OF ESTIMATION

Data collection by the Working Group involved accessing public information and collecting information through direct appeals to funding agencies (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 the donor disbursed them, 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, Family Health International, 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 sectors: public, philanthropic or commercial (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

DEFINITIONS

A broad definition of R&D was used. 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 linkages (e.g., platform technologies) but was not directed primarily at these technologies.

PROCESS

A four-step process was followed to estimate annual investment levels for both microbicide and preventive HIV vaccine R&D. 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.³² However, not all organizations were able to provide disbursement data, and for these organizations, commitment data were used instead.

Many public-sector and philanthropic agencies do not specifically track R&D funding for HIV vaccines, microbicides or other new prevention technologies. In these situations, the information provided was generally from a keyword 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 development of HIV vaccines,

TABLE A2: THE PROCESS FOLLOWED TO ESTIMATE ANNUAL INVESTMENTS FOR HIV VACCINES, MICROBICIDES AND OTHER NEW PREVENTION TECHNOLOGIES

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.

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 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.

microbicides or other new prevention technologies. In these cases, we reviewed the description of the project and estimated the percentage of the overall grant directly related to those technologies. 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.

For the commercial sector, we contacted the main companies engaged in HIV vaccine and microbicide R&D as of mid-2006 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 contacted companies 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, and should not be considered exhaustive.

ALLOCATION STRATEGY

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-upon 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 for vaccine expenditures. The first four categories are based on the US National Institutes of Health definitions.³³ To prepare these allocations, we primarily relied upon investment data, except in the cases where intermediary organizations, such as IAVI, 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.

For this exercise, we have allocated funding to seven categories for microbicide expenditures. The first six categories are based on the US National Institutes of Health definitions.³⁴ 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, such as the IPM, were excluded from the 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 seven expenditure categories.

In some cases, no project descriptions were provided and allocations were made based upon the research and development goals of the intermediary or funding agency. In these cases, assumptions were made about the allocations within these seven categories. Accordingly, for funders or intermediaries engaged primarily in basic microbicide research, most of the funds were allocated to mucosal transmission research, with the remainder allocated to pre-clinical research. For funders or intermediaries engaged primarily in microbicide product development, allocations were made to pre-clinical research, clinical research and formulation, with typically 5 to 10% allocated to formulation. For funders or intermediaries engaged primarily in clinical trials of microbicide products, allocations were made to clinical research, behavioral research and microbicide infrastructure, with typically 80 to 90% allocated to clinical research..

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 R&D funding for HIV vaccines, microbicides or other new prevention technology. 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 cases, annual investment and funding estimates were extrapolated from 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:

We tried to make the data collated consistent across funders and over time so that accurate

trends and comparisons could be drawn. However,

* Some funders reported disbursement data based on their own fiscal years and contracting mechanisms, rather than by calendar year.

* The funding allocation estimates are based on a combination of expenditure data from intermediaries and investments by non-intermediary organizations.

* Most funders and intermediaries do not break down their expenditures and investments by type of activity or stage of product development. Where they do so, they 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). The data presented here reflect, to the best of our ability, only the investments of the companies' own resources.

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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 Cohort Development. 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 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.

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The NIH microbicide categories are: Basic Mechanisms of Mucosal Transmission (Basic Mechanisms); Discovery, Development, and Preclinical Testing (Preclinical Research); Formulations and Modes of Delivery (Formulation); Clinical Trials; Microbicide Behavioral and Social Science Research (Social Science); Microbicide Research Infrastructure; and Advocacy and Policy Development (Advocacy). 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.

APPENDIX 2

FUNDING INSTITUTIONS AND DEVELOPERS INCLUDED IN THE HIV VACCINE AND MICROBICIDE ESTIMATES

PUBLIC-SECTOR - COUNTRIES

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

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 | * Phoebe W. Haas Charitable Trust B | * James B. Pendleton Trust |
| * Bristol Myers Squibb Foundation | * Henry M. Jackson Foundation | * Perls Foundation |
| * Broadway Cares/Equity Fights AIDS | * John M. Lloyd Foundation | * Rockefeller Foundation |
| * Crusaïd | * John D. and Catherine T. MacArthur Foundation | * San Francisco AIDS Foundation |
| * Deutsche AIDS Stiftung | * James S. McDonnell Foundation | * Starr Foundation |
| * Ford Foundation | * Mercury Phoenix Trust | * Stichting Aids Fonds |
| * Bill & Melinda Gates Foundation | * Moriah Fund | * Tides Foundation/John Lee Fund |
| * Elizabeth Glaser Pediatric AIDS Foundation | * NY Community Trust | * Turner Foundation |
| * Gill Foundation | * Overbrook Foundation | * Until There's A Cure Foundation |
| * John & Marcia Goldman Foundation | * Parthenon Trust | * Vanderbilt Family Foundation |
| * Linda & John Gruber 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 | * Epimmune Inc. | * Novartis International AG |
| * AlphaVax Human Vaccines Inc. | * EpiVax, Inc. | * Novaflex Technologies |
| * AVANT Immunotherapeutics, Inc. | * FIT Biotech Oyj Plc. | * Osel, Inc. |
| * Bavarian Nordic | * GenVec, Inc. | * PAREXEL International Corporation |
| * Berna Biotech Ag | * Gilead Sciences | * Polydex Pharmaceuticals Ltd. |
| * Biofem, Inc. | * GlobeImmune, Inc. | * Progenics Pharmaceuticals, Inc. |
| * Bioption AB | * GeoVax, Inc. | * ReProtect LLC |
| * Bioqual Inc. | * Idenix Pharmaceuticals | * Starpharma Ltd. |
| * Cellegy/Biosyn, Inc. | * Impfstoffwerk Dessau Tornau GmbH | * Targeted Genetics Corporation |
| * Chiron Corporation | * ImQuest BioSciences | * Therion Biologics Corporation |
| * Cobra Pharmaceuticals Plc | * Indevus Pharmaceuticals, Inc. | * Tibotec Pharmaceuticals Ltd. |
| * Crucell N.V. | * Mapp Biopharmaceutical Inc. | * VaxGen, Inc. |
| * Dow Pharmaceutical Sciences | * MaxyGen, Inc. | * Vical Inc |

INTERMEDIARY AGENCIES

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

APPENDIX 3

DESCRIPTIONS OF THE FIVE VACCINE EXPENDITURE CATEGORIES

BASIC RESEARCH

Seeking correlates of immune protection for HIV-infected/highly exposed but seronegative

Developing in vitro tools to analyze vaccine responses

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

PRE-CLINICAL RESEARCH

Supporting novel vaccine design and testing for safety/ immunogenicity

Fostering collaboration between academia, industry, government agencies, and NGOs

Optimizing vaccine characteristics 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 candidates

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 in development

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 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)

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

Exploring alternative strategies for supporting R&D efforts and the purchase of HIV vaccines

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

DESCRIPTIONS OF THE SEVEN MICROBICIDE EXPENDITURE CATEGORIES

BASIC MECHANISMS OF MUCOSAL TRANSMISSION

Defining mechanisms of systemic/mucosal immunity

Developing in vitro tools to analyze microbicide 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

Discovery, Development And Pre-Clinical Testing

Supporting novel microbicide design and testing for safety/ immunogenicity

Fostering collaboration between academia, industry, government agencies, and NGOs

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 microbicide candidates

Developing reagents and standardized methods to assess microbicide-induced immune response in animals and humans

Conducting research on safety and regulatory considerations of 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

FORMULATIONS AND MODES OF DELIVERY

Optimizing microbicide characteristics and microbicide formulation for broad international use (cheap, easy to produce/administer, stable)

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 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)

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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)

MICROBICIDE RESEARCH INFRASTRUCTURE

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 microbicides

|
Exploring alternative strategies for supporting R&D efforts and the purchase of 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

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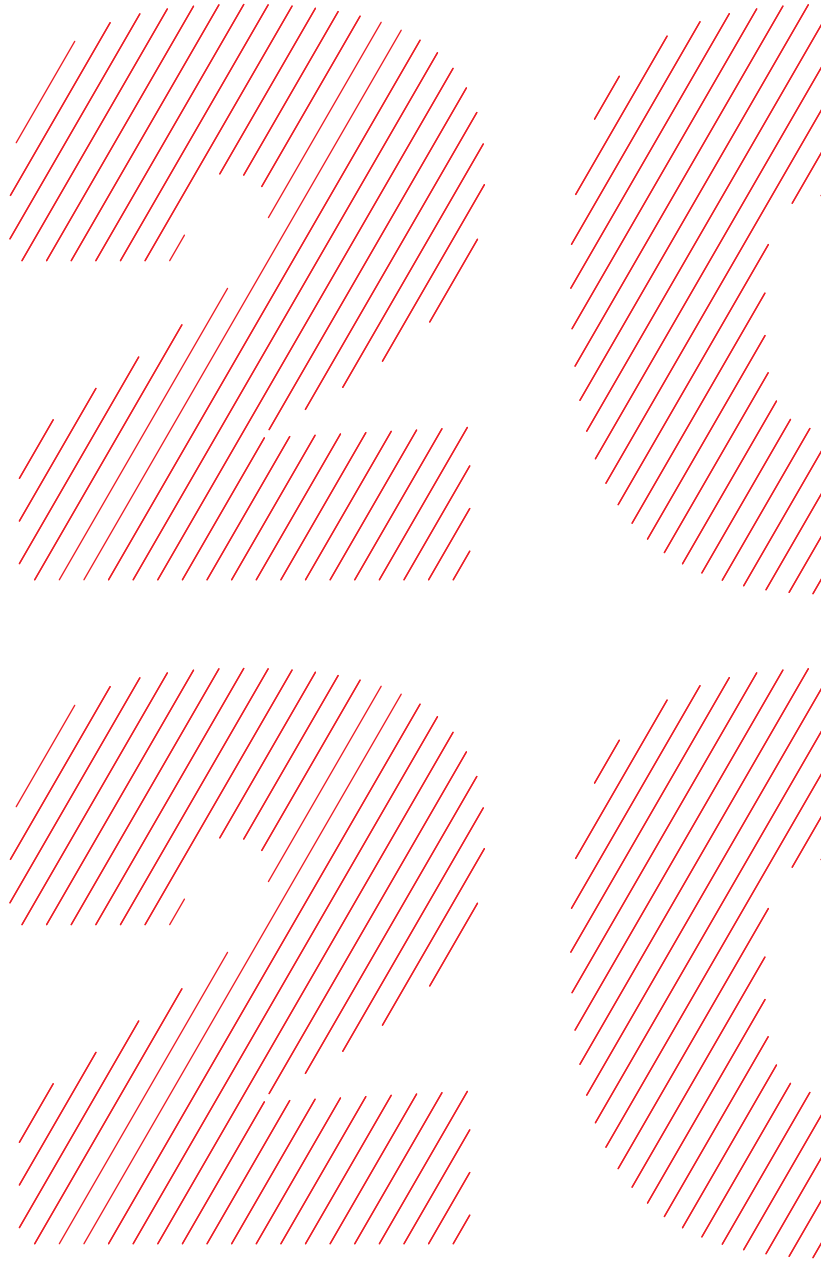
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- Resource Tracking Working Group – A Short History
- Canadian HIV Vaccine Initiative
- The Office of AIDS Research
- The Russian Vaccine Center
- European Commitment to New Prevention Technologies



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