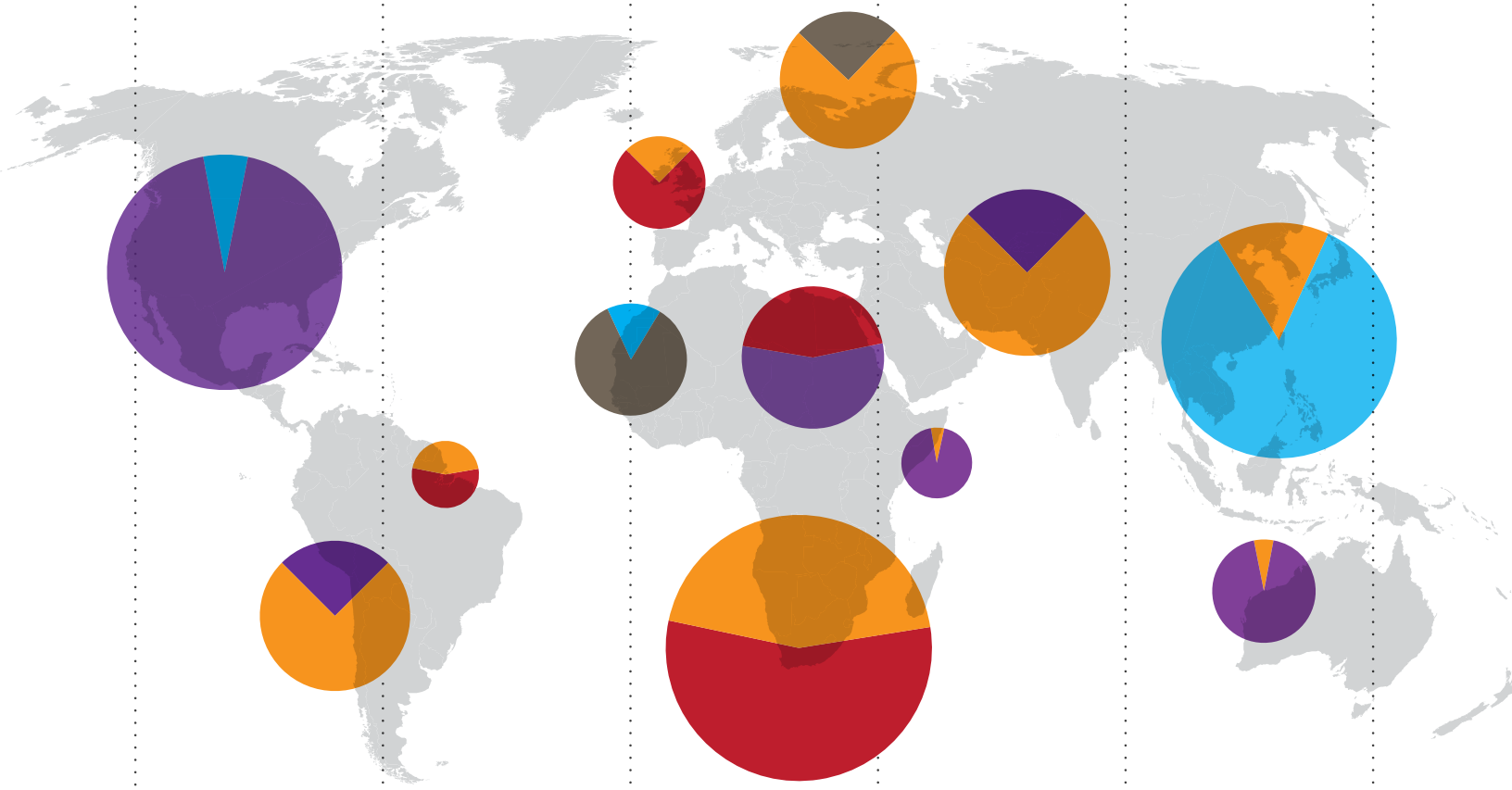
# From Research to Reality

## Investing in HIV Prevention Research in a Challenging Landscape

# 2013



HIV VACCINES
& MICROBICIDES
RESOURCE TRACKING
WORKING GROUP

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SUMMARY

# The US remains main contributor, call for broader global partnering

In 2012, reported funding for HIV prevention research and development (R&D) increased by six percent compared to 2011, reaching a total of US$1.31 billion. However, a significant portion of this increase is likely due to improved reporting by several donors. The actual increase is thought to be moderate, and the overall funding prospect is essentially one of stagnation.[a]

The US remained the largest public-sector investor overall, spending a total of US$925 million in 2012—70 percent of the total investment in HIV prevention R&D. European public-sector investment totaled US$86 million, other governments invested US$69 million, philanthropic organizations invested US$203 million and the commercial sector invested US$34 million.

**Over the past eight years total investment in HIV prevention R&D[b] reached nearly US$10 billion. Investment in HIV vaccine research accounted for nearly US$7 billion of that total and funding for microbicide research for almost US$2 billion.**

A more diverse global cadre of funders, both involved in and dedicated to advancing HIV prevention R&D, would better utilize global resources and represent a powerful force in the effort to bring down new infections. An expanded and more diversified investment base could draw on nontraditional sources, such as emerging economies and countries hosting clinical and other HIV prevention research, along with recommitted member states of the Organization for Economic Co-operation and Development (OECD), whose support for HIV prevention R&D has waned over the past several years.

The foundation for such efforts is in place. The HIV prevention field has worked to catalyze innovative partnerships across the public, private, philanthropic and academic sectors in order to capitalize on available resources and advance promising pipeline candidates. Still, greater efficiency and clarity in directing funding toward the most effective programs, and assuring that such investments are complementary rather than duplicative, would go a good distance toward optimizing investments across all areas of research. Always a desirable state of affairs, such participation, partnering, and shared processes for managing HIV prevention R&D must now become even more rigorous as economic and budgetary pressures become features of the global health research landscape that are unlikely to change in the near future.

[a] See Methodology in Appendix section for further details.
[b] The Working Group defines HIV prevention R&D as including funding for: preventive HIV vaccines; microbicides; pre-exposure prophylaxis; treatment as prevention; adult male circumcision; and prevention of vertical transmission. The Working Group also tracks annual investment in HSV-2 vaccine, female condom, HIV cure and therapeutic HIV vaccine R&D—these amounts are not included in the HIV prevention R&D total.

Box 1

## Trial Participants as Research Investors

HIV prevention research cannot be accomplished without those who volunteer to participate in clinical trials, or without engagement of communities in which those trials take place. In 2012, there were 99,931 participants in HIV prevention research trials, primarily based in sites with high HIV burdens in South Africa, Uganda and the US. Trial participants gain access to HIV programs through trials in which they participate. Additionally, assuming successful trial results, these are the populations most likely to be the first to receive any new safe and effective HIV prevention method ensuing from such research. But importantly, they are also the populations that have taken on the risks inherent in biomedical research and contributed their time, effort and commitment. Without their generous contributions to the field, research will not progress. There is no way to quantify the contribution of such participants in economic terms—it is both immeasurable and essential.

FIG. 1

### Trial Participants by Prevention Research Area in 2012

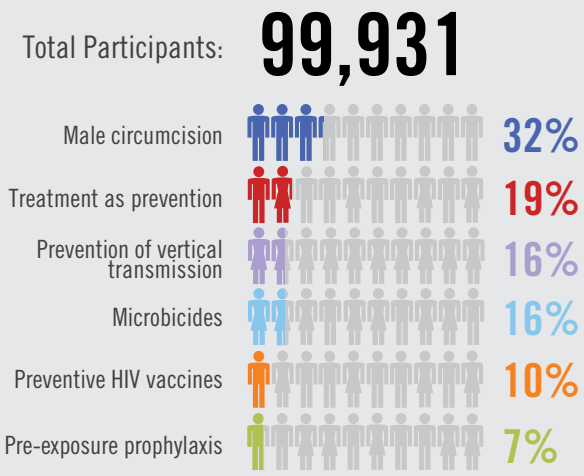
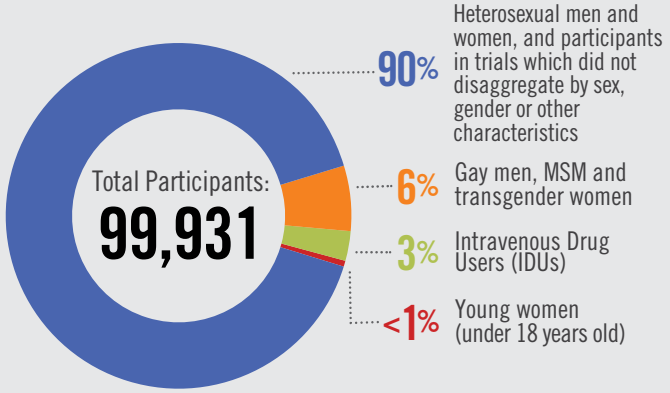



FIG. 2

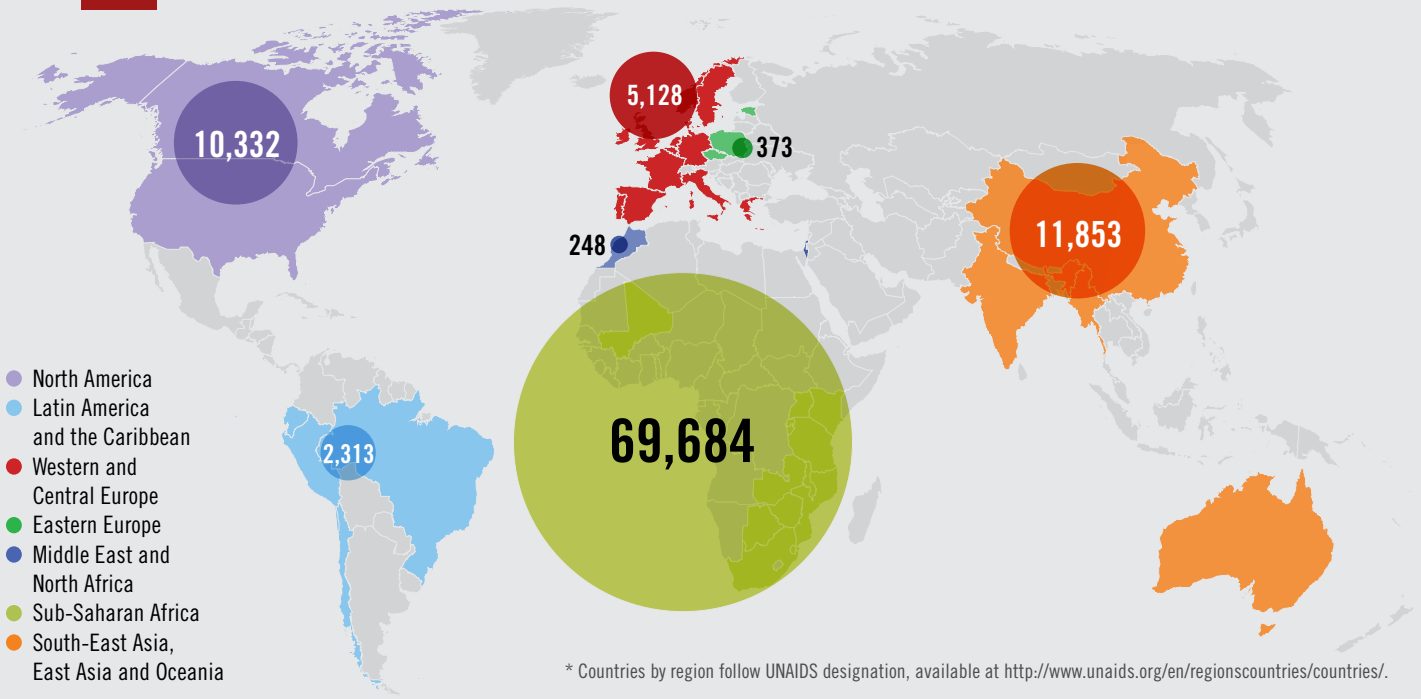
### Key Populations in HIV Prevention Clinical Trials in 2012*




*Approximation

FIG. 3

### HIV Prevention R&D Trial Participants by Region in 2012*




* Countries by region follow UNAIDS designation, available at http://www.unaids.org/en/regionscountries/countries/.

# 1.0 Introduction

## 1.1 Ending AIDS Is Possible: Context and perspectives

2012 saw a shift in the HIV/AIDS field toward a growing consensus that the end of the global epidemic is an attainable goal. HIV science has taken rapid strides toward new, safe and effective methods of prevention and treatment that have the potential to drive down infection rates. Yet, the fact that there are still 2.5 million new HIV infections globally each year[1] speaks to the need for continued investment implementing existing prevention modalities, while also developing new ones, in order to ultimately take that number to zero.[2]

Thirty years after the Institut Pasteur report of a new retrovirus, eventually dubbed the human immunodeficiency virus, or HIV,[3] challenging basic immunologic questions remain to be answered —and ultimately those answers need to be translated into new products and strategies and moved through the development pipeline. Meanwhile, late-stage trials of vaccine and microbicide candidates must continue to proceed in parallel with demonstration projects for pre-exposure prophylaxis (PrEP) and treatment as prevention, as well as the translational research needed to keep new concepts and products moving expeditiously through the pipeline.

The development of new HIV prevention tools will take place in the context of steady increases in research costs,[4] driven by the annual rise in the consumer price index,[5] and is likely to be of particular concern as new prevention interventions are rolled out, standards of care[6] and prevention[7] change, and larger numbers of trial participants are required for efficacy trials.[8] The road from scientific discovery to health impact has rarely been quick, easy or straightforward, but the track record of HIV research efforts, in terms of infections prevented and lives saved, underscores the importance of continued support for an expanded, more comprehensive set of tools.

## 1.2 HIV Prevention Science in 2012: Steady progress despite challenging results

Following the scientific breakthroughs of 2011, during which preventive HIV vaccines,[9] PrEP,[10, 11] and treatment as prevention[12] all advanced faster and further along the scientific path, 2012 was largely a year of follow-up research seeking to confirm results of past studies, move forward with new clinical research and roll out proven new prevention modalities. Even though 2012 brought steady progress, it also brought results that have both challenged the resiliency of the HIV prevention research field and raised new questions that the field is compelled to answer.

**Vaccines.** In September 2012, analysis of specimens from RV144, the first HIV vaccine clinical trial to show modest efficacy, offered additional clues as to how the vaccine may have worked.[13] The findings built on results published in April 2012,[14] showing that certain antibodies may have contributed to protection against HIV infection, whereas other antibodies may have mitigated the effects of protection. In light of these results, the year was one of planning and preparing for trials for the Pox-Protein Public-Private Partnership (P5), launched in 2010 to build on the RV144 results; trials are set to begin in Thailand and South Africa in 2016.

Box 2

### What the HIV Prevention R&D Field Learned in 2012:

- **ARV-based products work when used.** HIV prevention methods, including antiretroviral (ARV)-based products, can work, but it is impossible to prove their effectiveness when they are not used. PrEP trials showed that high levels of adherence to ARV use correlate with protection from HIV, but it also has become apparent that in many settings adherence will be difficult to achieve. Developing effective strategies to improve adherence is critical to maximizing impact of ARV-based prevention tools.
- **A vaccine is still needed as part of a combination prevention approach to end HIV/AIDS.** The UNAIDS Investment Framework models a strategic approach under which available HIV prevention tools can significantly drive down levels of new HIV infections, but not to zero. To control and ultimately end the pandemic a preventive vaccine needs to be added to a comprehensive prevention strategy.
- **The pipeline is robust.** All areas of HIV prevention R&D have promising and innovative candidates under development. The microbicide pipeline includes gels, rings, tablets and films, and exploration of dual and multipurpose technologies is accelerating; the PrEP pipeline includes long-acting injectable formulations; mounting evidence shows that expanding treatment, along with other interventions, has a major impact on the epidemic even at lower treatment coverage levels; and the preventive vaccine pipeline includes eight different strategies being tested in over 20 ongoing trials and several promising preclinical concepts in development.

A Phase IIb trial ongoing in 2012, HVTN505, was halted in April 2013 after an independent scientific review board determined that the DNA/rAd5 vaccine regimen being tested was not effective in preventing HIV infection. While not providing the answers hoped for by the field, the results allow for homing in on other vaccine strategies currently in development. In 2012, there were more than 30 vaccine candidates in Phase I trials, with new approaches continuing to enter clinical evaluation.

As in 2011, substantial progress was made in preclinical research on broadly neutralizing antibodies. New knowledge regarding the detailed structure of these antibodies, how they are produced by the immune system, and which sites they target on HIV is paving the way for the design of new vaccine candidates that can elicit these antibodies, and ultimately prevent HIV—in most of its variations—from establishing an infection.

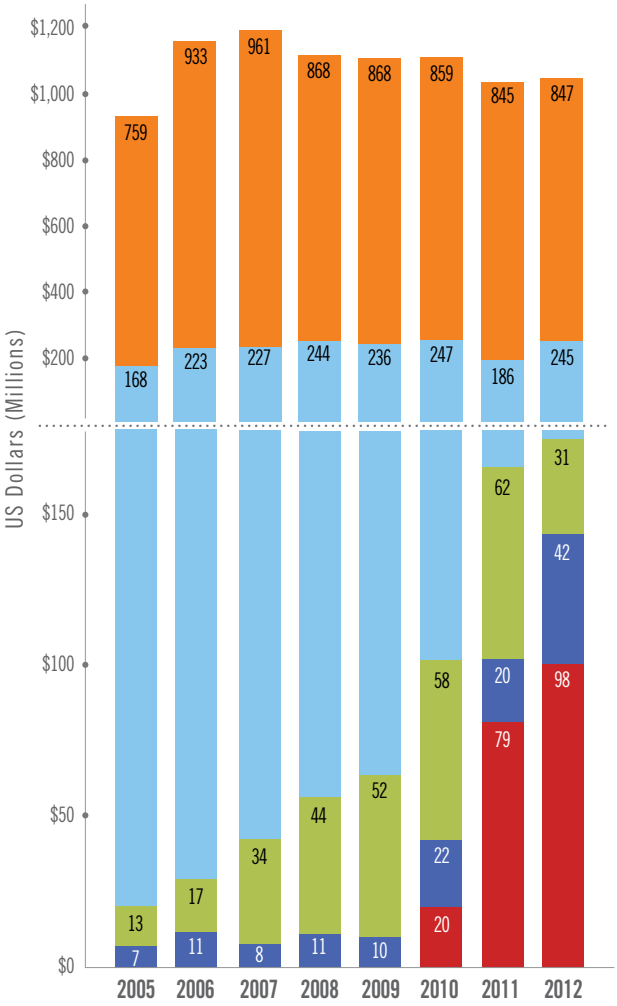
**Microbicides.** In March 2013, researchers from the VOICE (MTN 003) trial announced that none of the three interventions tested—daily oral tenofovir, daily oral TDF/FTC and daily 1% tenofovir gel—provided protection against HIV among the women in the study population. VOICE data are being examined, but preliminary results suggest that too few women in the trial adhered to prescribed use of the trial products to allow for evaluation of their effectiveness. Several factors may have contributed to the lack of effect seen in VOICE, but there is little doubt that low levels of adherence were a major contributor to trial failure.

**Pre-Exposure Prophylaxis.** In July 2012, the US Federal Drug Administration (FDA) announced approval of daily application of Gilead Science Inc.'s oral TDF/FTC as PrEP. Also in July 2012, the World Health Organization (WHO) released guidance for PrEP demonstration research trials in serodiscordant couples, men who have sex with men (MSM) and transgender women. Finally, the Southern African HIV Clinicians Society also issued guidance in 2012 for use of TDF/FTC as PrEP in gay men and other MSM—providing the first guidance from the Global South. PrEP demonstration projects advanced in 2012,[15] aiming to provide answers to questions around implementation and rollout.

**Treatment as Prevention.** Throughout 2012, implementers and normative agencies continued their efforts to add treatment as prevention to HIV prevention agendas and national strategies. The research field moved forward with additional studies to examine the health impact of earlier treatment and the population impact of treatment as prevention. This focus is reflected in continued funding increases—since the Working Group began tracking treatment as prevention, investment has increased exponentially. Large-scale trials are taking place in nearly 40 countries around the world, demonstrating a global commitment to explore the potential of treatment as prevention.

FIG. 4

## Global HIV Prevention R&D Investments 2005–2012




| HIV PREVENTION OPTION | TOTAL INVESTMENT 2005 – 2012 |
|---|---|
| Preventive Vaccines | US$7 billion |
| Microbicides | US$1.8 billion |
| Pre-Exposure Prophylaxis | US$0.3 billion |
| Adult Male Circumcision | US$0.1 billion |
| Treatment as Prevention | US$0.2 billion |
| Total 2005 – 2012 | US$9.4 billion |

Preventive Vaccines
Microbicides
Pre-Exposure Prophylaxis
Adult Male Circumcision
Treatment as Prevention*

* The Working Group began tracking funding for treatment as prevention in 2010.

Box 3

## US HIV/AIDS Prevention Research Investment

As of the end of 2012, the US Congress had made no progress toward resolving pressing budget issues, nor had it reached consensus on a strategy to avoid "sequestration"—automatic and widespread cuts to all federally-funded programs. HIV advocates in the US and supporters of global health and research rallied against the potential impacts of imminent five percent across-the-board funding cuts that would specifically affect almost all non-defense discretionary programs. Analysis by the Foundation for AIDS Research (amfAR), concluded that those cuts would cost the US National Institutes of Health (NIH) US$153.7 million in AIDS research funding, with 280 AIDS research grants going unfunded, 31 of which support AIDS vaccine research. The sequestration cuts not only threaten NIH-funded research, but would also negatively impact budgets of the US Centers for Disease Control and Prevention (CDC), the US Agency for International Development (USAID) and the Military HIV Research Program (MHRP) at the Department of Defense—all important funders of, and collaborators in, HIV prevention R&D.

These budget cuts would not only impact US funding for HIV prevention R&D in 2013, but are likely to have negative reverberations for years to come. Since the US is the largest funder of HIV research globally, these budgetary constraints may well have a crippling impact on innovation and overall progress in developing and delivering safe and effective prevention technologies.

TBL. 1

## HIV Prevention R&D Investment Snapshot for 2012[a]

| HIV Prevention Option | Amount 2012 | Amount 2011 | Change from 2011 | Headlines |
|---|---|---|---|---|
| Preventive Vaccines | US$847 million | US$845 million | +US$2 million (+0.2%) | Preventive HIV vaccine funding remained flat from 2011 to 2012. The year was one of planning and preparation, with the next large-scale efficacy trial on the horizon and a number of other concepts in early-stage development. In 2012, there was one ongoing, large-scale trial, HVTN505, testing a combination of two vaccine candidates. This trial was halted in April 2013; and its outcome may affect the make-up of the global pipeline, as the field is considering the value of pursuing similar vaccine approaches. A number of novel vaccine candidates entered Phase I studies in 2012 and substantial progress continued to be made in basic and preclinical research aimed at designing vaccines that can elicit broadly neutralizing antibodies. Finally, new knowledge obtained from further analysis of the RV144 trial results is building the scientific bedrock for the P5's follow-on trials in South Africa and Thailand, although protein manufacturing complications have delayed the expected starting date, now anticipated for 2016. |
| Microbicides | US$245 million | US$186 million | +US$59 million (+32%) | Microbicide funding increased significantly in 2012, with greater investment by all sectors—public, philanthropic and commercial. Although the VOICE trial did not provide the confirmation needed to advance 1% tenofovir gel, the FACTS 001 study evaluating the gel is continuing and the field is proceeding with other products as well. A critical lesson learned is that, absent sufficient levels of adherence to trial product use, there is so far no way to confidently evaluate product effectiveness. Thus, the microbicide field is focusing most intensely on candidate products more likely to promote adherence, such as vaginal rings, films and fast-dissolve tablets. Also being pursued are multipurpose technologies: combinations of products that have the potential to address more than one reproductive and sexual health need simultaneously. |
| Pre-Exposure Prophylaxis | US$31 million | US$62.3 million | -US$31.3 million (-50%) | Upon FDA approval in July 2012 of oral TDF/FTC for prevention of HIV in all adults, work in the PrEP field advanced from research to implementation. Thus, 2012 consisted of planning for demonstration projects to better understand how best to roll out PrEP and to which populations and to answer key questions around product use, delivery and access. |
| Adult Male Circumcision | US$42 million | US$20.3 million | +US$21.7 million (+107%) | 2012 saw intensified focus on faster rollout of adult male circumcision for maximum prevention impact. Funding for R&D and operations research increased, with an emphasis on research that would better inform delivery and demand and enhance understanding of current constraints. |
| Treatment as Prevention[b] | US$98 million | US$79.4 million | +US$18.6 million (+23%) | Funding for treatment as prevention research increased substantially in 2012, due largely to expanded efforts to develop an optimal strategy for integrating treatment as prevention into combination prevention programs. Treatment as prevention studies are ongoing in over 40 countries worldwide. As countries begin to include it in their national strategic plans, it is essential that research continue in order to show how to effectively expand access to treatment as prevention on a population scale. |
| **All HIV prevention R&D** | **US$1.31 billion** | **US$1.24 billion** | **+US$70 million (+6%)** | **Despite widespread budget constraints, global HIV prevention R&D spending virtually flatlined in 2012.** |

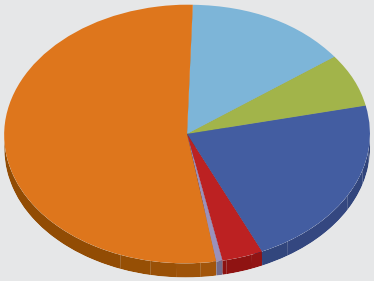
[a] Data reported in non-US currency were converted to US dollars using the 1 July 2012 currency exchange rate for 2012 amounts provided by the OANDA Corporation. Available at: http://www. oanda.com/currency/converter.

[b] The Working Group includes in its "treatment as prevention" investment figure that research which focuses on the primary outcome of transmission. Going forward, the Working Group will be developing a new "treatment as prevention" figure that includes all relevant research as recently defined by the WHO to include provision of, "antiretroviral therapy (ART) irrespective of CD4+ cell count for the prevention of HIV and TB, including provision of ART to people living with HIV who are: severely immunocompromised with AIDS and/or have a CD4+ count; ≤350 cells/mm3; those with higher CD4+ cell counts >350 cells/mm3." The Working Group's current definition of treatment as prevention and the WHO definition do not include use of antiretrovirals (ARVs) for post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PrEP) or ARV-based microbicides.

FIG. 5

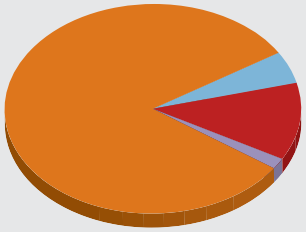
## Top Philanthropies Investing in HIV Prevention R&D: Philanthropic-sector investment in 2012*

BMGF
**US$160 million**



| BMGF | | Wellcome Trust |
|---|---|---|
| 86 | Preventive HIV Vaccines | 8.2 |
| 22.9 | Microbicides | 0.5 |
| 10.6 | Pre-exposure Prophylaxis | 0 |
| 34.2 | Adult Male Circumcision | 0 |
| 5.8 | Treatment as Prevention | 1.2 |
| 0.5 | Prevention of Vertical Transmission | 0.15 |

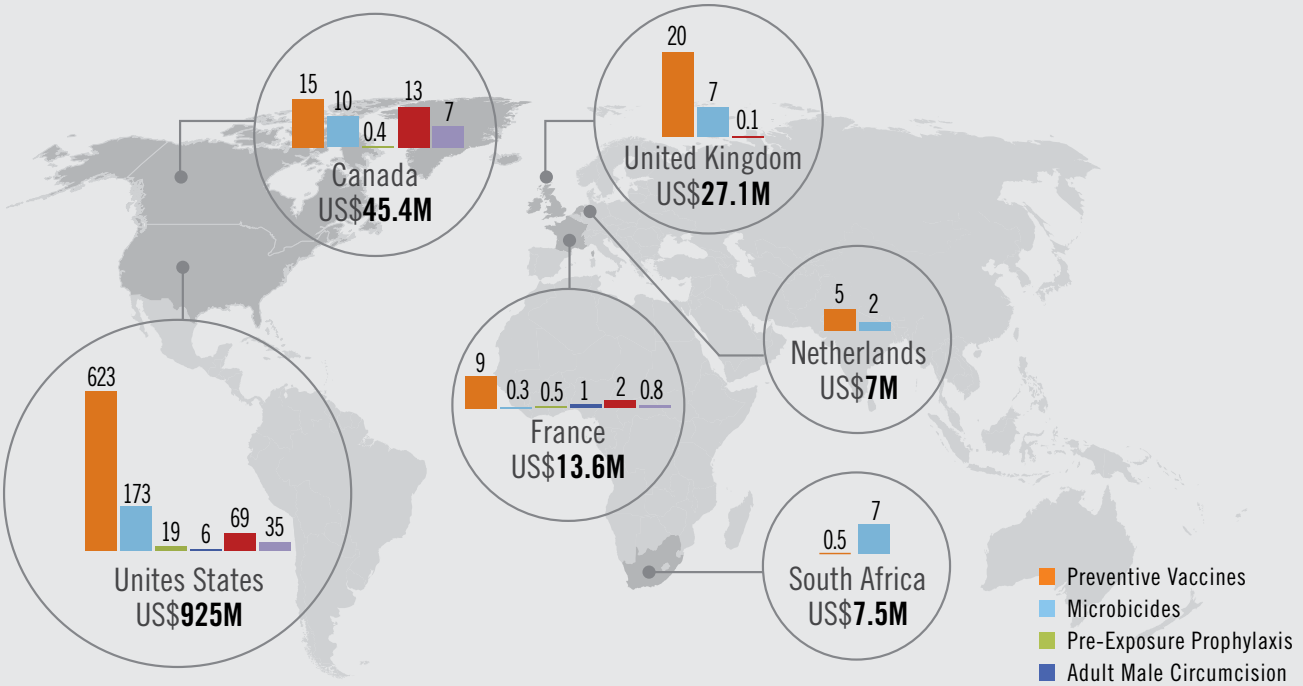
Wellcome Trust
**US$10 million**



*Numbers may be rounded.

FIG. 6

## Top Countries Investing in HIV Prevention R&D: Public-sector investment in 2012*

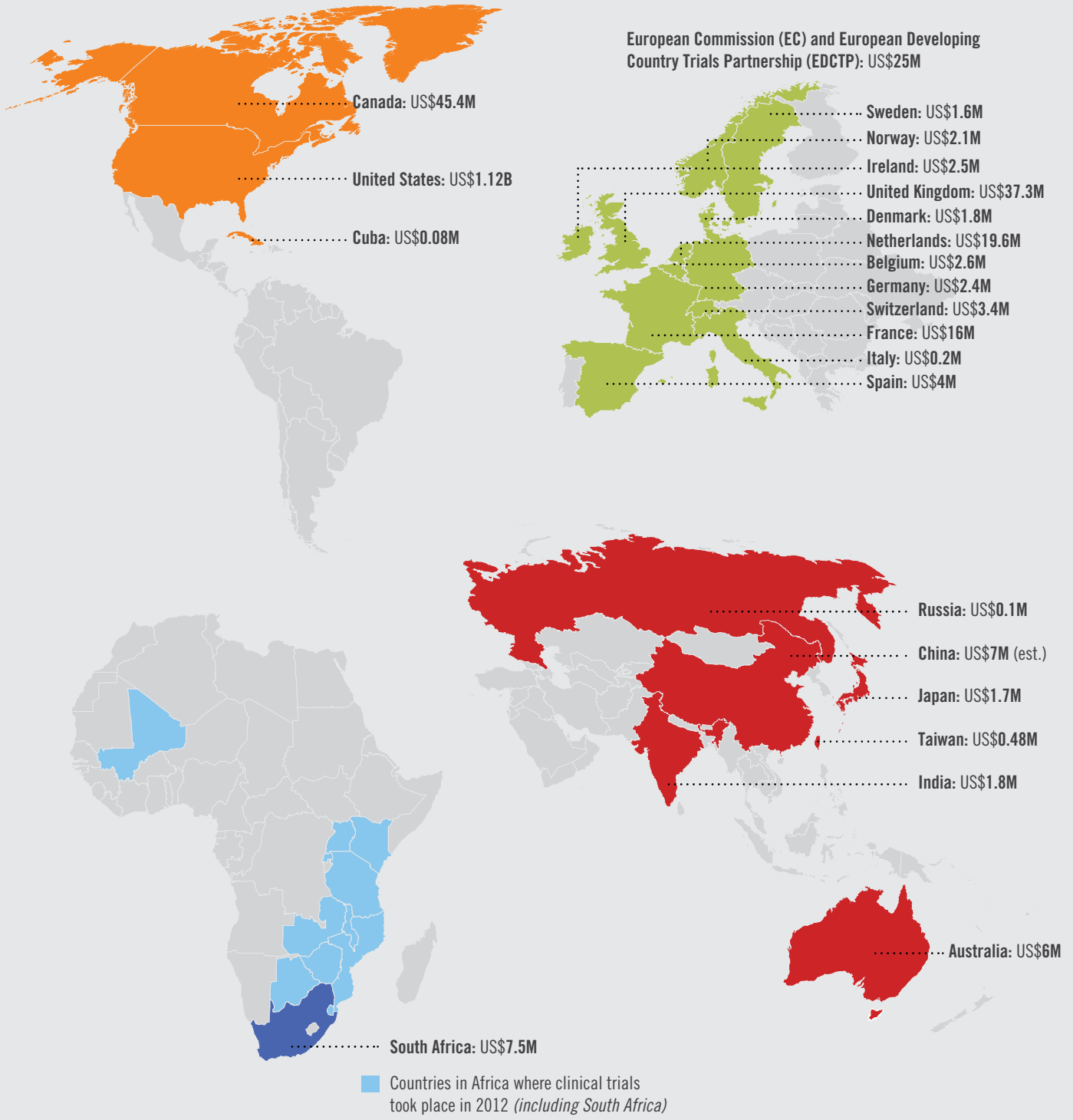



*Numbers may be rounded.

FIG. 7

## 2012 Global Investment in HIV Prevention R&D by Region

Public-, philanthropic- and commercial-sector funding from countries investing in HIV prevention R&D*




*Information collected includes funding from those agencies, organizations and companies within countries that responded to the Working Group's annual survey, or where public information on sources of funding was available. Commercial sector investment is underestimated due to a lack of reporting by companies.

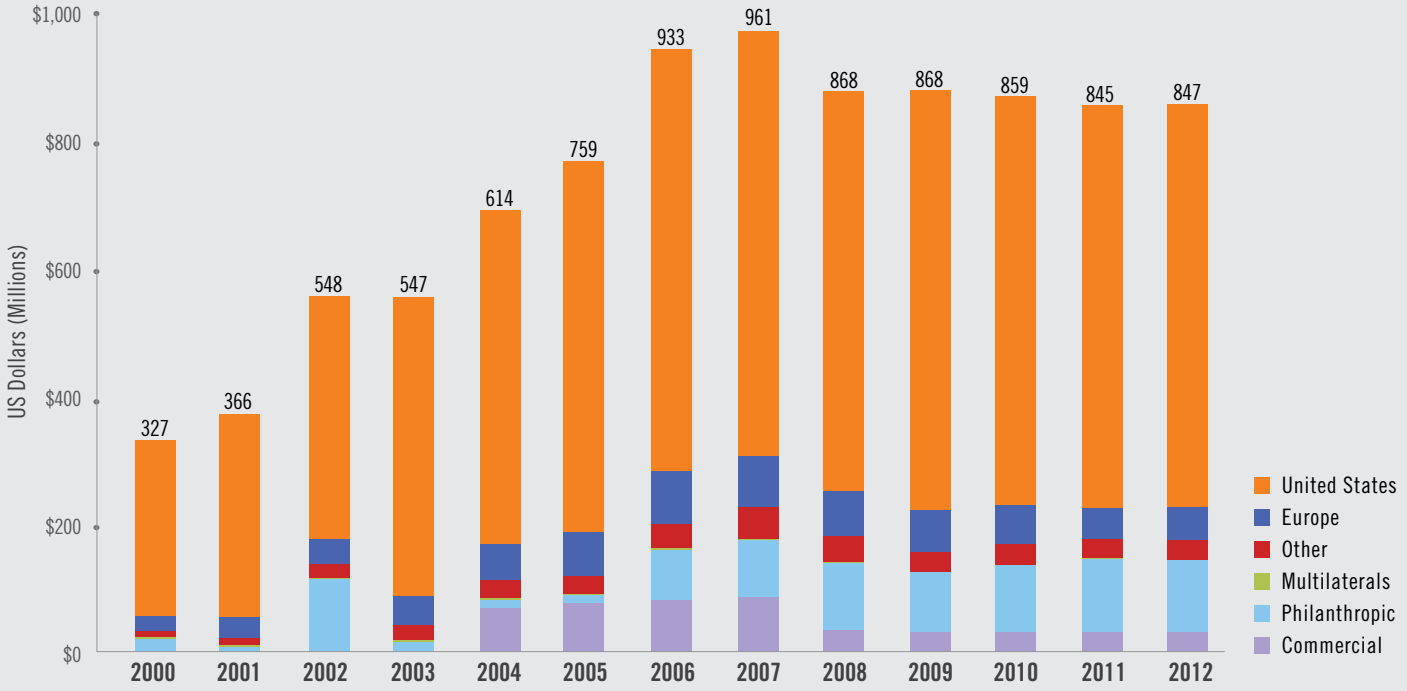
# 2.0 HIV Prevention Research & Development

## 2.1 Global Investments in HIV Vaccine Research & Development

In 2012, investments in global preventive HIV vaccine R&D were virtually flat—increasing by just US$2 million over the previous year to total US$847 million. While funding has gradually declined since 2007, the field has responded with attempts to increase efficiency by forming collaborations to better utilize the collective knowledge and research infrastructure of organizations and institutions globally.

Four years ago, the vaccine regimen used in the RV144 trial in Thailand showed 31.2 percent efficacy against HIV infection by the end of the study, providing the first evidence that a safe and effective preventive HIV vaccine is possible. Analysis of the study in 2012 and early-2013 provided additional insight into the vaccine's effectiveness. Collaborating researchers from the MHRP, the National Institute of Allergy and Infectious Diseases (NIAID) of the NIH, Duke University and the Thai Ministry of Public Health, along with 25 other institutions, discovered immune response clues that may have played a role in protecting some trial volunteers from HIV, finding that different types of antibody responses were associated with a higher or lower rate of HIV infection. Further research confirmed these results and provided insights into variables that may have influenced the efficacy seen in RV144. These findings have sparked new research, including a trial to see if the results can be repeated and improved in a high-incidence setting, an adaptive design trial looking at multiple vaccine candidates and an efficacy trial using the same regimen as in RV144 in an MSM population in Thailand.

FIG. 8 **HIV Vaccine Funding 2000–2012**
(US$ millions)



Box 4

### Pox-Protein Public-Private Partnership Advancements

The Pox-Protein Public-Private Partnership (P5) was established in 2010 to build on the results of RV144 and to advance and, eventually, license HIV pox-protein vaccine candidates. The partnership consists of the MHRP, the US NIAID, the BMGF, the HIV Vaccine Trials Network (HVTN), Sanofi Pasteur and Novartis Vaccines and Diagnostics. In 2012, the MHRP invested US$5 million of its budget in the P5 effort, representing just four percent of overall funding for the field but leading to one of the field's signature successes.

A clinical trial has already begun to re-boost some of the volunteers in the RV144 trial to see if the immune responses can be sustained and improved. The P5 has also outlined plans for two trials in South Africa and Thailand that could lead to licensure, in addition to a Southern Africa discovery trial with an adaptive design to obtain information on multiple vaccine combinations. The timelines for these trials have continued to change, as the products and trial designs evolve.

With more than 30 candidates moving forward in clinical trials, basic research to identify biological mechanisms that can be translated into new vaccine candidates has increasingly become a focus in the HIV vaccine field. Research funded by several of the largest investors—including the US NIH, the International AIDS Vaccine Initiative (IAVI) through USAID, the Bill & Melinda Gates Foundation (BMGF) and private pharmaceutical and biotechnology companies—is enabling the discovery and further study of broadly neutralizing antibodies that block the HIV virus' ability to infect cells. Analysis of the structure and evolution of antibodies and the way that they bind to HIV is being used to design new antigens to elicit antibodies through vaccination. Human clinical trials to test these concepts are in planning stages.

In 2012, the BMGF and US NIH invested a significant portion of their resources in antibody-related research. Other major funders of antibody-related research include the European Commission (EC), and the government of the Netherlands. Investments in antibody-related research were especially crucial for collaborations seeking to utilize expertise across different organizations, such as NIAID's Centers for HIV/AIDS Vaccine Immunology & Immunogen Discovery (see Box 5), the IAVI-coordinated Neutralizing Antibody Consortium (NAC) and the European Consortium on Neutralizing Antibodies Using gp41 (EuroNeut-41).

Excitement about advances along the entire HIV vaccine research continuum in 2012 and prior years was tempered by the early futility finding in April of 2013 from the HVTN 505 vaccine trial. Immunizations under HVTN 505, the only large ongoing efficacy trial of a candidate vaccine, were halted by its Data Safety and Monitoring Board due to milestone findings that the vaccine used in the trial was not effective. The trial, funded by the US NIH, was estimated to cost between US$75 million and US$80 million.[16]

Box 5

### Centers for HIV/AIDS Vaccine Immunology and Immunogen Discovery

In 2012, the US NIH's NIAID awarded US$31 million to Duke University and the Scripps Research Institute, which led to the creation of two new Centers for HIV/AIDS Vaccine Immunology & Immunogen Discovery (CHAVI-ID). The project will receive upward of US$186 million over the next six years to accelerate HIV vaccine development by supporting multidisciplinary research into immune responses that protect against HIV infection and generate vaccine components capable of inducing protective immune responses.

At Duke, awarded US$19.9 million in 2012, researchers will identify and target vulnerabilities of HIV to immune responses and design vaccines that induce protective immunity at the site of HIV transmission. The work will largely focus on inducing broadly neutralizing antibodies to prevent HIV infection, as well as on generating protective T-cell and innate immune system responses.

At Scripps, awarded US$11.1 million in 2012, researchers will conduct B-cell and antibody research in animal models. The scientists will study the ability of CD4-positive T-cells to help other cells produce antibodies.

Already releasing promising results in the second quarter of 2012, scientists at both institutes have made important discoveries about how to induce broadly neutralizing antibodies.[a,b]

[a] H Liao, R Lynch, T Zhou et al. Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus. Nature 496;469–476(2013).
[b] J Jardine, JP Julien, S Menis et al. Rational HIV immunogen design to target specific germline B cell receptors. Science 340 (6133); 711-716(2013).

TBL. 2

## Annual Investments in HIV Vaccine R&D 2006 – 2012 (US$ millions)[a,b]

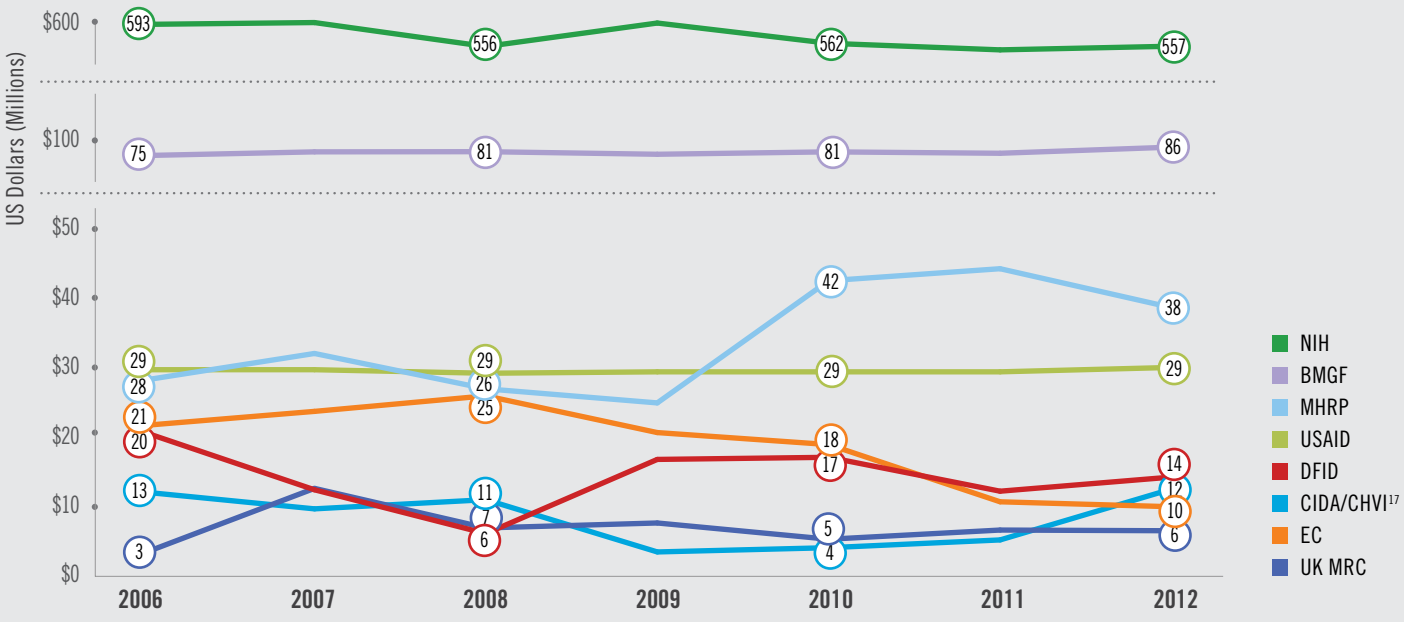
| | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|
| **PUBLIC SECTOR** | | | | | | | |
| US | 654 | 659 | 620 | 649 | 632 | 615 | 623 |
| Europe | 82 | 79 | 69 | 65 | 61 | 48.5 | 52 |
| Other | 38 | 49 | 41 | 31 | 32 | 30 | 31 |
| Multilaterals | 2 | 2 | 1 | 1 | 1 | 0.5 | 0.5 |
| **Total public** | **776** | **789** | **731** | **746** | **726** | **702** | **707** |
| **PHILANTHROPIC SECTOR** | | | | | | | |
| **Total philanthropic** | **78** | **88** | **104** | **92** | **103** | **113** | **110** |
| **NON-COMMERCIAL SECTOR** | | | | | | | |
| **Total non-commercial** | **854** | **877** | **835** | **838** | **829** | **815** | **817** |
| **COMMERCIAL SECTOR** | | | | | | | |
| **Total commercial** | **79** | **84** | **33** | **30** | **30** | **30** | **30** |
| **Total global investment** | **933** | **961** | **868** | **868** | **859** | **845** | **847** |

[a] Numbers may be rounded.

[b] Data submitted in currency other than US$ is converted using a 1 July 2012 conversion rate; otherwise, inflation is not taken into account.

FIG. 9

## Top Preventive HIV Vaccine Funder Trends 2006–2012




*Numbers may be rounded.

### 2.1.1 Public Investments in HIV Vaccine Research & Development

Public-sector funding for preventive HIV vaccine research has accounted for the majority of investments since the inception of vaccine research programs. In 2012, public-sector funding increased nominally to total US$707 million—US$5 million more than in 2011. Public-sector funding made up 83 percent of the total HIV vaccine investment in 2012. Despite the negative effects of a constrained global economy on funding for medical R&D, both US and European funding for preventive HIV vaccines was maintained at similar levels, with 2012 seeing a slight overall increase over 2011, but still significantly less than in prior years.

US government agencies alone accounted for 74 percent of total HIV vaccine R&D funding, with the US NIH contributing 66 percent of the total. The US NIH increased its investments in 2012 by US $6.6 million. NIH provided funding for more than two-thirds of the more than 30 ongoing HIV vaccine clinical trials in 2012. While US investment increased in 2012, sequestration could lead to cuts of as much as five percent from the budgets of those federal agencies supporting HIV vaccine research, with unclear implications for the HIV vaccine field. Public agencies in six countries increased their investment from 2011 to 2012: the Australian Research Council (ARC); Australia's National Health and Medical Research Council (NHMRC); the Canadian Institutes of Health Research (CIHR); the Canadian HIV Vaccine Initiative (CHVI)[17]; the Netherlands Ministry of Foreign Affairs; the UK Department for International Development (DFID); and the US NIH;. The United Kingdom (UK) and Canada were

TBL. 3

**Top HIV Vaccine Funders 2010 – 2012 (US$ millions)[a]**

| 2010 Rank | Funder | Amount | 2011 Rank | Funder | Amount | 2012 Rank | Funder | Amount |
|---|---|---|---|---|---|---|---|---|
| 1 | NIH | 561.6 | 1 | NIH | 550.4 | 1 | NIH | 557.0 |
| 2 | BMGF | 80.9 | 2 | BMGF | 78.5 | 2 | BMGF | 86.0 |
| 3 | MHRP | 41.6 | 3 | MHRP | 43.3 | 3 | MHRP | 37.8 |
| 4 | USAID | 28.7 | 4 | USAID | 28.7 | 4 | USAID | 28.7 |
| 5 | EC | 19.9 | 5 | DFID | 11.8 | 5 | DFID | 14.0 |
| 6 | Chinese Government | 18.3 | 6 | Ragon Foundation | 10.0 | 6 | CHVI[17] | 12.0 |
| 7 | DFID | 16.6 | 7 | EC | 10.3 | 7 | Ragon Foundation | 10.0 |
| 8 | Ragon Foundation | 10.0 | 8 | ANRS | 7.3 | 8 | EC | 8.4 |
| 9 | ANRS | 6.6 | 9 | Chinese Government | 6.9 | 9 | Wellcome Trust | 8.2 |
| 10 | Wellcome Trust | 5.1 | 10 | Wellcome Trust | 6.5 | 10 | China[b] | 7.0 |
| 11 | UK MRC | 5.0 | 11 | UK MRC | 6.2 | 11 | MRC | 6.2 |
| 12 | EDCTP | 4.5 | 12 | CHVI | 5.8 | 12 | Institut Pasteur | 4.8 |
| 13 | CIDA | 3.8 | 13 | CIDA | 4.9 | 13 | The Netherlands | 4.8 |
| 14 | AECID | 3.6 | 14 | NHMRC | 3.9 | 14 | NHMRC | 4.4 |
| 15 | Norad (Norway) | 2.5 | 15 | The Netherlands | 3.8 | 15 | ANRS | 4.0 |

[a] See appendix for list of acronyms.
[b] The Working Group did not receive a response from China regarding investments made in 2012; thus, an estimate was developed and sent to China's National Center for AIDS/STD Control and Prevention. The estimate was developed based on public information submitted by the National Center for AIDS/STD Control and Prevention and China's Center for Disease Control and Prevention on clinicaltrials.gov regarding a Phase II preventive HIV vaccine trial started in August 2012, as well as other basic research underway.

Box 6

### Taiwan-NAC Collaboration

Taiwan, China, spends close to three percent of its annual gross domestic product on R&D, among the highest in Asia. Taiwan's National Science Council (NSC) carries out Taiwan's science and technology efforts as articulated in its "National Science and Technology Development Plan," which it redrafts every four years to guide priorities across the government agencies engaging in research. The NSC oversees funding of more than 14,000 research projects each year, across five major scientific areas: engineering and applied sciences; life sciences; natural sciences; the humanities and social sciences; and science education.

In 2012, the NSC formally joined the global effort to develop an HIV vaccine by providing a three-year grant of approximately US$1.5 million to the global research program on HIV vaccine design at Taipei's research institute, the Academia Sinica. The grant is part of a collaboration between Academia and the IAVI Neutralizing Antibody Center (NAC) at the Scripps Research Institute and is focused on the design and synthesis of carbohydrate-based HIV vaccines. Building on the recent discovery of dozens of broadly neutralizing antibodies against HIV led by the NAC and NIAID's Vaccine Research Center, the collaboration is looking at the design of glycans-based antigens that could be utilized in HIV vaccine candidates meant to elicit such broadly neutralizing antibodies.

once again the second- and third-largest public-sector contributors, investing US$20 million and US$15 respectively.

Funding from the EC has declined dramatically in recent years. In 2010, the EC invested US$20 million in HIV vaccine R&D and in 2011 EC funding decreased to US$10 million. In 2012, the investment declined further by US$2 million. 2013 will be the last year of funding from the EU's Seventh Framework Programme (FP7). The EC has proposed a significant increase in EU's investment in all areas of research and innovation, through a program called Horizon 2020. However, budget negotiations with member states are still ongoing and it remains to be seen if the EU budget will include a significant increase in funding for HIV vaccine and other HIV prevention research.

Box 7

### South-South HIV Vaccine Research Collaboration

The bilateral Indo-South Africa partnership, focusing on preventive HIV vaccine research, was launched at the end of 2010. The project involves research groups from both countries and is looking at designing antibodies against clade C of the virus, which accounts for 90 percent of infections in India and South Africa. Additionally, the partnership aims to identify T-cell epitopes associated with control of viral replication in Indian and South African populations and to compare immunogenicity of novel Indian and South African HIV-1 subtype C envelope peptide and recombinant protein constructs.

In India, the project was initiated by the Ministry of Science and Technology, under the auspices of the Department of Science and Technology and the Indian Medicinal Chemistry Program—a joint initiative of the Department of Biotechnology (DBT) and IAVI. Between 2011 and 2014, through the DBT and the Indian Council of Medical Research, India will contribute US$740,000 to the collaboration.

TBL. 4

**Philanthropic Investment in HIV Vaccine R&D by Foundations and Commercial Philanthropy in 2012 (US$ millions)**[a]

| Amount | Investors |
|---|---|
| **US$86 million** | BMGF |
| **US$5 million to US$10 million** | Ragon Foundation, Wellcome Trust |
| **US$1 million to US$5 million** | Starr Foundation |
| **US$500,000 to US$1 million** | New York City Economic Development Corporation |
| **US$250,000 to US$500,000** | Aids Fonds, Fundació la Caixa, GSK, Institut Mérieux, Sidaction |
| **<US$250,000** | amfAR, Broadway Cares/Equity Fights AIDS, Carlsberg Corporation, Fundación Lilly, Gilead Foundation, Glickenhaus Foundation, James B. Pendleton Charitable Trust |

Box 8

### Wellcome Trust

The Wellcome Trust focused its investments largely on research into broadly neutralizing antibodies in 2012. In 2011 and 2012 the Trust also funded the first clinical trial of an injectable vaccine containing an envelope protein, gp140. The trial, Mucovac2, brought together researchers from St George's University London, Imperial College, Hull York Medical School, the Medical Research Council (MRC) and the Infectious Disease Research Institute (IDRI). The trial was funded under the Grand Challenges in Global Health Initiative,[a] and and also received funding from the UK HIV Vaccine Consortium (UKHVC).

While the Trust has invested substantial resources into preventive HIV vaccine research, other significant efforts have centered on capacity building and supporting universities and scientists in developing countries to build robust infrastructure and research programs. General capacity building is not an area that's covered in the Working Group's categories, but it has a significant impact on the ability of researchers from the Global South to play a role in scientific innovation.

[a] The Grand Challenges in Global Health Initiative is supported by a US$450 million commitment from the BMGF, a US$27.1 million commitment from the Wellcome Trust and US$4.5 million from the Canadian Institutes of Health Research (CIHR). The initiative is managed by the Foundation for the National Institutes of Health (FNIH), the BMGF, the Wellcome Trust and CIHR.

## 2.1.2 Philanthropic Investments in HIV Vaccine Research & Development

Investment from the philanthropic sector decreased by US$3 million in 2012 accounting for US$110 million, 13 percent, of the total funds disbursed for preventive HIV vaccine R&D. The BMGF has been the top philanthropic funder in this area for over a decade, investing US$86 million in 2012. The BMGF has held its investment in preventive HIV vaccine R&D roughly steady since 2006, but in 2012 the BMGF exceeded its highest level of funding, which had been at US$81.2 million since 2008. The Ragon Foundation and the Wellcome Trust ranked second and third at US$10 million and US$8 million respectively in 2012.

## 2.1.3 Commercial Investments in HIV Vaccine Research & Development

Commercial-sector funding for preventive HIV vaccine R&D totaled US$30 million in 2012, making up approximately three percent of the total global investment in vaccine R&D. Several large pharmaceutical companies have historically invested in preventive HIV vaccine research, and biotechnology firms are increasingly engaging in R&D efforts; yet, apart from a few companies, commercial-sector engagement is waning. Once robust programs by Merck & Co. and GlaxoSmithKline (GSK) have scaled back from prior years and biotechnology research is largely conducted with funding from the public sector.[18]

Multinational pharmaceutical companies engaging in substantial research efforts include Novartis International AG, Sanofi Pasteur and Crucell. Each has participated in public-private partnerships, contributing expertise to the development and manufacture of vaccines.

Novartis collaborated with the National Center of the Istituto Superiore di Sanità (ISS) in Italy, supplying envelope proteins for the first phase of clinical testing of a preventive HIV vaccine. The company also continued its research into adjuvants for use as a boost to the ALVAC vaccine for the RV144 follow-on trials as part of the P5. Sanofi Pasteur, also part of the P5, is contributing its vaccine ALVAC to the trial, as well as the company's expertise. Crucell is collaborating with the Beth Israel

Deaconess Medical Center (BIDMC), the Ragon Institute, the Walter Reed Army Institute of Research, HVTN and IAVI to look at several prime-boost combinations of its Ad26 adenovirus vector.

The biotechnology firm GeoVax is developing plans for a Phase II trial of the company's promising DNA vaccine, set to begin in 2014 upon completion of a Phase I safety study, GeoVax is working with HVTN on the study design and protocol. While GeoVax is responsible for securing funding for part of the trial, public-sector funding from the NIH supports the trials conducted at the HVTN.

### 2.1.4 Funding Allocations for HIV Vaccine Research & Development

In 2012, spending by the public and philanthropic sectors on preventive HIV vaccine R&D was allocated to five categories: basic research (28 percent); preclinical

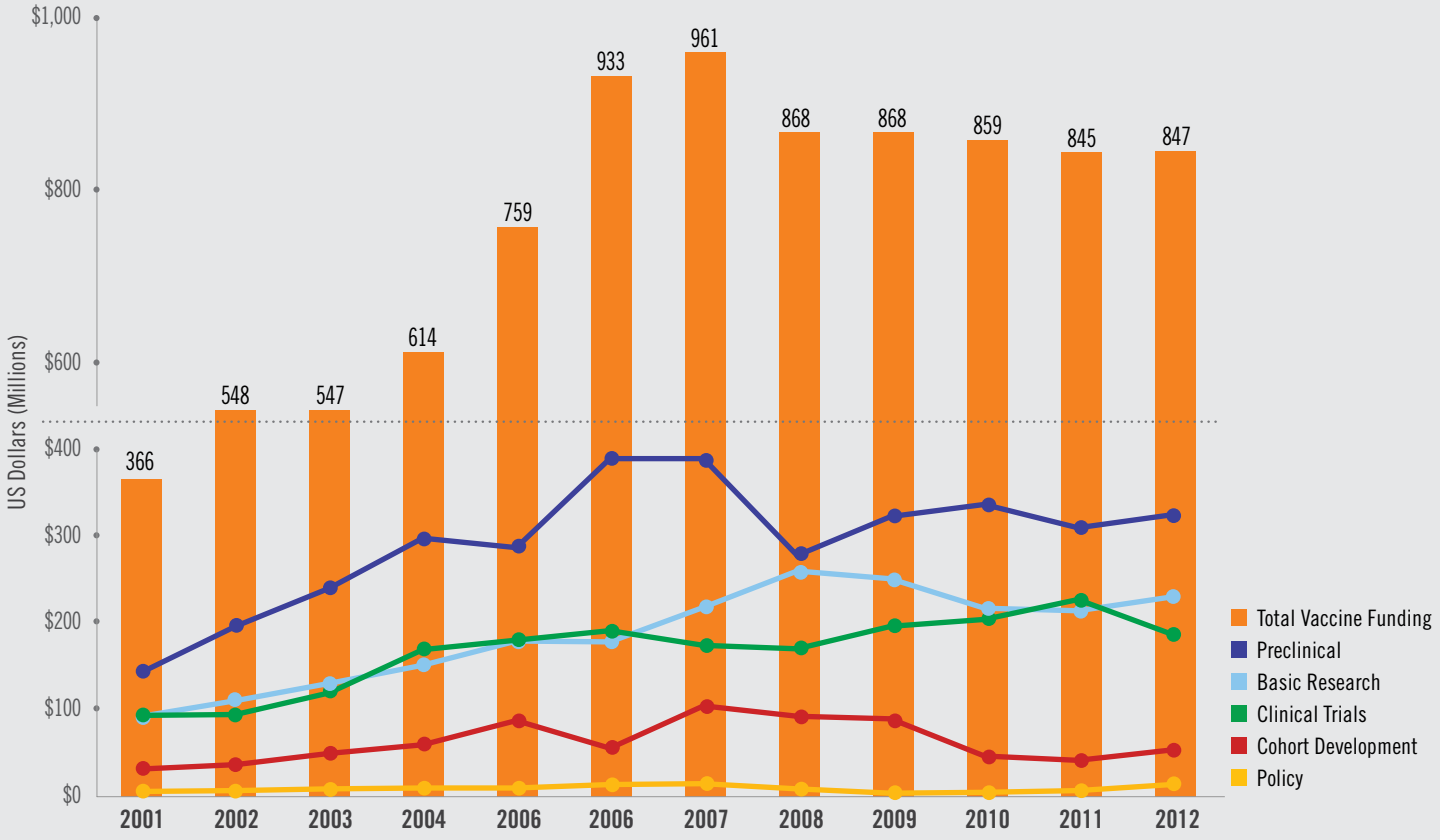
TBL. 5

**Estimated Commercial Engagement in HIV Vaccine R&D by Company in 2012**

| Amount | Investors |
|---|---|
| **US$5 million to US$10 million** | Crucell, Novartis International AG, Sanofi Pasteur |
| **US$1 million to US$5 million** | ESTEVE, GSK, Merck & Co, Mymetics |
| **US$100 thousand to US$1 million** | Advanced BioScience, Argos Therapeutics, Bionor Immuno, FIT-Biotech, Genvec, GeoVax, Ichor, Inovio Pharmaceuticals, Vical |

FIG. 10

**HIV Vaccine Expenditures 2001–2012**
(US$ millions)




*With the exception of "policy and advocacy," these are the categories used by the NIH to categorize HIV vaccine research. Because not all data from funders permits the allocation according to these five categories, these percentages were estimated from an US$809 million subset that did permit such allocations.

research (40 percent); clinical trials (23 percent); cohort and site development (7 percent); and advocacy and policy (2 percent). The percentage distribution of investment among the five categories in 2012 was similar to that of 2011 with a small decrease in clinical research and an increase in cohort and site development and advocacy and policy. Further information about the categories used to define R&D can be found in Table 12 of the Methodology section of the Appendix.[19]

## 2.2 Global Investments in Microbicide Research & Development

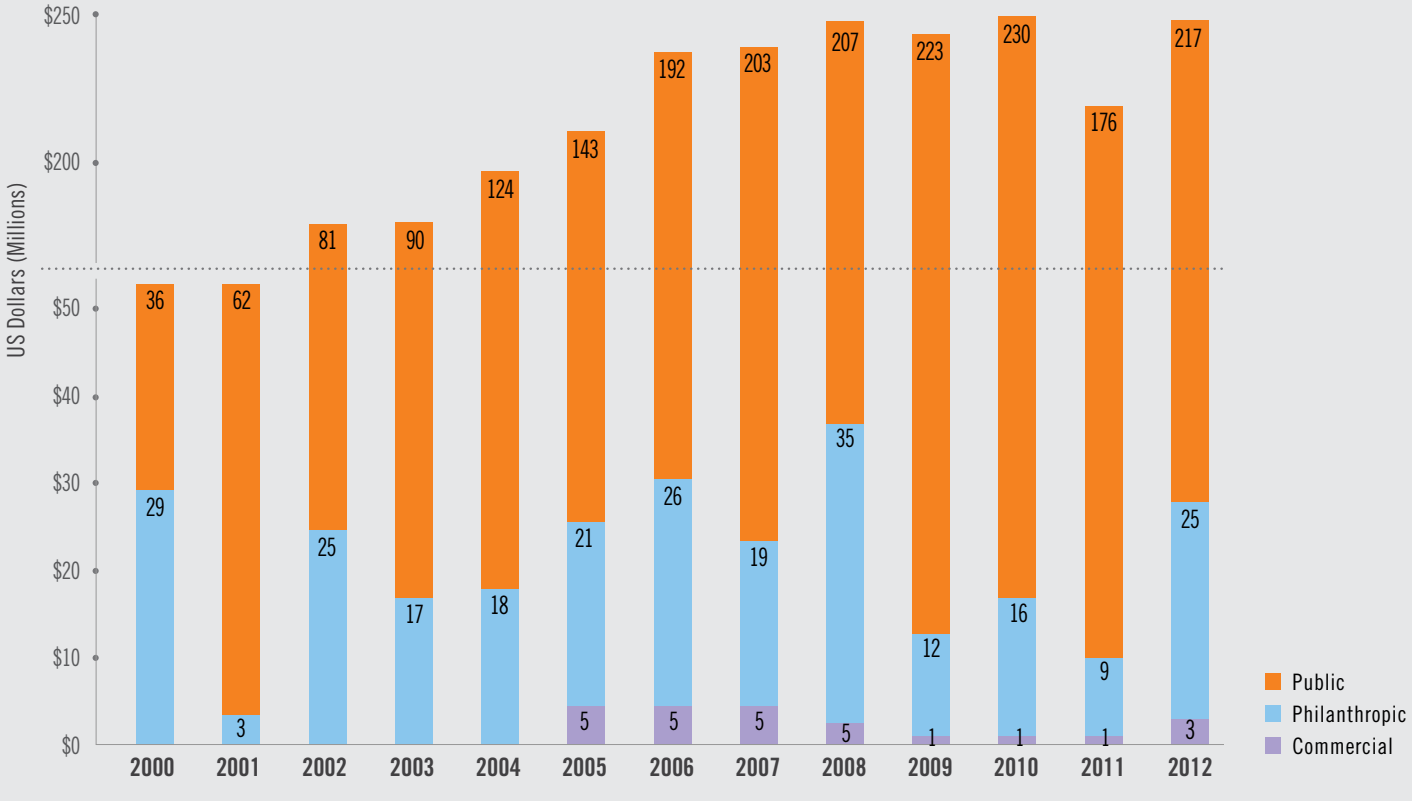
Global investment in microbicide R&D grew by US$59 million from 2011 to 2012 to a total of US$245 million. Of the 2012 total, the public sector provided US$217 million (89 percent); the philanthropic sector, US$25 million (10 percent); and the commercial sector, US$3 million (1 percent). While funding grew in all sectors in 2012, the largest increases came from major public and philanthropic donors.

Public-sector funding grew by US$41 million over the 2011 level, reflecting substantial increases in funding from the US NIH and USAID. The US public sector was the largest source of microbicide funding overall in 2012, increasing by US$25 million to total US$173 million.

As for the philanthropic sector, the BMGF also substantially increased its contribution in 2012, to nearly US$22.9 million. The OPEC Fund for International Development (OFID)[20] almost doubled its investment in 2012, and new funders appeared, including the Netherland's Aids Fonds and the US-based Campbell Foundation.

FIG. 11

**Microbicide Funding 2000–2012**
(US$ millions)



TBL. 6

## Annual Investments in Microbicide R&D 2006 – 2012 (US$ millions)[a, b]

| | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|
| **PUBLIC SECTOR** | | | | | | | |
| US | 129.7 | 139.8 | 154.4 | 172.6 | 181.7 | 148 | 173 |
| Europe | 56.3 | 59.6 | 39.9 | 44.4 | 40.3 | 16 | 27 |
| Other | 4.7 | 3.4 | 12.1 | 5.7 | 8.3 | 12 | 17 |
| Multilaterals | 1.4 | 0.2 | 0.2 | 0.2 | 0.1 | 0.1 | 0.1 |
| **Total public** | **192.1** | **203** | **206.6** | **222.9** | **230.4** | **176** | **217** |
| **PHILANTHROPIC SECTOR** | | | | | | | |
| **Total philanthropic** | **26.2** | **19** | **34.6** | **11.8** | **15.9** | **9** | **25** |
| **NON-COMMERCIAL SECTOR** | | | | | | | |
| **Total non-commercial** | **218.3** | **222** | **241.2** | **234.7** | **246.3** | **185** | **242** |
| **COMMERCIAL SECTOR** | | | | | | | |
| **Total commercial** | **4.5** | **4.5** | **2.5** | **1** | **1** | **1** | **3** |
| **Total global investment** | **222.8** | **226.5** | **243.7** | **235.7** | **247.3** | **186** | **245** |

[a] Numbers may be rounded.
[b] Data submitted in currency other than US$ is converted using a 1 July 2012 conversion rate; otherwise, inflation is not taken into account.

TBL. 7

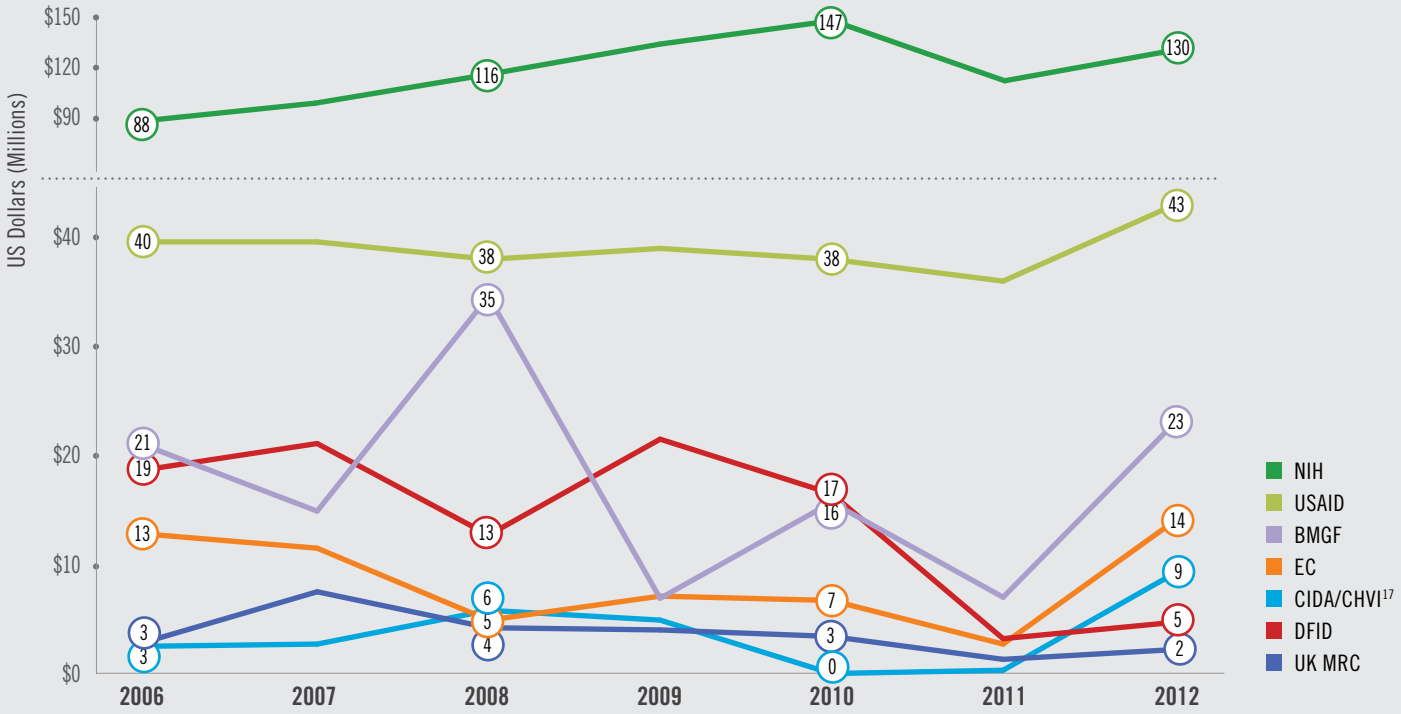
## Top Microbicide Funders for 2010 – 2012 (US$ millions)[a]

| 2010 Rank | Funder | Amount | 2011 Rank | Funder | Amount | 2012 Rank | Funder | Amount |
|---|---|---|---|---|---|---|---|---|
| 1 | NIH | 147.0 | 1 | NIH | 111.8 | 1 | NIH | 129.9 |
| 2 | USAID | 38.0 | 2 | USAID | 36.0 | 2 | USAID | 43.2 |
| 3 | DFID | 16.5 | 3 | South African DST/DOH | 10.0 | 3 | BMGF | 22.9 |
| 4 | BMGF | 15.7 | 4 | BMGF | 7.0 | 4 | EC | 13.6 |
| 5 | EC | 6.7 | 5 | DFID | 3.2 | 5 | CHVI[17] | 9.2 |
| 6 | China | 3.6 | 6 | Netherlands | 2.7 | 6 | South Africa[b] | 7.0 |
| 7 | UK MRC | 3.4 | 7 | Norad | 2.5 | 7 | DFID | 4.7 |
| 8 | Norad | 3.3 | 8 | Wellcome Trust | 1.6 | 8 | UK MRC | 2.2 |
| 9 | EDCTP | 2.0 | 9 | Irish Aid | 1.4 | 9 | Netherlands | 1.7 |
| 10 | Spain | 1.9 | 10 | UK MRC | 1.3 | 10 | Ireland | 1.2 |
| 11 | Netherlands | 1.7 | 11 | Denmark | 0.9 | 11 | Norway | 1.0 |
| 12 | Denmark | 1.7 | 12 | NHMRC | 0.6 | 12 | OFID | 1.0 |
| 13 | Germany | 1.3 | 13 | OFID | 0.5 | 13 | Denmark | 0.9 |
| 14 | Irish Aid | 1.1 | 14 | Spain | 0.4 | 14 | Wellcome Trust | 0.5 |
| 15 | CDC | 0.7 | 15 | ARC | 0.4 | 15 | NHMRC | 0.5 |

[a] See Appendix for list of acronyms.
[b] Figure includes South African Department of Science and Technology (DST) and Department of Health (DOH), as well as other local sources of funding.

FIG. 12

**Top Microbicide Funder Trends 2006–2012**




*Numbers may be rounded.

## 2.2.1 Public Investments in Microbicide Research & Development

Public-sector investment accounted for 89 percent of combined global funding for microbicide research, development and advocacy in 2012. While the US remained the primary source of funding, European national governments and the EC together accounted for US$27 million, a US$11 million increase over 2011. Still, European investment continued to lag behind that of earlier years due to overall declining research budgets, and its future is unclear. 2013 is the last year of the FP7, under which microbicide R&D has been funded, and the investment strategies of European countries might change going forward. The Horizon 2020 initiative, the next iteration of the Framework strategy for research and innovation, to be launched in 2014, will have a US$82.5 billion budget, but whether that will include funding for microbicide R&D is presently unknown.

The US NIH-funded VOICE (MTN 003) trial results in early-2013 found that none of the study interventions—daily oral tenofovir, daily oral TDF/FTC and daily 1% tenofovir gel—provided protection against HIV and that levels of adherence to product use by the women involved in the trial were insufficient to permit evaluation of product efficacy. These two conclusions and their interrelationships are being explored in a series of secondary analyses and at least one follow-on trial. The ongoing FACTS 001 trial, funded by the BMGF, the South African Department of Science and Technology (DST), the South African National Department of Health (DOH) and USAID, is scheduled to release results in 2014 on the safety and effectiveness of 1% tenofovir gel.

At the same time, the microbicide field has been forging ahead with new products in the pipeline. These include a monthly dapivirine vaginal ring being advanced through clinical trials by the International Partnership for Microbicides (IPM) and the Microbicide Trials Network (MTN). The IPM Ring Study (IPM 027), and the MTN's parallel ASPIRE study (MTN 020), are both evaluating the safety and effectiveness of the dapivirine ring. ASPIRE is funded by the US NIH which in 2012, invested more than US$20 million in the MTN. The IPM Ring Study was funded by the BMGF, the OPEC Fund for International Development (OFID) and USAID at a combined US$11.6 million in 2012. The IPM and the MTN are also collaborating on a Phase I study of maraviroc-based vaginal rings, including a combination dapivirine-maraviroc ring.

Other microbicide candidates that are receiving considerable attention include rectal microbicides, films, vaginal tablets and multipurpose technologies (MPTs). The Combined Highly Active Anti-Retroviral Microbicides (CHAARM) project, a large collaboration co-funded by the EU under the FP7 at a level of US$15.2 million over five years, continues its wide-ranging basic research into specifically targeted ARV combinations for topical application. CHAARM funding under the FP7 is set to end by December 2014.

### 2.2.2 Philanthropic Investments in Microbicide Research & Development

In 2012, the philanthropic sector as a whole provided US$25 million (10 percent) of the funds disbursed for microbicide R&D, a US$16 million increase over 2011. As in 2010 and 2011, almost all philanthropic funding came from the BMGF, with OFID the second largest donor. The Wellcome Trust decreased its investment by US$1.1 million in 2012. The majority of the increase was a result of the BMGF funding several large projects, including one study with a focus on HIV and contraception.

Box 9

### Multipurpose Prevention Technologies[a]

Women worldwide confront two major and often concurrent reproductive health challenges: the need for contraception and the need for protection against sexually transmitted infections, particularly HIV/AIDS. While conception and infection occur at the same anatomical site via the same mode of transmission, there are no reproductive health technologies to date that *simultaneously* address that reality. Available single-indication technologies are either contraceptive or anti-infective, limited in number or require different modes of administration and management, and therefore do not fully respond to pivotal events in many women's lives.

In contrast, multipurpose prevention technologies (MPTs) are being designed to address two or more sexual and reproductive health indications simultaneously, combining protection against unintended pregnancy and at least one sexually transmitted infection. A number of MPTs, in sustained-release forms, e.g., intravaginal rings (IVR); long-acting injectables; or "on-demand"/pericoital formulations, are in the preclinical and early-clinical stages and combine prevention of unintended pregnancy and HIV and, unless otherwise noted, HSV-2. These include:

- 60-day IVR delivering the ARV dapivirine and hormonal contraceptive levonorgestrel (LNG);
- 90-day IVR delivering LNG and tenofovir;
- IVR or on-demand formulations combining MIV-150, LNG, zinc acetate, carrageenan (also targets HPV);
- MZL combination topical gel; and
- "One size fits all" SILCS diaphragm, delivering nonhormonal contraceptive gel and/or tenofovir gel.

While the pipeline of MPT components and combination options is substantial and growing, it faces basic scientific questions and challenges regarding formulation, regulatory requirements, manufacturing, cost, market variability, adherence and acceptability and, inevitably, funding. It also requires prioritization and donor collaboration on investment decisions. The work of the developers involved—CONRAD, IPM, PATH and the Population Council—is almost entirely supported by USAID funding, as is the advocacy work done by the Coalition Advancing Multipurpose Innovations (CAMI), which also received small contributions in 2012 from the Mary Wohlford Foundation, the NIH Office of AIDS Research (OAR) and the Wellcome Trust. Recent calls for concepts and grant submissions from the BMGF, the NIH Division of Acquired Immunodeficiency Syndrome (DAIDS), and USAID are expected to attract further funding for MPT development in 2013.

[a] PF Harrison, A Hemmerling, J Romano, KJ Whaley, B Young Holt. Developing multipurpose reproductive health technologies: An integrated strategy. AIDS Research and Treatment, Volume 2013, Article ID790154. Open Access. dx.doi.org/10.1155/2013/790154

### 2.2.3 Commercial Investments and Contributions to Microbicide Research & Development

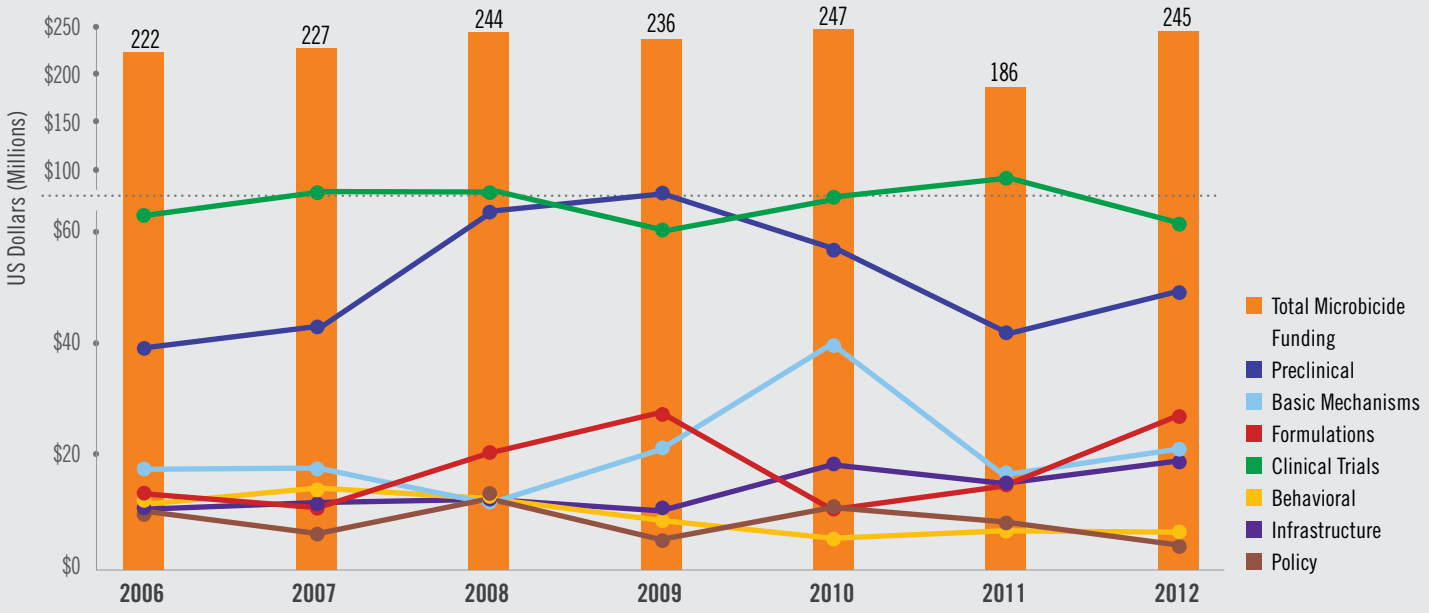
The Working Group increased its 2012 estimate of commercial-sector contributions to microbicide R&D to US$3 million in order to account for reporting from Company X.[21] The most significant contributions from the private sector have been royalty-free transfers of ARVs for use as active agents in microbicide development. Microbicide developers continue to receive product information, technical support, and advice from commercial partners, as well. CONRAD and the Population Council also received royalty-free licenses and material transfers from pharmaceutical companies, including licenses to develop ARVs as components of combination products. Biotechnology companies, through a variety of grant and contract mechanisms, have developed both ARV- and non-ARV-based products.

The in-kind contribution of companies is not readily quantifiable, but it continues to include a range of expertise and support, such as legal support for material transfer agreements and licenses; regulatory and scientific advice; access to preclinical toxicology studies and clinical safety or surveillance data; drug and product supplies; advice on manufacture of microbicide delivery systems; participation in development meetings and teleconferences; and timeline guidance.[22]

### 2.2.4 Funding Allocations for Microbicide Research & Development

In 2012, expenditures on microbicide R&D were allocated across the following seven categories: basic mechanisms of mucosal transmission (11 percent); preclinical testing (28 percent); formulations and modes of delivery (14 percent); clinical trials (32 percent); microbicide behavioral and social science research (3 percent); microbicide research infrastructure (10 percent); and policy and advocacy (2 percent).

FIG. 13 **Microbicide Expenditures 2006–2012**
(US$ millions)




*With the exception of "policy and advocacy," these are the categories used by the NIH to categorize microbicide research. Because not all data from funders permits the allocation according to these seven categories, these percentages were estimated from an US$196 million subset that did permit such allocations.

Preclinical testing and clinical trials remained the categories with the largest expenditures, but clinical trial expenditures fell from 48 percent in 2011 to 32 percent in 2012. This shift was a reflection of the large number of products in the pipeline that are entering early-stage trials which have lower costs than the large-scale, later-stage trials that necessitated greater expenditure in earlier years.

### 2.2.5 Investments in Rectal Microbicide Research & Development

In 2012, R&D for rectal microbicides was funded at approximately US$4.4 million. Between 2001 and 2012, global spending on rectal microbicide research totaled US$34.4 million. In 2012, most of this funding came from US and European sources and was dedicated to support for preclinical development and clinical testing of rectal microbicide products.

Funded by the NIH, Combination HIV Antiretroviral Rectal Microbicide Program (CHARM) is a five-year, US$11 million, multi-center grant intended to advance rectal microbicide candidates from discovery into early clinical development. CHARM is currently working on preclinical development of a rectal version of tenofovir gel as well as studying maraviroc for rectal use.

The first clinical studies of the rectal formulation of tenofovir started in late-2012 at the MTN. The MTN's Phase II trial of tenofovir gel for rectal use in gay men, MSM and transgender women is set to begin in the second half of 2013 at US sites, and 2014 at sites in Peru, South Africa and Thailand. The trial is the first Phase II rectal microbicide study—and the first rectal microbicide study to take place in sites outside the US.

Both CHARM and the MTN are evaluating maraviroc for rectal use. Clinical evaluations of maraviroc products will start in late-2013.

## 2.3 Global Investments in Research & Development and Operations Research for Other HIV Prevention Options

The Working Group tracked 2012 investments in R&D for additional biomedical prevention strategies, including: PrEP, treatment as prevention, operations research for implementation of male circumcision for HIV prevention, improvement of the female condom and refining and developing strategies for prevention of vertical transmission to infants at birth and during breastfeeding. The Working Group also has continued to track funding for HSV-2 vaccines, of interest because of the role of HSV-2 in HIV infection. Additionally, the Working Group continues to track HIV cure and therapeutic HIV vaccine research.

### 2.3.1 Investments in Follow-up Studies and Operations Research Related to Adult Male Circumcision

Global public-sector and philanthropic investment in R&D and operations research related to adult male circumcision totaled nearly US$42 million in 2012, US$21.7 more than in 2011.[23] Male circumcision is in an implementation phase. WHO recommends full implementation and a target has been set to provide circumcisions for 20 million men in 14 African countries by 2015.[24] Data from Kenya, South Africa and Uganda have already shown that male circumcision reduces the individual risk of HIV infection by 60 percent.[25] Study results released in 2011 by France's National Agency for Research on AIDS and Viral

TBL. 8

**Annual Investments in Adult Male Circumcision 2006 – 2012 (US$ millions)***

| | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|
| PUBLIC SECTOR | | | | | | | |
| Total public | 6.9 | 4.8 | 6.2 | 7.5 | 5.0 | 6.1 | 7.2 |
| PHILANTHROPIC SECTOR | | | | | | | |
| Total philanthropic | 4.3 | 2.9 | 4.3 | 2.1 | 16.7 | 14.2 | 34.4 |
| Total global investment | 11.2 | 7.7 | 10.5 | 9.6 | 21.7 | 20.3 | 41.6 |

* Numbers may be rounded.

Box 10

### Innovative Adult Male Circumcision Devices

The availability of innovative devices that could increase uptake and accelerate scale-up of adult male circumcision is imminent. These new devices simplify the procedure, minimizing the need for surgical intervention and, thus, ease some of the health systems challenges posed by implementing adult male circumcision in resource-poor settings. Both PrePex[a] and the Shang Ring[b] are new devices that were shown in 2011 to be safe and effective—both require less surgical skill than traditional male circumcision techniques. Studies to confirm the results of evaluations of PrePex and the Shang Ring are ongoing, supported by funds from the BMGF and USAID. In June 2013, PrePex received prequalification from WHO. Three other devices—the Shang Ring, Plastibell and Tara KLamp—are in the WHO prequalification process, but have not yet been approved.

[a] JP Bitega, ML Ngeruka, T Hategekimana et al. Safety and efficacy of the PrePex device for rapid scale-up of male circumcision for HIV prevention in resource-limited settings. Journal of Acquired Immune Deficiency Syndrome 15:58(2011).
[b] MA Barone, F Ndede, PS Li et al. The Shang Ring device for adult male circumcision: a proof of concept study in Kenya. Journal of Acquired Immune Deficiency Syndrome 57:1:e7-12(2011).

Hepatitis (ANRS) showed that rollout in the southern and eastern regions of Africa was able to significantly decrease the community level of HIV in high-prevalence areas,[26] and new research in 2012,[27, 28] and early-2013[29] confirmed the effectiveness of male circumcision in reducing the risk of HIV infection.

Ongoing research in 2012, funded by the NIH at a level of US$4.2 million, focused on the socio-behavioral aspects of adult male circumcision, such as public outreach campaigns for effective implementation of circumcision programs and risk compensation studies, and continuing R&D related to the effect of circumcision on HIV risk.

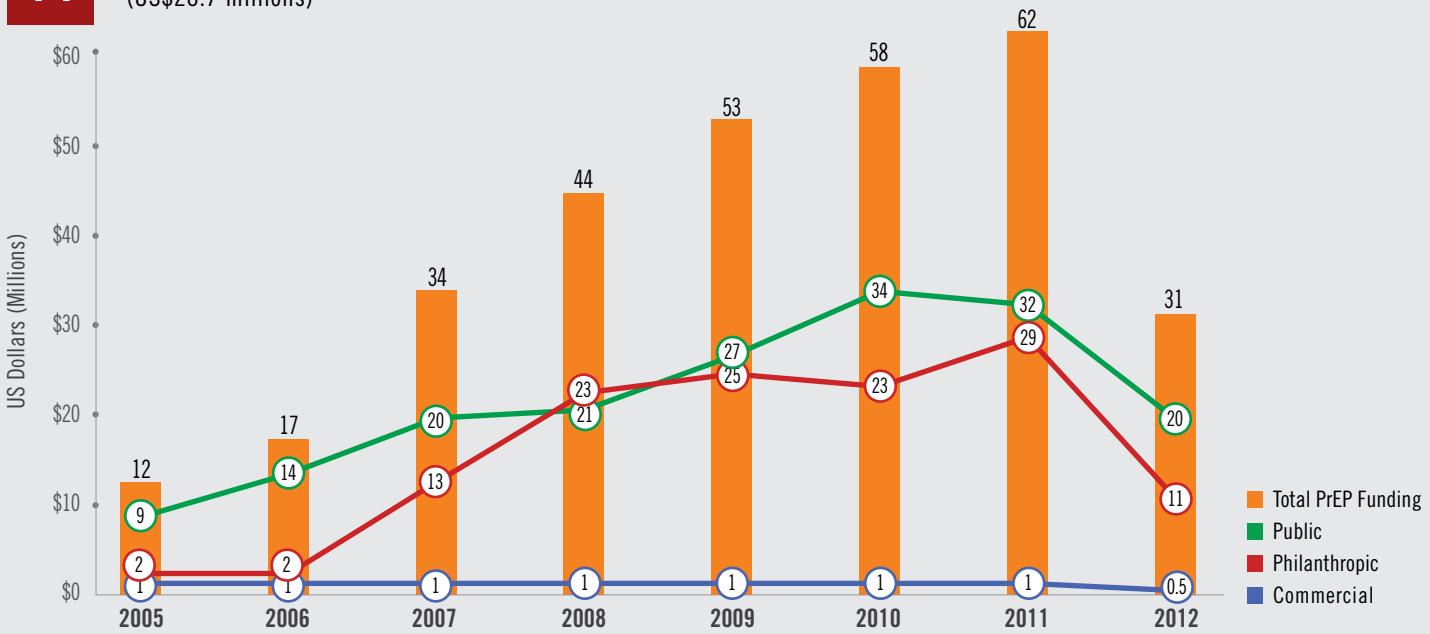
The largest funder of adult male circumcision implementation research remains the BMGF, which increased its investment from 2011 to 2012 by US$20.3 million—accounting for most of the 2012 investment increase in this area. BMGF grants focused on various circumcision strategies, including PrePex and the Shang Ring (see Box 10), monitoring of scale-up, demand creation and delivery. The US President's Emergency Plan for AIDS Relief (PEPFAR) is also investing in research involving nonsurgical devices.

## 2.3.2 Investments in Research & Development Related to Pre-Exposure Prophylaxis

Global public, philanthropic and commercial investment in PrEP was US$31 million in 2012, bringing the total investment in this technology over the past seven years to US$297 million. However, funding for PrEP fell by US$20.7 million between 2011 and 2012, a significant decline. In July 2012, based on evidence from several trials, the US FDA approved daily oral TDF/FTC for use as PrEP for HIV prevention in HIV-negative women and men. Daily TDF/FTC has now been proven effective at reducing risk of HIV via sexual exposure in heterosexual men and women, gay men and other MSM and transgender women. This marked the first time the FDA approved a drug to reduce HIV risk via sexual exposure. The FDA decision led to preparation for, and initiation of, demonstration projects and follow-on trials to better assess and understand how to roll out PrEP for prevention. 2012 was a year of planning, with nearly 15 PrEP demonstration projects slated to begin in 2013 and the years beyond.

FIG. 14

**Investment in Pre-Exposure Prophylaxis 2005–2012***
(US$28.7 millions)




* Numbers may be rounded.

TBL. 9

**Annual Investments in Pre-Exposure Prophylaxis 2005 – 2012 (US$ millions)**[a, b]

| | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|
| **PUBLIC SECTOR** | | | | | | | | |
| Total public | 8.7 | 13.5 | 19.7 | 20.6 | 26.6 | 33.8 | 32.3 | 19.6 |
| **PHILANTHROPIC SECTOR** | | | | | | | | |
| Total philanthropic | 2.4 | 2.4 | 12.6 | 22.5 | 24.6 | 23.2 | 28.7 | 10.9 |
| **COMMERCIAL SECTOR** | | | | | | | | |
| Total commercial | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 0.5 |
| Total global investment | 12.4 | 17.2 | 33.6 | 44.4 | 52.5 | 58.3 | 62.3 | 31 |

[a] Numbers may be rounded.
[b] The Working Group is beginning to track funding towards PrEP demonstration projects and will provide an investment figure in the next iteration of the report. See *www.avac.org/prepdemo* for all ongoing and planned demonstration projects.

In June 2013, results from the Bangkok Tenofovir Study were published, finding that a daily dose of oral tenofovir reduced the risk of HIV infection in a population of IDUs by 49 percent overall. The study began in 2005 and enrolled more than 2,400 men and women. Ongoing studies are exploring different dosing strategies, including intermittent, time-driven and exposure-based use of PrEP. New PrEP strategies are also in development, including testing of long-acting TMC278 and, in another trial, maraviroc as an HIV prevention agent together with TDF and FTC.

### 2.3.3 Investment in Research & Development Related to Treatment as Prevention

Since the 2011 publication of the HPTN 052 trial results[30] galvanized the field of HIV prevention, treatment as prevention has continued to excite-—and challenge—both research and implementation

TBL. 10

**Annual Investments in Treatment as Prevention 2011 and 2012 (US$ millions)***

| | 2011 | 2012 |
|---|---|---|
| **PUBLIC SECTOR** | | |
| US | 55 | 68.6 |
| Europe | 4.7 | 4.6 |
| Other | 13.5 | 13 |
| **Total public** | **73.2** | **86.2** |
| **PHILANTHROPIC SECTOR** | | |
| **Total philanthropic** | **6.2** | **11.8** |
| **Total global investment** | **79.4** | **98** |

* Numbers may be rounded.

science. The field reacted enthusiastically in 2012 as treatment as prevention was added to the national strategies of countries and models showed that it could dramatically alter the course of the epidemic. However, the field now confronts the question of how best to implement it programmatically. In this report, the Working Group's calculation of treatment as prevention investment includes only research that has the primary outcome of decreasing HIV transmission at all CD4 levels (i.e., other health outcomes are included, but research needs to measure transmission and/or incidence impact).[31] Total global investment in treatment as prevention R&D in 2012 was US$98 million, an increase of approximately US$18.6 million from 2011.

Public-sector agencies from the US provided a significant portion of funding, with more than US$57 million from the NIH and an estimated US$11.3 million for combination prevention from PEPFAR. US NIH funding is supporting ongoing trials in Botswana, South Africa, Tanzania, Thailand, Zambia and Zimbabwe, as well as combination prevention trials in South Africa and Uganda. PEPFAR is supporting four-year studies on combination prevention in Botswana, South Africa and Zambia with a total investment of US$45 million.

Canada provided a substantial amount of funding with the Government of British Columbia investing nearly US$12 million in its Stop HIV/AIDS campaign. European funding came from France, Belgium, Germany, Sweden and Switzerland. ANRS is funding the Start ART trials, focusing on the acceptability and feasibility of treatment and prevention at the individual and community levels. China is also funding large-scale implementation efforts in treatment as prevention.

The majority of philanthropic funding came from the BMGF, the Dream Fund of the Dutch Postcode Lottery, Médecins Sans Frontières (MSF) and the Wellcome Trust. The Dream Fund of the Dutch Postcode Lottery is funding the MaxART trial taking place in Swaziland and sponsored by STOP AIDS NOW! and the Clinton Health Access Initiative (CHAI).

While there is no direct commercial investment in R&D for treatment as prevention, substantial quantities of ARV drugs have been donated for clinical trials. In HPTN 052, for example, study drugs are being donated by Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GSK and Merck & Co.

### 2.3.4 Investments in Operations Research Related to Vertical Transmission Prevention

Funding for operations research related to prevention of vertical transmission of HIV from mother to child at birth and during breastfeeding was virtually flat from 2011 to 2012 at US$43.8 million. The public sector accounted for most of this funding, with the US, through the NIH and USAID, contributing 79 percent. Other public-sector agencies—ANRS, Canada's CHVI, India's DBT, the Swedish Research Council (SRC) and the EC, contributed 19 percent of total funding for prevention of vertical transmission R&D, while philanthropic funding accounted for 2 percent.

In 2012, this area of HIV prevention R&D shifted its focus to Option B+, a new approach recommended by the WHO in which all HIV-infected pregnant and breastfeeding women are

TBL. 11

**Funding for Vertical Transmission Prevention R&D 2008 – 2012 (US$ millions)***

| | | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|
| **PUBLIC SECTOR** | | | | | | |
| **France** | ANRS | 3,429,355 | 1,820,086 | 418,890 | 203,100 | 816,969 |
| | Institut Pasteur | 0 | 0 | 0 | 384,900 | 0 |
| **Canada** | CHVI | 0 | 0 | 0 | 3,956,400 | 6,556,557[17] |
| | CIDA | 0 | 0 | 1,250,000 | 570,600 | *[Included in CHVI figure for 2012]* |
| | CIHR | 0 | 0 | 0 | 634,000 | 88,489 |
| **US** | CDC | 1,716,928 | 488,132 | 0 | 0 | 0 |
| | NIH | 8,533,594 | 44,101,000 | 55,348,000 | 34,012,000 | 33,154,000 |
| | USAID | 0 | 0 | 1,600,000 | 2,225,000 | 1,400,000 |
| **Sweden** | SIDA | 128,041 | 263,158 | 1,127,820 | 102,800 | 0 |
| | SRC | 0 | 0 | 0 | 0 | 108,133 |
| **UK** | MRC | 374,600 | 448,105 | 0 | 448,000 | 0 |
| **EC/EDCTP** | | 3,393,500 | 3,393,500 | 0 | 0 | 815,145 |
| **India** | DBT | 0 | 0 | 0 | 0 | 34,135 |
| **Total public** | | **17,576,018** | **50,513,981** | **59,744,709** | **42,613,680** | **42,973,428** |
| **PHILANTHROPIC SECTOR** | | | | | | |
| **Total philanthropic** | | **3,641,800** | **904,065** | **0** | **500,700** | **841,956** |
| **Total global investment** | | **21,217,800** | **51,418,000** | **59,744,700** | **43,114,344** | **43,815,384** |

* Numbers may be rounded.

eligible for lifelong antiretroviral therapy (ART) regardless of CD4 count. In April 2012, after having publicized the Option B+ approach, the WHO released a technical update explaining its advantages and challenges, including the need to evaluate the experiences of those countries that adopted it. As a result, evaluations and studies of implementation of Option B+ are now underway.

Additional research endeavors are exploring the ways ARVs function in prevention of vertical transmission, both at birth and through breastfeeding; ARV resistance in HIV-positive women taking regimens designed to prevent vertical transmission; and retention and recruitment of women and infants in prevention of vertical transmission.

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

Prevention of HSV-2 infections in HIV-negative people may prove to be an effective component of an HIV prevention strategy. While HSV-2 suppression with acyclovir and its analogues has not been shown to affect HIV acquisition, research on other therapeutic and prophylactic methods is ongoing and some basic questions continue to be pursued.

In 2012, a total of US$2.3 million was provided for HSV-2 vaccine research, most from the US NIH; the Australian ARC and NHMRC also provided funding. As in previous years, commercial investors were often subsidized by public-sector institutions, such as the US NIH. Pharmaceutical and biotechnology companies investing in HSV-2 vaccine R&D include GSK, Genocea Biosciences, Juvaris BioTherapeutics and Vical.

In mid-2012 results of GSK's NIH-funded Phase III trial assessing the company's HSV vaccine, Simplirix, were published, shedding light on GSK's decision in 2010 to halt the trial due to lack of efficacy. GSK and NIH investigators are conducting further analysis of the results from that study to gain better understanding of the vaccine.

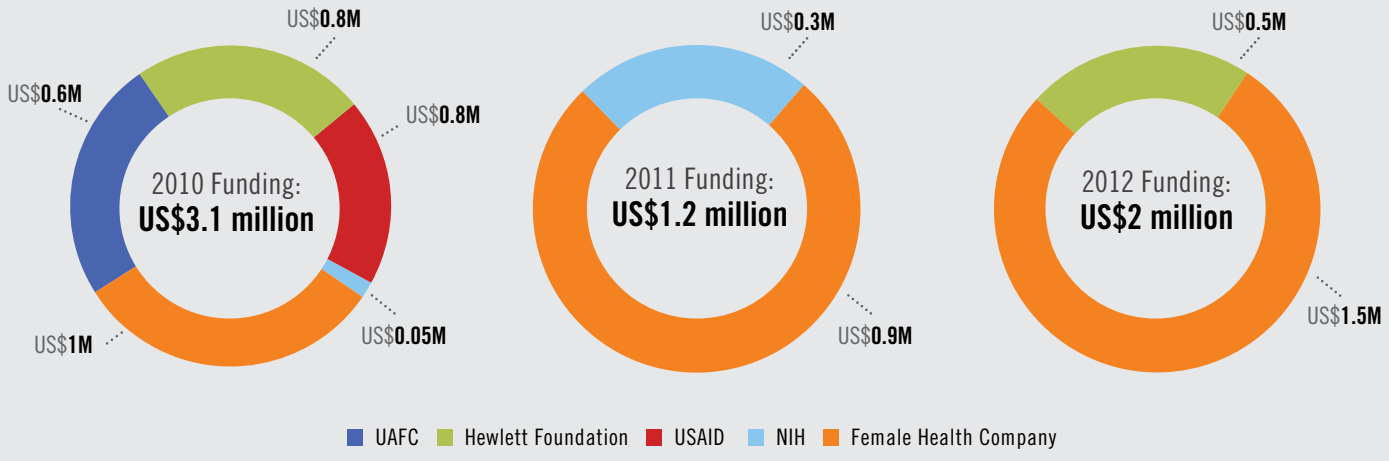
### 2.3.6 Investments in Research & Development and Operations Research Related to Female Condoms

Although the female condom has been on the market since 1993, research questions remain with respect to its design, rollout and implementation. R&D work—including product development efforts, community education and advocacy and demonstration studies—continues. In 2009, the Female Health Company created the next-generation female condom, FC2, a less expensive version made of nitrile, a thinner, non-latex material.

In 2012, a cost-effectiveness study conducted in Washington, DC, explored provision of the FC2 female condom, together with education about its particular benefits to high-risk women. The city's health department, along with researchers from the Johns Hopkins Bloomberg School of Public Health, found that, after two years and distribution of 500,000 female condoms, the program prevented 23 new infections saving the city US$8 million in future costs of HIV treatment and care.

In 2012, global investment related to female condom R&D totaled US$2 million, from the Female Health Company and the Hewlett Foundation, an increase of nearly US$800,000 over 2011.

FIG. 15 **Female Condom Research & Development and Operations Research Investment 2010 – 2012**
(US$ millions)

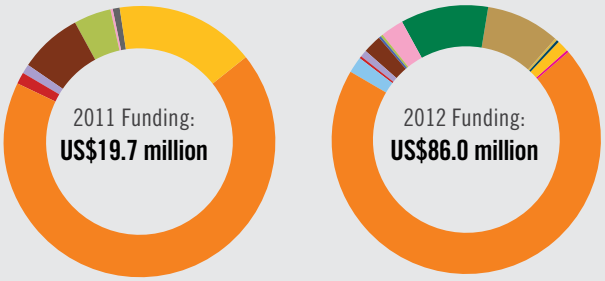


## 2.4 Global Investments in Cure Research

Cure research saw substantial progress in early-2013, with preliminary results that further energized the field. In light of recent findings, and in response to a growing interest in organizing the field of HIV cure research, the NIH OAR developed a definition that allows the OAR to track cure research

FIG. 16

### Investment in Cure Research in 2011 and 2012




| 2011 | | 2012 |
|---|---|---|
| 0.03 | amfAR | 2.40 |
| 1.50 | Australian National Health and Medical Research Council (NHMRC) | 1.90 |
| 0.20 | Australian Research Council (ARC) | 0.68 |
| 0.90 | Bill & Melinda Gates Foundation | 0.30 |
| 0 | California Institute for Regenerative Medicine (CIRM) | 7.65 |
| 0 | Canadian HIV Vaccine Initiative (CHVI)[17] | 0.20 |
| 0 | Canadian Institutes of Health Research (CIHR) | 0.10 |
| 0 | Center for Genetic Engineering and Biotechnology of Cuba (IGBC) | 0.08 |
| 0.14 | Doris Duke Charitable Foundation | 0 |
| 0 | European Commission (EC) and European & Developing Countries Clinical Trials Partnership (EDCTP) | 1.60 |
| 3.30 | French National Agency for Research on AIDS and Viral Hepatitis (ANRS) | 1.20 |
| 0 | Ontario HIV Treatment Network (OHTN) | 0.20 |
| 0 | Research Foundation Flanders (FWO) | 0.05 |
| 0 | Sangamo BioSciences, Inc. | 8.90 |
| 0.25 | Swedish Research Council (SRC) | 0.19 |
| 0 | Swiss National Science Foundation (SNSF) | 0.30 |
| 0 | UK Medical Research Council (MRC) | 0.28 |
| 19.70 | US National Institutes of Health (NIH) | 60.0 |

Box 11

### US NIH Toward a Cure Program Definition: Eradication of Viral Reservoirs*

*"Research conducted on viral latency, elimination of viral reservoirs, immune system and other biological approaches, as well as therapeutic strategies that may lead to either a functional (control of virus rather than elimination, without requirement for therapy) or sterilizing (permanent remission in absence of requirement for therapy) cure of HIV infection.*

***Pathogenesis studies:*** *Basic research on viral reservoirs, viral latency, and viral persistence, including studies on genetic factors associated with reactivation of the virus, and other barriers to HIV eradication.*

***Animal models:*** *Identification and testing of various animal and cellular models to mimic the establishment and maintenance of viral reservoirs. These studies are critical for testing novel or unique strategies for HIV reactivation and eradication.*

***Drug development and preclinical testing:*** *Programs to develop and preclinically test new and better antiretroviral compounds capable of entering viral reservoirs, including the central nervous system.*

***Clinical trials:*** *Studies to evaluate lead compounds, drug regimens, and immune-based strategies capable of a sustained response to HIV, including clinical studies of drugs and novel approaches capable of eradicating HIV-infected cells and tissues.*

***Therapeutic vaccines:*** *Design and testing of vaccines that would be capable of suppressing viral replication and preventing disease progression.*

***Adherence/compliance:*** *Development and testing of strategies to maintain adherence/compliance to treatment, in order to improve treatment outcomes and reduce the risk of developing HIV drug resistance."*

* Department of Health and Human Services National Institutes Of Health Office of AIDS Research, Trans-NIH AIDS Research Budget FY2014. www.oar.nih.gov/budget/pdf/2014_OAR_CJ_Trans-NIH.pdf

separately, as it has done for vaccines and microbicides. Given this modification, the Working Group revised its data collection process to adopt the OAR definition so as to further standardize the grants defined within that cure research.

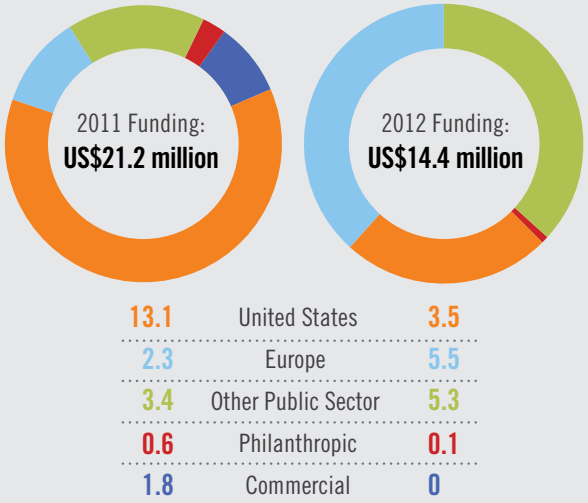
As the definition substantially evolved from 2011 to 2012, the Working Group's estimate of cure research funding has increased, in part due to a more expansive definition of cure research by the OAR. The Working Group allocated US$13.4 million in NIH grants to cure research in 2011. However, in 2012 under the new OAR definition, the NIH reported US$60 million invested in cure research.

Finally, the Working Group underreported the level of cure research funding in 2011. The US$16.4 million figure did not include the ANRS investment of US$3.3 million in 2011. Figure 16 reflects the correction, as well as the new definition of cure research set by the US NIH for all grants collected in 2012.

### 2.4.1 Global Investments in Therapeutic HIV Vaccine Research & Development[32]

Therapeutic vaccine research is defined by the Working Group as studies that increase scientific knowledge through research on protective immune responses and host defenses against HIV—studies now included by the OAR in a subcategory under the umbrella of cure research. While in the past the Working Group has distinguished these studies from those that focus on cure research [as defined in Box 11], the OAR has included these studies under the umbrella of cure research. The Working Group categorized seven NIH grants toward therapeutic vaccine research in 2012, totalling US$3.5 million. Overall investment in therapeutic vaccine research decreased in 2012 by US$6.8 million from 2011 to total US$14.4 million.

FIG. 17 **Investment in Therapeutic HIV Vaccines in 2011 and 2012**




Research in this area continued throughout 2012 and is ongoing at several biotechnology firms and through collaborations, including France's Vaccine Research Objective AIDS (ORVACS), the Argos Therapeutics, Bionor, Pfizer and Merck.

# 3.0 Discussion and Conclusions

In a climate of continuing fiscal austerity, HIV prevention R&D has fared relatively well, having managed to maintain investment and support for ongoing research. As US budgets are inevitably cut in 2013, it is likely that funding for HIV prevention research could decline in subsequent years. Given such a scenario, it will be essential for other funders and non-traditional investors to begin to step up with greater participation.

Considering the 2012 funding patterns identified by the Working Group in this report and the science it has supported, the following conclusions regarding the state of HIV prevention R&D investments are advanced:

## 2012 HIV Prevention R&D Investment Conclusions

- **Partnerships are vital to advancing products in the pipeline.** Collaborations bring together the collective knowledge and expertise of the partners. Collaborations such as the P5, the IPM and the MTN joint trials and the START treatment as prevention trial—which includes collaborators from all sectors and sites in 36 countries—are clearly advancing the field of HIV prevention.
- **Resource allocation must reflect ongoing, strategic prioritization of candidates in the pipeline.** As trials proceed and information on the safety and efficacy of new products accumulates, the pipeline and the basis for decisions about prioritization are illuminated. Each technological area of HIV prevention R&D should be scrutinized in order to reflect on how best to prioritize limited funds to advance those products and approaches most likely to succeed, and to halt those that are less promising.
- **In order to effectively roll out products and approaches, implementation research needs to expand.** Treatment as prevention, PrEP and medical male circumcision all offer great potential for curbing the epidemic. However, to effectively implement these technologies, there must be continued research into how to best deliver them to the populations most in need and in combinations that foster their acceptance, use and impact. As policies change to incorporate new interventions it will be critical to include operations research to help with course corrections during implementation.
- **HIV prevention R&D investment should be seen in the context of the larger global health landscape.** With the agenda for the post-2015 Millennium Development Goal strategies forming and Horizon 2020—the next funding package for research and innovation in the EU, set to launch in 2014—investors in HIV prevention R&D need to ensure that it fits within the new, emerging global health and development landscape.
- **Budget realities in the US highlight the need for other donors to enter (and re-enter) the HIV prevention R&D funding space.** The US government provided 75 percent of all global investments in HIV prevention R&D in 2012, but austerity-driven budget reductions across US government agencies are very likely to have an impact on this significant public-sector portion of the field's support. A more diversified and stable funding base for HIV prevention R&D could include BRICS countries, countries in which HIV prevention R&D takes place and recommitment from traditional HIV/AIDS donor countries within the OECD that have deprioritized funding R&D over the last five years. It is vital that advocates, researchers and policy-makers in both donor countries and regions heavily impacted by HIV seek to engage non-traditional donors in HIV prevention R&D.

# Appendix Methodology

This report was prepared by Emily Donaldson (AVAC), with contributions from Kevin Fisher (AVAC), Reuben Granich (UNAIDS), Thomas Harmon (IAVI), Polly Harrison (AVAC), Naomi Saelens (IAVI) and Mitchell Warren (AVAC) of the HIV Vaccines and Microbicides Resource Tracking Working Group (herein referred to as "the Working Group"). The Working Group developed and has utilized a systematic approach to data collection and collation since 2004. These methods were employed to generate the estimates of funding for R&D presented in this report. A detailed explanation of the methodology can be found on the Working Group website (*www.hivresourcetracking.org*). The two sets of categories used to describe different R&D activities—one for HIV vaccines and one for HIV microbicides—were derived from those developed by the US NIH and are shown in the following tables.

Box 12

## Data Collection Methods and Fluctuation in Investment Levels

HIV prevention R&D investment figures are collected annually by the HIV Vaccines & Microbicides Resource Tracking Working Group through an email survey. For the present report, the Working Group reached out from January to May 2013 to 210 funders in the public, philanthropic and commercial sectors and collected information on 663 grants and line-item investments that the Group allocated to HIV prevention R&D.

The accuracy of investment data to a certain extent depends on the level of response from those surveyed. Due to improved reporting by several European donors, funding for preventive HIV vaccines and microbicides from Europe increased both in 2011 and 2012.

In contrast, survey responses from industry are historically low, so that the figures provided in the annual Working Group reports for commercial-sector investment is an estimate by the Working Group based on its knowledge of current industrial engagement in HIV prevention research.

TBL. 12

## Categories Used to Classify Preventive HIV Vaccine R&D Funding

| Category | Definition |
|---|---|
| **Basic Research** | Studies to increase scientific knowledge through research on protective immune responses and host defenses against HIV. |
| **Preclinical research** | R&D efforts directed at improving preventive HIV vaccine design. This includes vaccine design, development and animal testing. |
| **Clinical Trials** | Support for Phase I, II, and III trials testing the safety, immunogenicity, and efficacy of suitable preventive HIV vaccine candidates or concepts in domestic and international settings (including the costs of producing candidate product lots for clinical trials). |
| **Cohort & Site Development** | Support to develop the strategies, infrastructure, and collaborations with researchers, communities, government agencies, regulatory agencies, NGOs and industry necessary to identify trial sites, build capacity, ensure adequate performance of trials, and address the prevention needs of at-risk populations in trial communities. |
| **Advocacy & Policy Development** | Efforts directed at educating and mobilizing public and political support for preventive HIV vaccines and addressing potential regulatory, financial, infrastructure, and/or political barriers to their rapid development and use. |

TBL. 13

## Categories Used to Classify Microbicide R&D Funding

| Category | Definition |
|---|---|
| **Basic Mechanisms of Mucosal Transmission** | Elucidate basic mechanisms of HIV transmission at mucosal/epithelial surfaces that are important for microbicide research and development in diverse populations. |
| **Discovery, Development & Preclinical Testing** | R&D efforts directed at the discovery, development, and preclinical evaluation of topical microbicides alone and/or in combination. |
| **Formulations & Modes of Delivery** | Develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, and social sciences. |
| **Clinical Trials** | Conduct clinical studies of candidate microbicides to assess safety, acceptability, and effectiveness in reducing sexual transmission of HIV in diverse populations in domestic and international settings. |
| **Microbicide Behavioral & Social Science Research** | Conduct basic and applied behavioral and social science research to inform and optimize microbicide development, testing, acceptability, and use, domestically and internationally. |
| **Microbicide Research Infrastructure** | Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide research domestically and internationally. |
| **Policy & Advocacy** | Efforts directed at educating, mobilizing public and political support for microbicides and addressing potential regulatory, financial, infrastructure and/or political barriers to the rapid development and use of microbicides. |

TBL. 14

## Classification of Other HIV Prevention R&D Funding

| Category | Definition |
|---|---|
| **Pre-exposure Prophylaxis** | Includes biomedical R&D, follow-on studies, demonstration projects and operations research for implementation. |
| **Treatment as prevention** | Includes research focused on the primary outcome of transmission at all CD4 levels. |
| **Male circumcision** | Includes operations research for implementation, as well as biomedical R&D. |
| **Prevention of vertical transmission** | Includes operations research related to prevention of vertical transmission from mother to child at birth and during breastfeeding. |
| **HSV-2 vaccine** | Includes research related to prevention of HSV-2 infections in HIV-negative people via an HSV-2 vaccine. |
| **Female condom** | Includes R&D work focused on product development efforts, community education and advocacy and demonstration studies. |

TBL. 15

## Classification of Cure and Therapeutic Vaccine Funding

| Category | Definition |
|---|---|
| **Cure** | Includes research conducted on viral latency, elimination of viral reservoirs, immune system and other biological approaches, as well as therapeutic strategies that may lead to either a functional (control of virus rather than elimination, without requirement for therapy) or sterilizing (permanent remission in absence of requirement for therapy) cure of HIV infection. |
| **Therapeutic Vaccine** | Includes research into vaccines for HIV-positive individuals, designed to enhance immune responses to HIV in order to better control the infection. |

# Appendix List of Acronyms

| | |
|---|---|
| **AECID** | Spanish Agency for International Development Cooperation |
| **amfAR** | American Foundation for AIDS Research |
| **ANRS** | National Agency for Research on AIDS and Viral Hepatitis, France |
| **ANRS VRI** | ANRS Vaccine Research Institute |
| **ARC** | Australian Research Council |
| **ART** | Anti-retroviral therapy |
| **ARV** | Anti-retroviral |
| **BIDMC** | Beth Israel Deaconess Medical Center |
| **BMGF** | Bill & Melinda Gates Foundation |
| **BRICS** | Brazil, Russia, India, China, and South Africa |
| **CDC** | US Centers for Disease Control and Prevention |
| **CHAARM** | Combined Highly Active Anti-Retroviral Microbicides Project |
| **CHARM** | Combination HIV Antiretroviral Rectal Microbicide Program |
| **CHAI** | Clinton Health Access Initiative |
| **CHAVI-ID** | Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery, |
| **CHVI** | Canadian HIV Vaccine Initiative |
| **CIDA** | Canadian International Development Agency |
| **CIHR** | Canadian Institutes of Health Research |
| **DBT** | Department of Biotechnology at India's Ministry of Science and Technology |
| **DAIDA** | Danish International Development Agency |
| **DFID** | UK Department for International Development |
| **DST** | Department of Science and Technology, South Africa |
| **EC** | European Commission |
| **EDCTP** | European and Developing Countries Clinical Trials Partnership |
| **EGPAF** | Elizabeth Glazer Pediatric AIDS Fund |
| **ESF** | Estonia Science Foundation |
| **FACTS** | Follow-on African Consortium for Tenofovir Studies |
| **FDA** | US Food and Drug Administration |
| **FHI** | Family Health International, US |
| **HPTN** | HIV Prevention Trials Network |
| **HVTN** | HIV Vaccine Trials Network |
| **IAVI** | International AIDS Vaccine Initiative |
| **ICMR** | Indian Council of Medical Research |
| **IDRI** | Infectious Disease Research Institute |
| **IPM** | International Partnership for Microbicides |
| **IRMA** | International Rectal Microbicides Advocates |
| **MHRP** | US Military HIV Research Program |
| **MSF** | Médecins Sans Frontières |
| **MSM** | Men who have sex with men |
| **MRC** | UK Medical Research Council |
| **MTN** | Microbicide Trials Network |

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|---|---|
| **NAC** | IAVI Neutralizing Antibody Consortium |
| **NHMRC** | Australian National Health & Medical Research Council |
| **NIAID** | US National Institute of Allergy and Infectious Diseases |
| **NIH** | US National Institutes of Health |
| **NIHR** | UK National Institutes of Health Research |
| **NSC** | National Science Council, Taiwan |
| **OAR** | US NIH Office of AIDS Research |
| **OFID** | OPEC Fund for International Development |
| **ORVACS** | Vaccine Research Objective AIDS |
| **P5** | Pox-Protein Public-Private Partnership |
| **PDP** | Product development partnership |
| **PEPFAR** | US President's Emergency Plan for AIDS Relief |
| **PHAC** | Public Health Agency of Canada |
| **PrEP** | Pre-exposure prophylaxis |
| **R&D** | Research & development |
| **SA DOH** | South African Department of Health |
| **SIDA** | Swedish Agency for International Cooperation Development |
| **SNSF** | Swiss National Science Foundation |
| **SRC** | Swedish Research Council |
| **START** | Strategic Timing of AntiRetroviral Treatment (START) study |
| **TDF** | Tenofovir |
| **TDF/FTC** | Tenofovir/Emtricitabine |
| **UAFC** | Universal Access to Female Condoms Joint Programme |
| **UK** | United Kingdom |
| **UK HVC** | UK HIV Vaccine Consortium |
| **UNAIDS** | Joint United Nations Programme on HIV/AIDS |
| **US** | United States |
| **USAID** | US Agency for International Development |
| **VOICE** | Vaginal and Oral Interventions to Control the Epidemic |
| **VRC** | US Vaccine Research Center |
| **WHO** | World Health Organization |

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# Appendix Endnotes


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15 With many PrEP demonstration projects set to begin in 2013, the Working Group is developing a comprehensive methodology to track investment in them. Findings will be included in the next iteration of the resource tracking report.

16 R McEnery. HVTN 505 Trial expanded to see if vaccine candidates can block HIV acquisition. International AIDS Vaccine Initiative (IAVI), Vaccine Briefs 15;4(2011).

17 Participating CHVI Government of Canada departments and agencies are: the Canadian International Development Agency (CIDA), the Public Health Agency of Canada (PHAC), Industry Canada, the Canadian Institutes of Health Research (CIHR) and Health Canada. CIHR grants are reported separately.

18 While the Working Group received increased industry reporting in 2012, the overall estimate for the commercial sector held steady at US$30 million due to the scaling back of some larger industry HIV vaccine programs.

19 With the exception of "policy and advocacy," these are the categories used by the NIH to classify allocations for HIV vaccine research. Because not all data from funders can be parsed according to these five categories, these percentages were estimated based on a US$809 million subset that allowed for determining allocations. These expenditure estimates do not include therapeutic vaccines.

[20] The Working Group has historically reported the investment of OFID under the philanthropic category and recognizes that OFID is the development finance institution established by the Member States of OPEC and does not readily fit within a traditional category of investor. For consistency of funding trends, the Working Group has chosen to continue to include OFID in the philanthropic category.

[21] Company X was provided with a non-disclosure agreement by the Working Group and has been anonymized.

[22] Quantifying in-kind contributions, technical assistance, IP transfers and other non-direct financial contributions is challenging for pharmaceutical companies; thus, it is often not possible for companies to report this information to the Working Group.

[23] While the Working Group tracks investment in R&D and operations research for adult male circumcision, it does not track investment in rollout and scale-up of the procedure. In the context of this report, "male circumcision" refers specifically to voluntary adult male circumcision performed for the purposes of reducing transmission of HIV and other sexually transmitted diseases. "Operations research" aims to develop solutions to current operational problems of specific health programs or specific service delivery components of the health system. "Implementation research" aims to develop strategies for available or new health interventions in order to improve access to, and use of, these interventions by the populations in need. Definitions from JHF Remme et al. "Defining research to improve health systems," PLoS Med 7(11) (16 November 2010).

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[31] WHO defines treatment as prevention as provision of ART irrespective of CD4+ cell count for the prevention of HIV and TB, including provision of ART to people living with HIV who are severely immunocompromised with AIDS and/or have a CD4+ count ≤350 cells/mm3, as well as those with CD4+ cell counts >350 cells/mm3. The Working Group will publish an investment estimate later in 2013 based upon this expanded definition.

[32] Therapeutic vaccine research has been changed to a subcategory of cure research due to the reporting of NIH funding. The definition of HIV cure research given by the Office of AIDS Research (OAR) includes research into therapeutic vaccines.

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