MICROBICIDE WATCH

2006

ALLIANCE FOR MICROBICIDE DEVELOPMENT

"To watch: *to follow, observe, survey; to look at carefully or continuously; to keep up on or informed about."*

This inaugural issue of *Microbicide Watch* is intended to be the first of a regularly published review of the microbicide effort. *Microbicide Watch* is a monitoring report, offering information, assessment, analysis, and recommendations, all of which can serve as a reference for policy makers and advocates. It complements the forthcoming *Microbicide Development Strategy (MDS)*, which outlines the fundamental scientific gaps, obstacles, and priority actions needed in microbicide research and development.

While the Alliance takes sole responsibility for the information presented and opinions expressed in *Microbicide Watch*, this report draws its inspiration, content, and recommendations from voices and perspectives from around the world. Special acknowledgement is due the staff of the African Microbicides Advocacy Group, AIDS Vaccine Advocacy Coalition, CONRAD, Global Campaign for Microbicides, International Partnership for Microbicides, Microbicide Development Strategy Steering Committee and Working Groups, and the Population Council. The Alliance also thanks the numerous individuals who reviewed or contributed to this document, including William Ampofo, Sam Avrett, Emily Bass, Ward Cates, Manju Chatani, Chris Collins, Omololu Falobi, Anna Forbes, Barbara Friedland, Henry Gabelnick, Lori Heise, Sharon Hillier, Jeff Hoover, Quarraisha Abdool Karim, Tessa Mattholie, Sheena McCormack, Ian McGowan, Elizabeth McGrory, Pam Norick, Chidi Victor Nweneka, Gita Ramjee, Helen Rees, Renee Ridzon, Zeda Rosenberg, Alan Stone, Morenike Ukpong, Mitchell Warren, and Kevin Whaley.

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EXECUTIVE SUMMARY

The relentlessness of the HIV/AIDS epidemic and its growing feminization have prompted global health leaders to acknowledge the urgency of developing new prevention technologies. Microbicides are now recognized as among the most promising prevention technologies on the horizon. Significant advances have been made in microbicide research and development over the last 15 years. Numerous products are now advancing in clinical trials. New strategies for product design and delivery are moving through pre-clinical development. Involvement by governments and philanthropies is steadily increasing. Public-private partnerships and collaborations among research teams are making important contributions to the product pipeline and to clinical development.

Yet despite new resources and attention to the field, microbicide research still falls far short of the comprehensive, full-scale global effort that is needed to develop and deliver a product as quickly and efficiently as possible. Two years from now we may hear the results from at least one microbicide effectiveness trial. The field needs to be ready for this news, with plans in place for licensing, production, and delivery if a product proves safe and effective. In addition, regardless of the results of the first trials, we need a rich set of next-generation candidates in development and entering clinical studies.

This report takes stock of the microbicide field and looks to the future to understand what changes are needed to promote a more vigorous and strategic effort. It identifies six priorities for action:

- **DIVERSIFY THE LANDSCAPE.** The current stock of microbicides in development is a mix of truly innovative candidates and incremental improvements on products currently in clinical testing. Research and development must be better funded to support an expanded pipeline of candidates, refinement of current products, and evaluation of the potential of combination approaches. Equally important is expanded research into the basic mechanisms of sexual transmission, immunology, and physiology.
- **ENSURE FORWARD MOMENTUM IN CLINICAL RESEARCH.** Several clinical trials of the first generation of microbicide candidates may soon produce safety and effectiveness data. Microbicide clinical research is costly, but knowledge gleaned from microbicide clinical trials is already feeding into the development of the next generation of products and design of future trials. Researchers must also continue to attend to a variety of priorities that will make clinical research sustainable, including establishing standards of care for trial volunteers, implementing procedures and policies guaranteeing that communities are better off when they participate in research, creating a more robust behavioral research agenda, and monitoring safety and effectiveness in post-licensure studies. Substantial funding will be required for new trials. At the same time, it is essential that there be a more objective, collaborative process for deciding which products proceed to advanced testing so that resources are well invested.
- **IMPROVE THE REGULATORY TERRAIN.** The current multitude of regulatory systems and lack of clarity about trial design requirements for licensure threaten to delay testing, licensing, and delivery of microbicides. Expanded efforts are needed to improve regulatory capacity in less-developed countries and regions. The dominant regulatory agencies in the United States and Europe must do more to promote product development guidance and regulatory review that meet the needs

of populations in resource-constrained countries. In addition, the microbicide community must prepare for forthcoming needs associated with new drug applications (NDAs), such as funding the manufacture of registration batches and long-term toxicology studies.

- **ALLOCATE SUFFICIENT FUNDING TO REALIZE SCIENTIFIC OBJECTIVES.** Through hard work and focused efforts, microbicide development has gained substantial new funding over the last several years. But current investment levels are not sufficient to take advantage of the most promising scientific opportunities for product development or to move current and new products through pre-clinical and large-scale clinical research to commercialization. Current global investment is just over half of the calculated need in the field and less than a quarter of the level invested in parallel efforts for HIV vaccine development.

- **STEER THE RESOURCES WELL.** The microbicide field is moving toward greater coordination and collaboration, and these efforts must continue. New investments must be channeled more strategically into the most promising new pre-clinical and clinical research, as well as toward manufacturing and regulatory approval. Funders should collaborate more closely to expand resources dedicated to microbicide research and allocate them wisely. Trial designers should build firmer alliances and improve coordination in clinical trial design, thus facilitating comparison and validation of clinical research data across sites. In addition, clinical entities engaged in all aspects of HIV prevention research need to do a better job of coordinating site selection and strengthening activities to ensure expanded and sustained trials capacity.

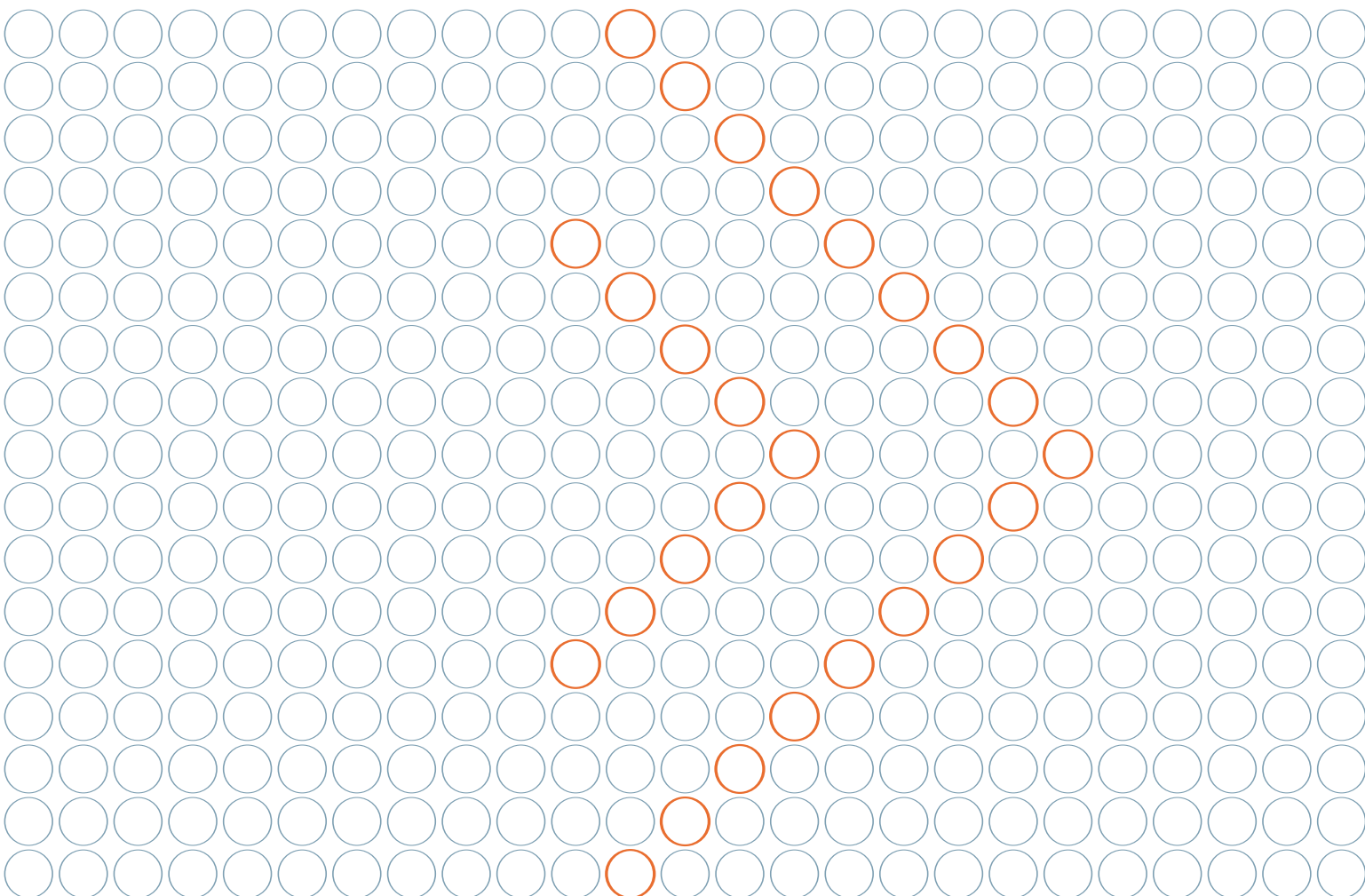
- **EXPAND A CLEARLY DEFINED RESEARCH PROGRAM IN THE UNITED STATES AND BUILD UPON NEW MOMENTUM IN EUROPE.** For years the US National Institutes of Health (NIH) has been a pioneer in its support of microbicide research. With additional funds, the agency can play an even greater role, launching a new clinical trials network and creating a branch dedicated to coordinated support for the field. Passage of the *Microbicide Development Act*, now being considered by the US Congress, could hasten such changes. In addition, Canada and European nations, individually and collectively, can build upon the current momentum and interest in this field by placing greater priority on microbicide funding.

Microbicides can only have a powerful and sustained impact on the AIDS pandemic if they are globally available to those most at risk of infection, particularly women in resource-limited countries. Advocates, policy makers, and donors are beginning to wrestle with the multiple challenges involved in global access, and these efforts deserve greater support.

Recent progress in microbicide research is due largely to 15 years of concerted advocacy by hundreds of people from civil society, the research community, donors, and health advocates—and to the commitment of the thousands of individuals participating in clinical trials. A growing international advocacy effort will be essential if this field is to successfully meet the many challenges ahead: running multiple large-scale trials; obtaining regulatory approval; maintaining the support of communities; pushing for new investments and accelerated research on new products; and ensuring rapid global access to successful products. Advocates, researchers, and donors across HIV prevention research and clinical testing have much to share with one another in the years ahead.

01

MICROBICIDES: MOVING TOWARD IMPROVED HIV PREVENTION



NEW PREVENTION TECHNOLOGIES ON THE HORIZON

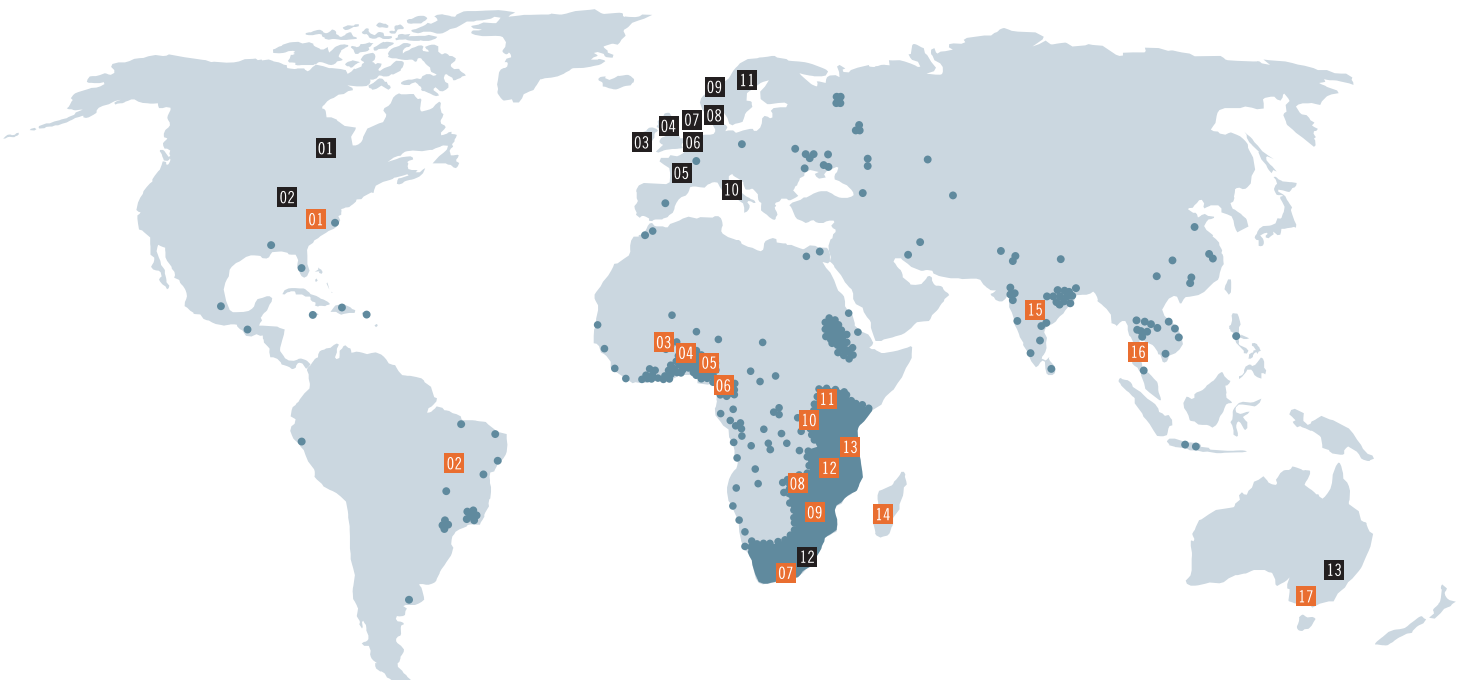
HIV infection is preventable. Increased investment in several core interventions—including safe blood supplies, risk-reduction education and support, access to male and female condoms, HIV testing and treatment, basic health care, and anti-stigma campaigns—could significantly reduce HIV incidence throughout the world.

But for many millions of people, current HIV prevention approaches are, and will remain, wholly inadequate. Millions of women are not able to insist on condom use with their male sexual partners. Poverty, unequal social and legal status, and other factors put women at particular risk. Today, 17.5 million women are living with HIV, and in Southern Africa, the region most devastated by AIDS, nearly six out of ten adults living with HIV are women.

Five million new HIV infections each year and a growing feminization of the epidemic make it obvious that the world needs better HIV prevention technologies. After years of lackluster investment and attention from the public and private sectors, microbicides now show increasing promise as an effective HIV prevention tool of the future. A variety of other potential HIV prevention interventions are now being tested as well, including male circumcision, diaphragms, acyclovir for HSV-2 suppression, and oral tenofovir. If shown to be effective, each of these tools, separately and together, would advance HIV prevention efforts. Ideally, several new HIV prevention methods, including microbicides, will be developed and licensed for use in the coming years.

Microbicides are compounds that, when applied topically, have the potential to prevent infection by HIV and a number of other sexually transmitted infections.

A GLOBAL EFFORT



CURRENT HIV PREVENTION OPTIONS AND STRATEGIES
Ensured safety of blood supplies
Behavioral risk-reduction interventions
Risk reduction in drug use
Post-exposure prophylaxis (oral antiretroviral treatment in occupational settings for HIV-uninfected adults after exposure to HIV)
Perinatal HIV treatment/prevention of mother-to-child transmission
Voluntary counseling, testing, diagnosis, and treatment of HIV infection

● **People newly infected with HIV in 2005:** *each dot represents an estimated 10,000 people newly infected with HIV in 2005.*[1]

■ **Countries with ongoing and planned clinical trials in 2005-2006:** includes countries where at least one clinical research site has a protocol submitted or awaiting approval, is in active recruitment, has begun or completed enrollment, or where clinical studies are completed but published analysis is pending.[2]

01 United States
02 Brazil
03 Burkina Faso
04 Benin
05 Nigeria
06 Cameroon
07 South Africa
08 Zambia
09 Zimbabwe
10 Rwanda
11 Uganda
12 Malawi
13 Tanzania
14 Madagascar
15 India
16 Thailand
17 Australia

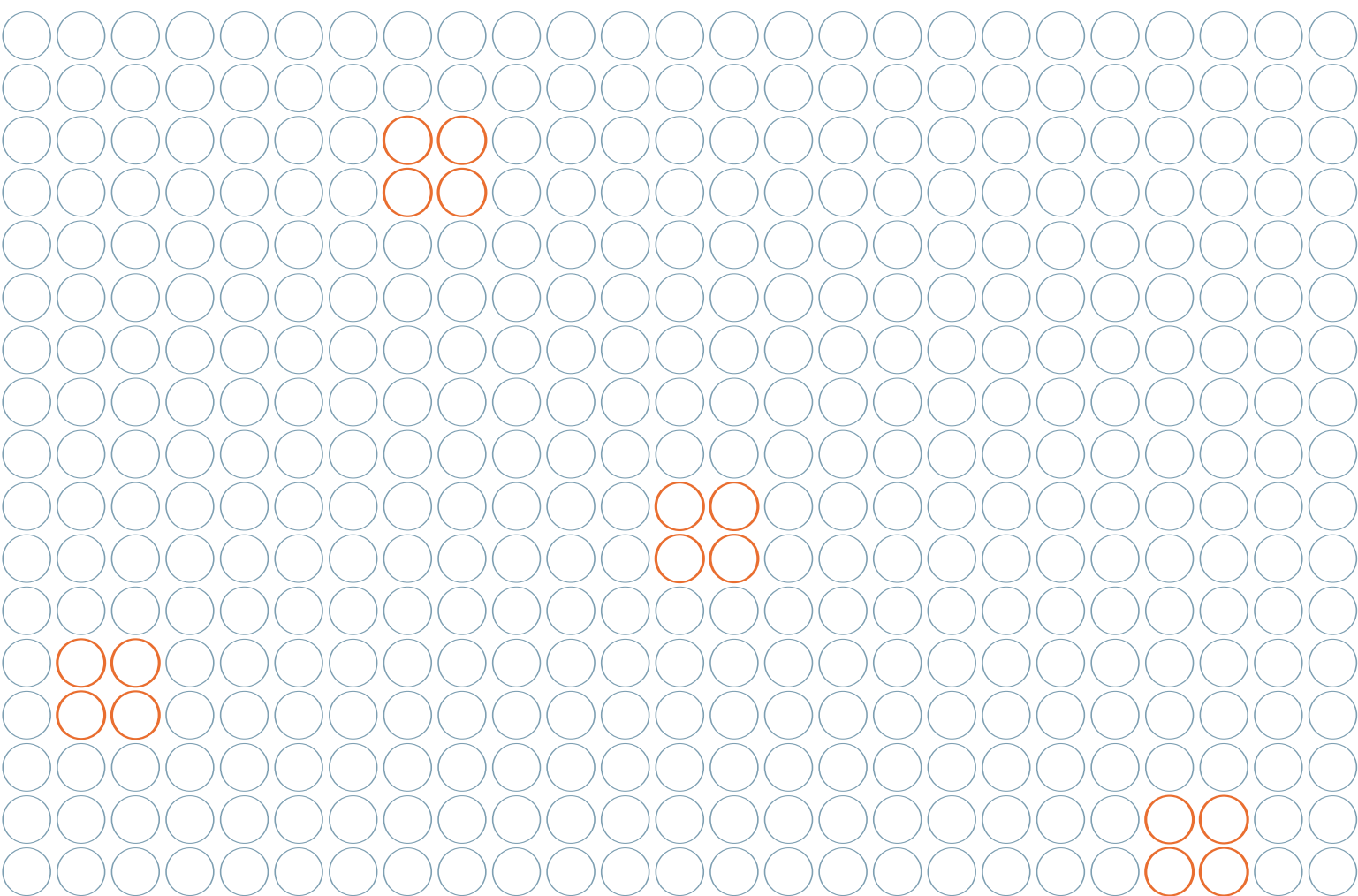
■ **Countries with public and/or private sponsors of microbicide development in 2000–2005:** indicates locations of agencies that fund microbicide development or directly develop products.[3] Multilateral agencies that have supported microbicide development include the European Commission, the United Nations Population Fund (UNFPA), and the World Health Organization (WHO).

01 Canada
02 United States
03 Ireland
04 United Kingdom
05 France
06 Belgium
07 Netherlands
08 Denmark
09 Norway
10 Italy
11 Sweden
12 South Africa
13 Australia

POTENTIAL HIV PREVENTION OPTIONS NOW BEING RESEARCHED
Microbicides
Post-exposure prophylaxis (oral antiretroviral treatment in non-occupational settings for HIV-uninfected adults after exposure to HIV)
Pre-exposure prophylaxis (oral antiretroviral treatment for HIV-uninfected adults before potential exposure to HIV)
Male circumcision
Preventive and therapeutic HIV vaccines
STI treatment for community-wide reduction of HSV-2 (herpes) and other STIs
Treatment to reduce viral load in HIV-infected individuals
Use of diaphragms and other barrier methods

02

PRODUCTS IN CLINICAL DEVELOPMENT



Sixteen candidate microbicides have reached the clinical stages of development. Of those, five have entered late-stage trials to assess their effectiveness. The earliest data about the effectiveness of these candidate microbicides might be available in 2008. It is possible that none of the current effectiveness trials will generate a microbicide sufficiently effective for licensing. However, much is already being learned from these trials that will be critical for the next generations of new, refined, and combined candidates coming down the pipeline into effectiveness testing.

Sixteen candidate microbicides are now in clinical evaluation; five are in large advanced studies.

The "present generation" of candidates in clinical development includes products utilizing three of the major mechanisms of action through which topical microbicides are intended to work: vaginal defense enhancement, cell surface disruption (surfactants), and entry and fusion inhibition. The fourth major category of action is replication inhibition. Below is a discussion of the central mechanisms of action, with examples of associated products that are now in clinical development.

VAGINAL DEFENSE ENHANCERS boost women's natural defenses against disease. The vagina is normally too acidic for sperm to survive. However, semen, which is alkaline, neutralizes the acidity of the vagina, thereby enabling sperm—and HIV and other pathogens—to survive more easily. Acid-buffering microbicides are designed to counteract semen's neutralizing effects and keep the vagina acidic in order to inactivate sperm and some STI organisms, including HIV. Concepts in development include BufferGel™, Acidform™ gel, Mucocept™, and a product that mobilizes the acidifying action of lactobacilli.

- **BufferGel™**, developed at Johns Hopkins University and ReProtect, Inc. (both in the United States), is a clear gel intended to keep the vagina acidic even in the presence of semen. It also creates a lubricating physical barrier that reduces passage of pathogens into vaginal and cervical tissue. BufferGel™ may be effective in preventing HIV and other STIs such as HPV, HSV, chlamydia, and gonorrhea, and clinical trials provide

evidence that it might also be used to treat bacterial vaginosis, a common condition that may increase risk of HIV infection. It has successfully completed Phase 2/3 contraceptive trials sponsored by NIH's National Institute of Child Health and Human Development (NICHD). Through the NIH-sponsored HIV Prevention Trials Network (HPTN), BufferGel™ has been tested in women in India, Malawi, the United States, and Zimbabwe for safety, and is now being evaluated in a large four-arm Phase 2b trial in five African countries together with PRO 2000 (an entry and fusion inhibitor). Both products are being compared against an inactive placebo gel and against no gel. Initial trial results for HIV prevention are due in 2008.

SURFACTANTS disable bacteria and viruses by damaging the organisms' membranes and outer coatings. In this activity they are similar to currently available spermicides such as nonoxynol-9 (N-9). For safety reasons, researchers have focused on low concentrations of surface-acting microbicidal agents that are unlikely to harm epithelium, the protective layer of cells lining the vagina and rectum.

- **Savvy™** (C31G) is a clear gel formulation containing a surface-acting agent that was developed by Biosyn Inc., later acquired by Cellegy (both small US-based biopharmaceutical companies). The product was recently licensed to CONRAD for potential public-sector development for resource-constrained countries. Pre-clinical results indicate activity against HIV as well as HSV, chlamydia, gonorrhea, and syphilis. A Phase 3 clinical trial is enrolling women in Nigeria to test Savvy's HIV prevention effectiveness, and a Phase 3 contraceptive effectiveness trial of the product has started in the United States.

ENTRY AND FUSION INHIBITORS form a large and highly varied product category that includes three candidate products now in effectiveness trials: Carraguard®, PRO 2000, and Cellulose sulfate (CS/Ushercell™). Some of these products are nonspecific blockers, which means that they do not inhibit specific viral pathogens, gene products, or transmission pathways but may act against multiple organisms. Some work by attaching themselves to pathogens, preventing attachment to host cells. Others bind to potential host target cells, forming a protective coating that prevents pathogens from attaching.

- **Carraguard®** (PC-515), developed by the Population Council, an NGO based in the United States, is a clear gel containing carrageenan, a sulfated polysaccharide derived from seaweed. Carraguard® provides a physical barrier between pathogens and vulnerable cells in the vaginal or rectal epithelium and may also bind to viruses, including HIV, HPV, and HSV, thereby blocking their

adherence to healthy cells. A Phase 3 trial began in March 2004 to evaluate the product's long-term safety and effectiveness in preventing HIV transmission. The trial, which has enrolled over 6,000 women in South Africa, is expected to continue through 2007.

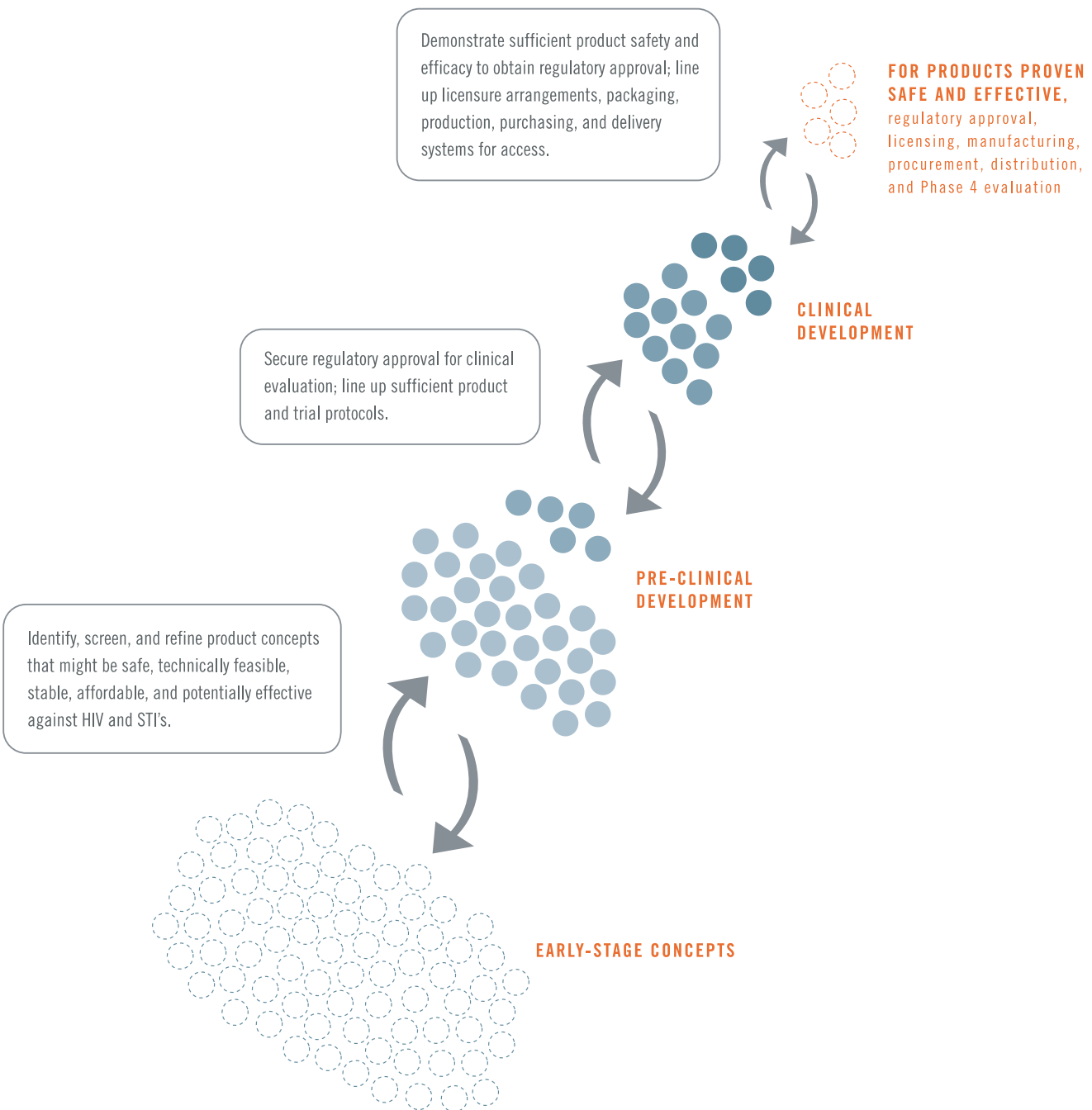
- **PRO 2000** (polynaphthalene sulphonate) is produced by Indevus Pharmaceuticals, Inc. (a US-based company). It binds to HIV and other STI pathogens such as chlamydia and HSV-2, preventing them from infecting human cells. A Phase 2 HIV prevention clinical trial, sponsored by the HPTN, started in late 2004 and involves 3,100 women in seven countries. The trial is evaluating the safety and effectiveness of BufferGel™ and a low dose of PRO 2000, and has been expanded into a Phase 2b trial in four African countries. PRO 2000 is also being evaluated in two dosages in South Africa, Tanzania, Uganda, and Zambia with the support of the UK Microbicides Development Progamme (MDP).

- **Cellulose sulfate (CS/Ushercell™)**, developed by the Canadian firm Polydex Pharmaceuticals Ltd. in partnership with CONRAD and Rush University's TOPCAD program in the United States, has been undergoing evaluation since the early 1990s. In laboratory and animal studies, cellulose sulfate acts against a broad range of STIs. Researchers are conducting two Phase 3 clinical trials to assess its effectiveness: Family Health International (FHI) is supporting a trial with over 2,000 participants in Nigeria, and CONRAD is supporting a trial with over 2,000 participants in Benin, Burkina Faso, India, South Africa, and Uganda. Completed Phase 2 trials suggested that the product also has contraceptive activity.

REPLICATION INHIBITORS prevent viruses from multiplying in the cells they have entered. Currently, the repertoire of replication inhibitors is limited to those that target the HIV reverse transcriptase enzyme, critical for HIV replication. Many replication inhibitors were initially explored as potential HIV therapies but were found inadequate because they are not readily absorbed, which, in contrast, enhances their plausibility as microbicide candidates.

- **Tenofovir** (PMPA Gel), produced by Gilead Pharmaceuticals in the United States, works in the same way as some of the antiretroviral drugs currently used for HIV therapy: it interrupts replication of the virus once it enters cells. The hope is that tenofovir can be absorbed by cells in the vaginal epithelium and then stop the virus once it enters the outer cells of the vaginal wall. Tenofovir for use as a microbicide will be evaluated in two Phase 2 studies.

STAGES OF MICROBICIDE RESEARCH AND DEVELOPMENT

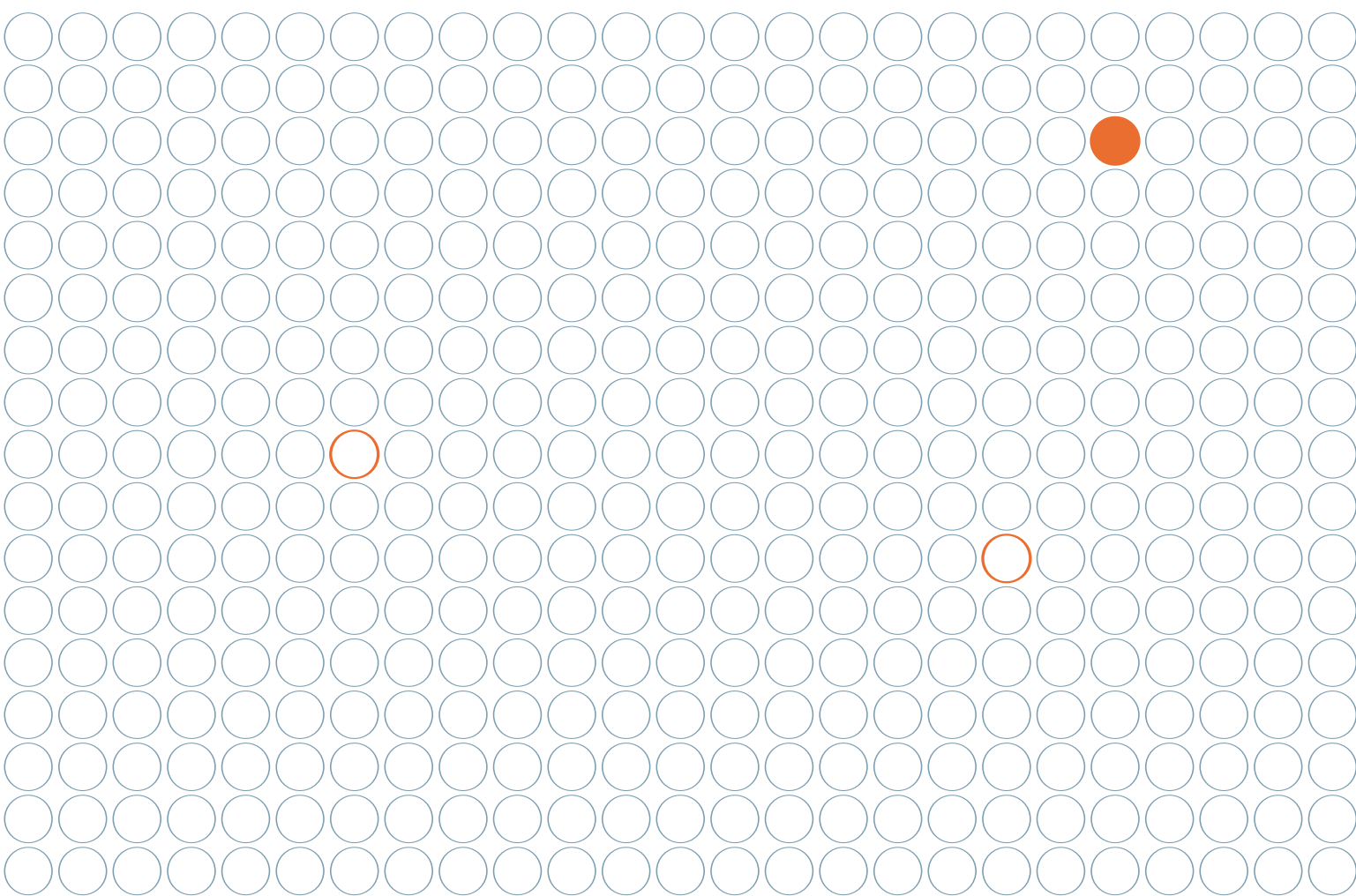


MICROBICIDES IN ONGOING CLINICAL TRIALS			
MECHANISM OF ACTION	CANDIDATE PRODUCT	DEVELOPER	PHASE*
Vaginal defense enhancers	ACIDFORM™/Amphora™ gel	CONRAD, Instead, Inc.	Phase 1
	Lime juice	CONRAD, University of California/Berkeley, University of Melbourne	Phase 1
	Protected lactobacilli in combination with BZK	Biofem, Inc.	Phase 2
	BufferGel™	ReProtect, Inc.	Phase 2/2B
Surfactants	Savvy™ (C31G)	Cellegy/Biosyn, CONRAD	Phase 3
Entry/fusion inhibitors	Cellulose acetate 1, 2-benzenedicarboxylate (cellacefate/CAP)	Lindsey F. Kimball Research Institute, Dow Pharmaceuticals	Phase 1
	VivaGel™ (SPL7013 gel)	Starpharma Ltd.	Phase 1
	Invisible Condom™	Laval University	Phase 1/2
	Carraguard®	Population Council	Phase 3
	Cellulose sulfate gel (CS)	CONRAD	Phase 3
	PRO 2000 (0.5% and 2%)	Indevus Pharmaceuticals, Inc.	Phase 2B/3
Replication inhibitors	UC-781	Cellegy/Biosyn, CONRAD	Phase 1
	TMC120	International Partnership for Microbicides	Phase 2
	Tenofovir/PMPA gel	Gilead Sciences, Inc.	Phase 2/2B
Uncharacterized mechanisms	Praneem Polyherbal Vaginal Tablet	Talwar Research Foundation	Phase 2
Combinations	PC 815 (Carraguard and MIV-150)	Population Council	Phase 1

Source: Alliance for Microbicide Development, Microbicide Research and Development Database (MRDD). March 2006.
Note: Some products are in more than one phases of clinical testing. The phase listed in this table represents the most advanced clinical trial currently underway for each product.

03

DIVERSIFYING THE PRODUCT LANDSCAPE



SCREENING CONCEPTS FOR FURTHER DEVELOPMENT

There are now an estimated three dozen candidate microbicides in pre-clinical research and development. Approximately 30 of these are in an early stage of discovery and pre-clinical development. A remaining few are in more advanced pre-clinical development, poised to cross from laboratory and animal testing into clinical evaluation if key scientific and regulatory criteria can be satisfied.

This number of potential products is not large enough. Attrition is an inevitable part of product development, and might be higher for a technology as new and innovative as microbicides. The majority of early candidates may not withstand closer scrutiny for reasons of technical feasibility or safety, and some may prove prohibitively expensive or unstable in the environmental conditions in the countries with the greatest burden of new HIV infections. Development of candidate products may also be delayed simply because of uncertainties surrounding technology ownership and development rights. To overcome these realities and advance a reasonable number of plausible candidates into safety studies in the clinic, a robust pre-clinical development effort is essential, with ongoing and sufficient funding support to continually identify, refine, and advance products.

Four of the five microbicide products now in effectiveness studies resulted from collaborations between the public and private sectors.

Beyond the need for more candidate products, all microbicide prospects need some level of assessment and "go/no go" determination before entering advanced pre-clinical development. Still further assessment is needed before candidates advance into early clinical testing, and then into the major resource commitments of large clinical trials.

The microbicide field is now faced with the challenge of developing some mechanism or mechanisms for this assessment, an agreed process by which candidate products can be objectively evaluated for further study in a way

MICROBICIDE CANDIDATES IN PRE-CLINICAL DEVELOPMENT[4]	
MECHANISM OF ACTION	CANDIDATE COMPOUND/PRODUCT
Vaginal defense enhancers (5)	Genetically engineered probiotics
	Lactobacillus-delivered Cyanovirin-N
	MucoCept HIV
	RANTES peptide
	Single chain anti-ICAM antibodies
Surfactants (2)	Alkyl sulfates
	Polybiguanides
Entry/fusion inhibitors (21)	Antibodies and fusion proteins (HIV, HSV, HPV), tobacco-derived
	Betacyclodextrin
	bKLA
	BMS-38806
	CMPD 167
	Cyanovirin-N
	Flavinoids
	K5-N, OS(H)
	Lactoferrin/DC SIGN
	Mandelic acid condensation polymer (SAMMA)
	Novaflux proprietary product
	Optimized dendrimers
	Pomegranate juice
	Porphyrins
	PSC-RANTES
	Recombinant lactic acid bacteria (LAB)
	Retrocyclin
	siRNA
	Soluble DC-SIGN
	TAK779
	TatCD
Replication inhibitors (1)	MC1220 (as lead compound in dihydroxy alkyl benzyl oxopyrimidine series)
Combination (2 or more actives or 2 or more mechanisms of action) (6)	BufferGel™ with dendrimers (SPL7013 and optimized dendrimers)
	CAP with NCp7 nucleocapsid inhibitors
	M167, BMS, polyanion
	PC 710 (Carraguard® and Zn)
	PC 815 (Carraguard® and MIV-150)
	SJ3366
Uncharacterized mechanism (1)	CO (ciclopiroxolamine)

Note: This chart includes only those candidate microbicides about which researchers and developers have provided information, and therefore is not exhaustive.

The cost of producing products for clinical evaluation

Development of microbicides involves putting active agents into a formulation (e.g., a gel, cream, or foam), and/or delivery device (e.g., applicator, vaginal ring, or pre-loaded diaphragm), and packaging the resulting product. For a candidate microbicide product to be considered for clinical evaluation, product developers must demonstrate that it has a consistent and stable formulation based on extensive laboratory and animal safety data. The candidate product is then manufactured in increasingly larger quantities for clinical trials, an expensive step that must be taken long before it is known whether the product is effective and marketable. For example, a Phase 1 trial involving 30 volunteers can require 1,000 applicators and individual product doses —a challenge for small biotech companies or university teams to produce, especially since funding for such pilot lots is elusive at best.

Over the next five years, dozens of microbicide products could be evaluated in multiple Phase 1 studies. Some will proceed to Phase 2 and 3 clinical evaluation. In the coming years it will be essential that major funders support the formulation, packaging, and manufacture of microbicide products for large–scale clinical trials.

that is evidence-based, fair, and transparent, and that demonstrates accountable and strategic use of resources. The need for this is immediate: several advanced pre-clinical and early clinical microbicide candidates are already vying for resources in a funding context that is challenging at best.

ENLISTING PRIVATE-SECTOR EXPERTISE

Large pharmaceutical and biotechnology companies have essential resources and expertise for microbicide research and development, including ownership of compounds for potential product development, capacity for manufacture of pilot lots for clinical research, and experience with marketing research that can inform product design and delivery.

Public-private partnerships (PPPs) are an important strategy to harness private-sector know-how in microbicide development. In fact, four of the five microbicide products now in effectiveness trials have been developed through collaborations between the public and private sectors, and more than a dozen small biotechnology companies are now researching and developing candidate microbicides. Recently, a few large pharmaceutical companies have made drugs available for evaluation or entered into royalty-free licensing agreements with microbicide organizations to develop, manufacture, and distribute any eventual products in developing countries. Organizations such as CONRAD, FHI, and the Population Council, and in Europe, the

European Microbicides Project (EMPRO) have each recruited some private-sector involvement (although less than any of them would like). And, during the past three years, the International Partnership for Microbicides (IPM) has executed several product development arrangements with private-sector partners. In addition, advocacy partnerships have already demonstrated success in mobilizing international policy awareness and commitment for microbicide development at the highest levels, catalyzing new governmental funding, and initiating innovative information-sharing arrangements with companies and government research entities.

However, commercial involvement in microbicide R&D has so far been extremely limited. A recent analysis found that in 2004 commercial investment in microbicides was between US$ 3 million and US$ 6 million.[5] Most small biotechnology companies involved in microbicide products rely on public-sector funding and technical assistance to develop their products for expanded clinical safety trials and for larger effectiveness trials. Public-sector funding is essential to help small companies and university teams maintain their development work through inevitable delays and technical complications.

To continue to assist product sponsors in development efforts, public-sector entities should:

- expand contractual support for scale-up of facilities, manufacturing processes for both drug product and formulations, packaging, and delivery mechanisms. This support is needed in advance of investigational new drug (IND) status and Phase 1 trials and then again in advance of Phase 3 trials;
- increase resources available for Phase 3 trial infrastructure and implementation, particularly in anticipation of the opportunity to evaluate combination products and run comparative (or non-inferiority) Phase 3 studies if a current Phase 3 trial demonstrates some level of effectiveness;
- expand support for collection of ancillary Phase 3 research data that might be required for regulatory review, such as information on adherence in the trials and likely consumer adherence for a prescription or over-the-counter product;

However commercial involvement in microbicide research and development has so far been extremely limited.

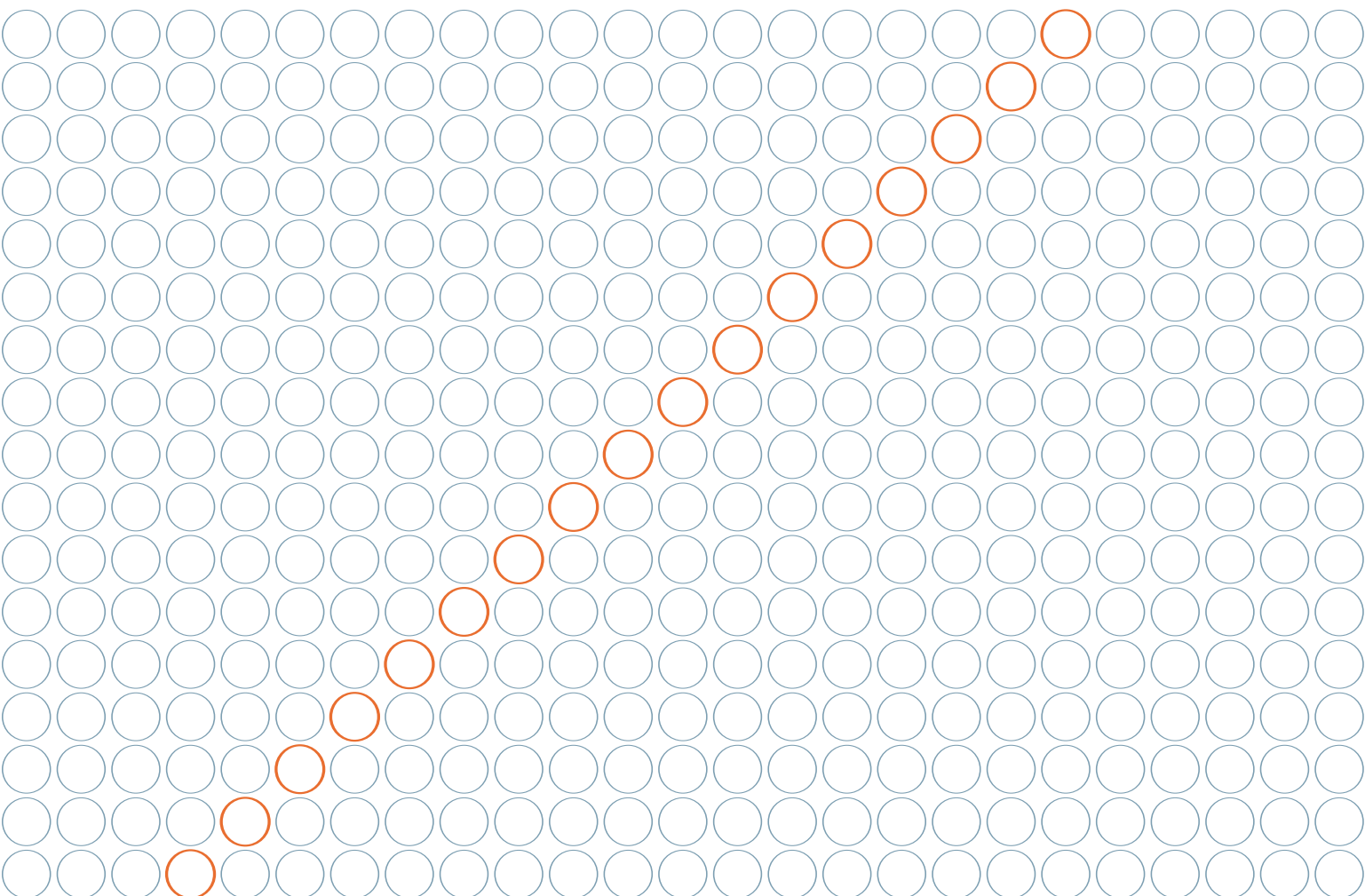
- provide funds to ensure approvable new drug applications (NDAs), including funding of FDA-mandated reproductive toxicology and carcinogenicity studies, registration batches and assembly of the NDA; and
- develop plans for bridging studies to assess safety in broader populations and Phase 4 trials to assess strategies for distribution.

Private-sector involvement in development and delivery of microbicides should also be facilitated through policy-oriented work by public sector and advocacy organizations to:

- estimate demand for various kinds of microbicide products;
- research product acceptability to determine optimal delivery mechanisms;
- document the feasibility of user education, product marketing and packaging;
- promote research on potential consumer use and acceptability;
- examine innovative product distribution methods;
- define public financing needs for product delivery to resource-poor communities; and
- identify strategies to reduce potential liability costs.

04

FORWARD MOMENTUM IN CLINICAL RESEARCH



Microbicide clinical research is conducted at dedicated research clinics, university teaching hospitals, large clinical research institutions, and community sites—usually far from the headlines of AIDS politics and global health policy. On these frontlines of prevention research, capacity and infrastructure are needed to support the researchers and research participants who are helping to assess the safety, acceptability, and potential effectiveness of candidate microbicides.

Partnerships with communities are pivotal to implementing and sustaining large-scale trials. The closing of several tenofovir trial sites in 2004 and 2005 attests to the importance of community understanding, ownership, and support. This is only possible if community members are involved from the beginning in the planning and implementation of clinical trials. There are six key aspects of clinical research that have significant implications for policy over the coming years. Each is discussed below.

A robust and long-term clinical evaluation effort is now an urgent priority for the microbicide field.

The timing is crucial. Over the next five years, new data will be generated from clinical trials in Africa, Asia, Europe, and the United States about possible effectiveness of at least one microbicide. A dozen or more microbicide candidates could soon be brought into early HIV clinical testing, and perhaps 20,000 to 60,000 participants will be recruited to enroll in new large-scale effectiveness trials. Additional participants will be needed to help determine effectiveness against STIs and evaluate contraceptive activity, and Phase 4 evaluation will make additional demands. A robust and long-term clinical evaluation effort is now an urgent priority for the microbicide field.

BUILDING CLINICAL TRIAL INFRASTRUCTURE, EXPERTISE, AND COMMUNITY SUPPORT

Clinical trial sites, researchers, participants, and communities on six continents are now engaged in the microbicide effort. Much of the funding for this comes from the US and UK governments, primarily from three US agencies—the NIH, the Centers for Disease Control and Prevention (CDC), and the US Agency for International Development (USAID)—and from the UK Department for International Development (DFID). Additional funding and support are provided by private-sector companies, philanthropy (the Bill & Melinda Gates Foundation),

government investment in product development initiatives such as the IPM and EMPRO, and direct or in-kind domestic government support to clinical research sites such as in South Africa. Building expanded clinical trial infrastructure, expertise, and community support is now an urgent and essential component of microbicide development. Several organizations have begun to inventory the exact projected infrastructure and funding needs for site and cohort development, ongoing clinical research training, and implementation of Phase 1, Phase 2, and Phase 2B/3 trials to sufficiently and successfully evaluate the effectiveness of candidate microbicides. These infrastructure and funding calculations have yet to be compiled and analyzed, but all told, a preliminary analysis indicates that the needed clinical trial effort will soon require an investment of no less than US$ 165 million per year.

Building expanded clinical trial infrastructure, expertise, and community support is not only urgent but essential.

ANTICIPATING 'NO EFFECTIVENESS' AND 'PARTIAL EFFECTIVENESS'

The international Phase 2B and Phase 3 clinical trials of microbicides now underway are asking several scientific questions that are crucial to determining product effectiveness and potential viability. These questions center on three issues:

- *proof-of-concept:* Is there evidence showing that the microbicide approach(es) under evaluation **can** work in human subjects to partly or entirely prevent HIV infection, indicating a useful direction for further product research and development?
- *effectiveness:* Is there evidence that the microbicide(s) **do** prevent HIV infection?
- *correlates of protection:* Is there evidence of any factors linked to microbicide-related prevention of HIV infection, such as immune responses or other biological markers?

The large clinical trials now evaluating current-generation candidate microbicides may very possibly not demonstrate effectiveness of any product. The microbicide field should be prepared for the communications challenges this news would bring, and should also be ready to emphasize that many trials that fail to show effectiveness can still produce information that is valuable to development of new products and planning of future clinical trials. Policy makers, the media, and the public also need

Anticipating and communicating developments

The Microbicide Media Initiative (MMI), currently spearheaded by the Global Campaign for Microbicides (GCM), was recently established to help build enthusiasm and political support for microbicides while avoiding raising unrealistic expectations. The MMI is expected to serve as an ongoing global forum for stakeholders to share information about scientific and clinical developments in the field. Participants include communications professionals from NGOs, research organizations, biotech companies, and government agencies involved in microbicide development and other HIV prevention initiatives, who work collaboratively to identify and address communication challenges, prepare materials, and discuss shared communications strategies.

to understand that a new generation of improved approaches will likely be needed regardless of the outcome of today's effectiveness trials.

DEVELOPING SURROGATE MARKERS OF SAFETY, ADHERENCE, AND BEHAVIOR

The need to characterize, assess, and predict safety pervades the non-clinical and clinical development and testing of microbicides, and there is consensus that the field requires more powerful and less subjective measures than those at hand. Surrogate markers to help evaluate not just the safety but the effectiveness of candidate products are vital to rationalizing the microbicide pipeline to ensure that resources are invested in candidates with the highest probability of success.

Furthermore, because microbicide effectiveness relies on correct and consistent product use, trials must evaluate the extent of that use as prescribed by the study protocol. However, since microbicides are self-administered products employed privately in the context of sexual behavior, use must be assessed through behavioral research to a degree not required in clinical trials of therapies or preventive technologies such as vaccines, where administration can actually be observed. Assessing adherence to microbicide study protocol requirements thus depends on participant self-report, frequently unreliable and typically hard to verify.

That microbicide development has been hampered by a lack of adequate biological markers has been recognized for some time, yet there has been no coordinated, cross-field effort to correct the deficit until recently. Driven by this recognition and a shift toward a new "critical path" for drug development in general, the field is beginning to organize itself to identify new markers of safety and validate old ones, mine other field for fresh approaches, and learn from its own experience in assessing best practices in measuring critical behaviors. Studies are accumulating a wealth of internationally comparable data on perceptions of microbicides, their acceptability over a period of years, attitudes of sexual partners, and use in the context of vaginal products and condoms. This crucial work must be accelerated.

Standards of care can change: The example of HIV treatment

In the mid-1990s many thought it acceptable for people enrolled in HIV prevention trials to not be provided ARV therapy if they became infected with HIV during the trial. Ethical norms were transformed as the Brazilian government successfully implemented a national HIV treatment program, as South African patients began demonstrating and litigating for treatment access, and as Thai and Indian generic companies began manufacturing low-cost ARVs. A growing number of researchers now agree that it is inappropriate for research participants who become HIV positive in one part of the world to have access to drastically different treatment than research participants in another region.

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Trials of oral tenofovir for pre-exposure HIV prophylaxis (PREP)

In 2004 and 2005, communities involved in research, international activists, and local governments were critical of some clinical trials evaluating the use of the antiretroviral drug tenofovir taken orally as a potential HIV preventive agent. They cited a range of concerns ranging from claims of inadequate community engagement activities to lack of adequate rights and protections for trial participants. Study sponsors responded that they had invested in community preparedness efforts before the trial and did have HIV treatment plans and other participant services in place. But the vocal criticism from activist and community groups was an important signal that a new level of scrutiny is now being brought to HIV prevention research.

The results of the tenofovir controversies were dramatic: Reduced political support and several research interruptions caused two large trials to be closed. However, the 2004–2005 tenofovir travails brought new clarity about the importance of sustaining government, community, and activist support for trials not only at a local level, but at national and international levels as well. The media and public attention also pointed to a fairly consistent set of issues that must be addressed more consistently and collaboratively, including the adequacy of informed consent, ongoing community engagement, compensation for physical harm, and access to HIV treatment for those who seroconvert.[7]

LEARNING FROM EXPERIENCE

One point of entry into learning from experience, both with respect to behavioral research and the validation of biomarkers and possible surrogates, is for the field to position itself to systematically and jointly extract such learning and share it. The Clinical Trials Working Group (still known as the "Quick Working Group" because of the relative speed of its founding) established as the earliest output from the Funders' Consultation in April 2004, has already gone some distance toward such systematic joint learning. The purpose of the Group was to facilitate exchange of ideas and coordinate across the current late-stage trials, optimize comparability of data, and work toward some system for assay validation. About to meet for the fourth time, the Group has inventoried commonalities and differences across all major elements of their respective protocols to launch processes for comparison. It has also taken on some hard issues, including measurement of adherence and the implications of recruit pregnancies during trials, and is about to tackle the knotty problem of assessing HIV incidence in trial sites.

EVALUATING COMBINATIONS

AIDS treatment research has demonstrated that combination strategies very often work better than single interventions. It is also entirely likely that combinations of microbicides will one day prove to be more protective than single products. There is growing consensus among microbicide researchers that studies evaluating two candidate microbicide products will be needed. Several product sponsors have already developed combination microbicide products, joining two or more mechanisms of action into one candidate microbicide. For example, PC-815 is being developed by the Population Council as a combination of Carraguard® (an entry and fusion inhibitor) and MIV-150 (a replication inhibitor). TMC120, being developed by IPM, is formulated with a polyanion.

Such developments are important, but their expansion is limited by a standard regulatory approach to research in which individual products are tested separately against placebo or the current standard intervention. This approach usually allows the launch of trials of combination approaches only after establishing safety and effectiveness for single products. Rigorously following this one-trial-one-product/application tradition could delay access to combination microbicide products for years.

Microbicide researchers—and regulators—should take a closer look at the potential of combination trials and other novel trial designs to accelerate evaluation of the most promising microbicide combinations. Research leadership and funding will be required during the next five years to initiate large multi-product trials with sufficient numbers of trial sites and trial participants to generate effectiveness data for each product, and of sufficient size to run sub-studies to evaluate multiple indications for use for microbicides and other prevention interventions.

Anticipating other potential applications

The growing feminization of the AIDS

pandemic and the urgent need for a female-controlled HIV prevention method have made prevention of HIV infection through vaginal exposure the top priority for microbicide research. But if microbicide effectiveness is established for vaginal use, there will likely be consumer demand for microbicide products that can prevent pregnancy, protect against HIV infection through rectal exposure, or be used by HIV-positive women to prevent onward (secondary) HIV transmission to their partners. Several working groups have been established to anticipate the potential safety and effectiveness of these additional uses for microbicides. For example, in 2005, an international group of prevention scientists and advocates from Australia, Belgium, Canada, Mexico, Nigeria, the United Kingdom, and the United States joined together to create the Rectal Microbicides Working Group (RMWG). The RMWG regularly reviews the work of top researchers and pharmaceutical company representatives and works to develop proposed protocols and policies to advance this research.

IMPLEMENTING ETHICAL RESEARCH

Ethical issues involved in clinical research are complex, high-profile, and informed by sometimes incomplete guidelines and opaque international agreements. Yet there is growing global consensus in several areas related to research ethics.

Ensuring informed consent

The importance of gaining the consent of individuals to participate in research is one of the most elemental values in clinical research ethics. International guidelines underscore the importance of informed consent, but provide very little guidance about how to measure a volunteer's understanding of the risks and benefits involved in trial participation.

To ensure participants are giving truly *informed* consent, many research studies test individual comprehension on key research concepts prior to enrollment. At a recent international workshop convened by the Population Council and FHI, a range of creative approaches to informed consent were discussed. These strategies go well beyond a "signature on a form" and include one-to-one counseling, group discussions, booklets, flip charts, fact sheets, and videos. Trial staff at the two organizations are exploring how best to evaluate participant understanding, including using a range of qualitative approaches. The results of these efforts will provide a wealth of new information about how to achieve informed consent. The several groups engaged in evaluating innovative informed consent approaches should be encouraged to share their findings with researchers across HIV prevention research and clinical research more generally.

ARVs for seroconverters

Treatment and other services provided or supported through clinical trial sites have helped expand public services in research communities and represent an important contribution of HIV prevention research regardless of the results of effectiveness trials. One headline issue in HIV prevention

CURRENT STANDARD HEALTH INTERVENTIONS FOR ALL MICROBICIDE CLINICAL TRIAL PARTICIPANTS
HIV counseling and testing (and, increasingly, treatment where needed)
HIV risk-reduction counseling
Male condoms and education about their use (and, at some sites, female condoms)
Medical history and physical exam
Pelvic exam (including Pap smear in some countries and colposcopy in Phase 1 trials)
Family planning counseling and pregnancy testing
Referral to hospital and clinic care as needed
Regular screening and treatment for STIs, including chlamydia, gonorrhea, HPV, HSV, syphilis, and trichomoniasis

research ethics in recent years has been access to antiretroviral medicines (ARVs) for HIV infection. How should HIV treatment be guaranteed to trial participants who become infected with HIV during the course of a trial, especially if many of those who seroconvert might not require ARV treatment until several years after the study ends?

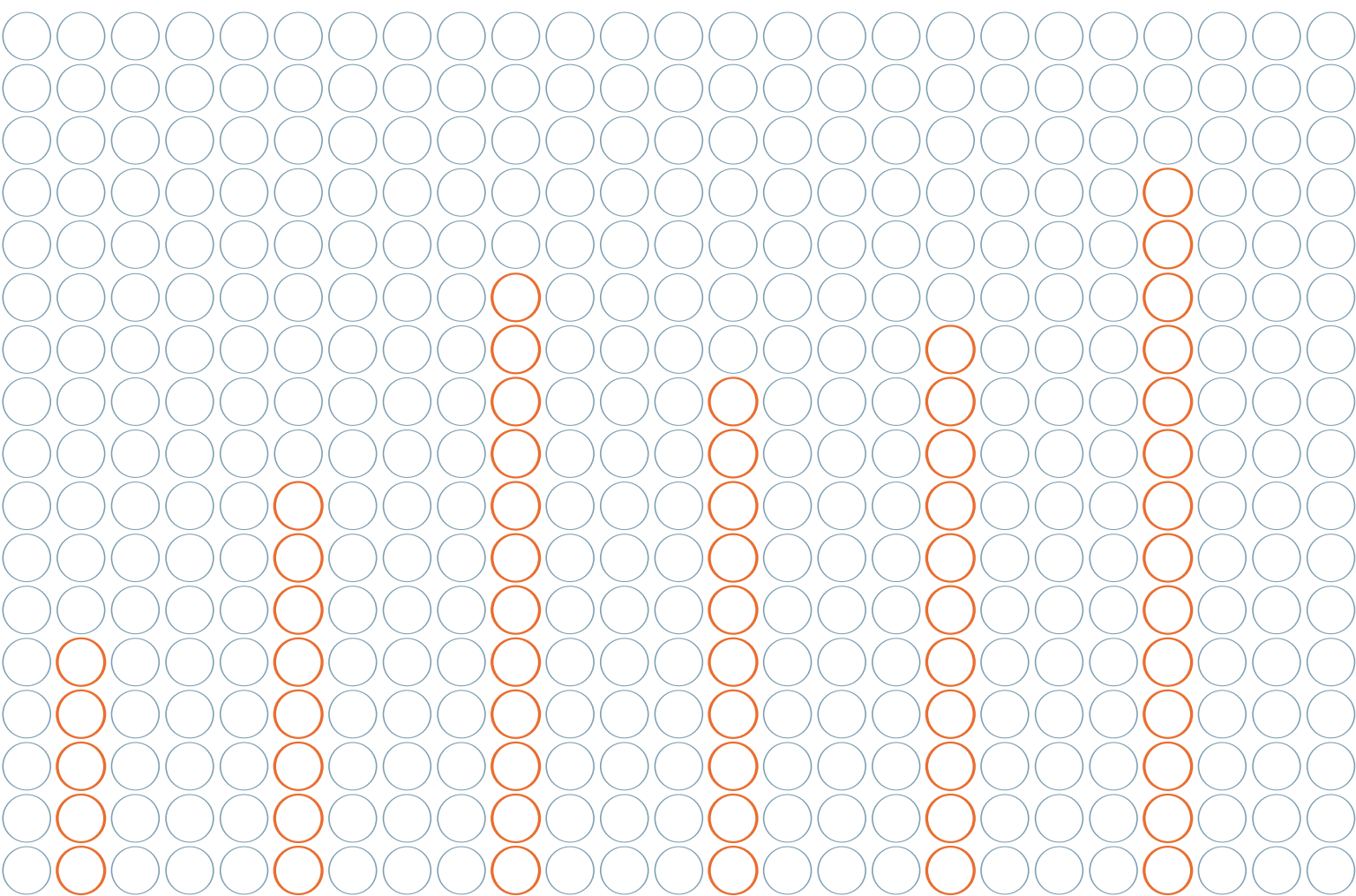
HIV prevention researchers are steadily moving in the direction of ensuring that trial sites establish arrangements for provision of ARVs and other HIV-related care to research participants who seroconvert in the course of a trial. Rather than debating "whether" to shoulder the serious long-term financial and logistical burden, the predominant question has become "how" to reasonably guarantee HIV-related care years after trials end.

In a statement issued in 2005, the Global Campaign for Microbicides argued for provision of ARVs to microbicide trial participants "based on ethical aspirations and existing social and political realities."[6] Several HIV prevention research organizations are formulating plans for ARV delivery in their trials, including FHI, the HIV Vaccine Trials Network, the International AIDS Vaccine Initiative (IAVI), IPM, and the South African AIDS Vaccine Initiative.

A remaining question for researchers, donors, and communities centers on what services should be provided to women who "screen out" of eligibility for a microbicide trial because they are HIV positive. Many trial sites now refer these individuals to support services in the community, and some sites provide financial support for these services. Many researchers and donors are concerned that providing ARVs to those who screen out would create substantial financial burden on researchers and would serve as an inappropriate inducement for women to volunteer for trials.

05

FUNDING AND MANAGING THE EFFORT



ALLOCATING SUFFICIENT RESOURCES

Microbicide research and development was sustained through the 1990s largely through the committed efforts of researchers at public and private institutions. Still, funding for this area of research was minimal for most of the first two decades of the AIDS epidemic.

An annual investment of $280 million is now needed.

In recent years, however, annual global investment has begun to increase markedly, rising from an estimated US$ 65 million in 2000 to US$ 163 million committed for 2005.[8] This increased global investment is due to the growing realization of the role microbicides could play in HIV prevention; mounting evidence of scientific feasibility; increases in overall AIDS and infectious disease research: and concerted efforts by advocates for microbicide research.

The US government has been the most significant public-sector funder of microbicide research from the beginning. In the last several years European governments have joined the effort, greatly expanding their investment in microbicide research.

The US government now allocates approximately US$ 117 million (fiscal year 2006 est.) to microbicide research and development. Just over half of that amount is spent through NIH, primarily through the National Institute for Allergy and Infectious Diseases and the National Institute for Child Health and Human Development. The annual microbicide budget at USAID increased from US$ 2.5 million in fiscal year 2002 to US$ 40 million in fiscal year 2006, and US$ 48 million has been requested for 2007. The agency's microbicide budget actually increased by US$ 10 million in the last session of Congress (for fiscal year 2006) even as funding for many other US government activities were being cut back. USAID is playing a crucially important role in the field and the agency has become a leading player in support of clinical research—approximately three-quarters of its microbicide budget is dedicated to clinical testing. In addition to increasing funding through these agencies, US policy makers should be encouraged to dedicate some funding through the President's Emergency Program for AIDS Relief (PEPFAR) in support of microbicide clinical trials and product development efforts.

FUNDING THE MICROBICIDE EFFORT

Investment in microbicide R&D by country in 2005.	$50,000 to $500,000	$500,000 to $1 million	$1 million to $5 million	$5 million to $10 million	$10 million to $25 million	over $25 million
AUSTRALIA	●					
BELGIUM	●					
CANADA			●			
CHINA	●					
DENMARK			●			
FRANCE		●				
GERMANY	●					
INDIA	●					
IRELAND			●			
ITALY	●					
NETHERLANDS				●		
NORWAY			●			
SOUTH AFRICA	●					
SWEDEN			●			
UNITED KINGDOM					●	
UNITED STATES						●

Latest available data on annual public-sector investment in microbicide research and development in 2004 and 2005. Only countries investing more than $50,000 are included. All amounts are US$.

The Microbicide Development Strategy: A new road map

In April 2004, the Bill and Melinda Gates Foundation and the Alliance for Microbicide Development co-sponsored a consultation among the primary funders of the late-stage clinical trials of microbicides. One major outcome from this Funders' Group meeting was agreement on the need to establish a coordinating mechanism for information-sharing and harmonization across microbicide research and development. This led to the establishment of the "Quick" Clinical Trials Working Group (Q/CTWG, described later) and, more recently, the Microbicide Development Strategy initiative (MDS).

The purpose of the MDS is to take account of changes in the microbicide field over the past five years, map the scientific and practical gaps along the field's research and development pathways, and identify and prioritize steps toward filling those gaps.

The MDS builds on progress in the microbicide arena and field-wide initiatives and should be a valuable tool for enhancing coordination and communication and tackling obstacles in developing and marketing microbicides. The MDS will serve multiple objectives: putting current and new efforts within a broader strategic context; driving communication and collaboration in priority areas; mobilizing new players and funding; and informing donors and policy makers. The MDS is based on the outputs of four working groups and its initial deliberations will be presented at the Microbicides 2006 Conference in Cape Town, South Africa, and the 16th International AIDS Conference in Toronto, Canada.

Funding outside the United States is on the rise as well. The governments of Canada and the Netherlands have each invested several millions of dollars each year in microbicide research and development. In December 2005, four European governments—Denmark, Ireland, Sweden, and the United Kingdom—collectively committed nearly US$ 30 million in new funding for microbicide research. Ireland and the Netherlands now lead the world in microbicide funding as a share of gross domestic product. The British government is now contributing more than US$ 14.5 million annually; the Dutch more than US$ 5 million; the Irish US$ 4 million; and the governments of Denmark, Norway, and Sweden each contributing approximately US$ 1.5 million.

The European Community's over-arching policy framework for confronting HIV/AIDS in the context of development is the European Programme for Action to Confront HIV/AIDS, Malaria and Tuberculosis through External Action, which will run from 2007–2013 and replaces the previous programme (2001–2006). Microbicides and increased R&D to accelerate their development—as well as support for clinical trial capacity, enhanced regulatory capacity, and support for international PPPs—are specifically mentioned within the new Programme for Action.

European Community support for microbicides is referenced in a specific budget line on poverty-related diseases.[9] Funding for microbicide development comes from the Research Framework Programmes 6 (FP6, which ended in 2006) and FP7 (which will run from 2007–2013). Under FP6 there was a specific call to establish a network of European researchers working on vaccines and microbicides. The European Community and member states also established the European and Developing Country Clinical Trials Partnership (EDCTP), which aims to support various clinical trials, including those involving microbicides. The EDCTP received €200 million (200 million euros; US$ 240 million) from FP6.

Several countries that have made extensive contributions to other HIV-related initiatives have yet to make substantial commitments to the microbicide effort. These nations—including Australia, Belgium, France, Germany, Italy, and Japan—should be encouraged to boost their microbicide funding.

From the philanthropic sector, the Bill and Melinda Gates Foundation has made the largest contributions to microbicide research, accounting for more than three-quarters of philanthropic giving between 2000 and 2004. The Foundation has committed itself to invest nearly US$ 55 million between 2005 and 2007. The Rockefeller Foundation also deserves commendation as a catalyzing early supporter of microbicide research and advocacy.

Innovative partnerships for clinical research capacity are now also seeing increased support at a national level in countries with relatively high HIV prevalence. Government agencies

Investment by African governments

Because the epidemic continues to take its greatest toll in Africa, it is important that more African countries become involved in and take leadership in microbicide research. The Nigerian and South African governments have stepped up their efforts. South Africa has just begun to directly fund microbicide development and clinical research, and the Nigerian HIV Strategic Framework is a strong example of a national AIDS plan acknowledging the importance of HIV prevention research. This national priority-setting around prevention research can help integrate microbicide research into larger HIV strategies and will respond to local and national needs.

Both the Nigerian and South African governments have also begun to strengthen their national ethics review boards and to increase support for their major universities and research institutions in an effort to improve the quality of research and forge international partnerships on clinical research.

At the same time, however, prevention research has still not been resourced as a national priority by either government. As microbicide research is given greater prominence in African national research agendas, new priorities are being considered by advocates, including national regulatory issues involving microbicides and plans for widespread access to a microbicide when one is licensed for use.

in Nigeria and South Africa, for example, are partnering with donor governments such as those of Canada, Ireland, the Netherlands, Norway, and Sweden to build stronger infrastructures for HIV prevention, health promotion, and clinical research.

The microbicide effort has now entered into an era of ambitious resource needs and commitments. The current annual global investment of US$ 163 million for microbicide research and development remains inadequate, however, to sustain the ongoing development of a robust array of candidate products and product combinations. Recent analyses by several agencies have concurred that an annual investment of US$ 280 million is now needed to take advantage of current scientific opportunities and to fulfill current commitments for accelerated microbicide research, development, and testing.[10]

US POLICY AND PROGRAMMING

The US government has been an engine of innovation, regulatory standards setting, and support for commercial involvement in

microbicide research. The NIH is the largest single agency supporting microbicide R&D, with a budget of approximately US$ 74 million in 2006. Two years ago, in 2004, NIH signaled new dedication to microbicides, issuing a strategic plan asserting that microbicides may provide "one of the most promising prevention interventions that could be inexpensive, readily available, and widely acceptable."

As noted earlier, USAID will dedicate a projected US$ 40 million for microbicide development in fiscal year 2006. USAID efforts have a significant impact in the field, supporting Phase 3 clinical research, development of clinical site capacity, and important aspects of product formulation, manufacture, and packaging. CDC has the smallest annual investment of the three US government agencies, at approximately US$ 3 million each year.

Creating a microbicide branch at the NIH

Authority over microbicide research at NIH is currently spread across multiple institutes and several offices with no single line of administrative accountability or specific funding coordination. Neither the NIH steering committee established in 2003 by the current NIH director, Elias Zerhouni, nor the NIH road map includes microbicides as a particular focus. In addition, microbicide R&D all too often falls outside the structure and capacity of NIH study sections and peer review committees. Together, these realities argue for the urgency of a well-defined scientific focus.

Advocates have long been pressing for a more cohesive and coordinated approach at NIH, and congressional directives and legislation have consistently proposed some sort of "organizational unit" dedicated to microbicide research. There are now indications that NIH is seriously considering establishing a microbicide branch together with a microbicide trials network. NIH should be encouraged to move forward with creation of this network. In addition, it should create and adequately fund an intramural (within NIH) scientific agenda, including sufficient funds for basic research; animal studies and other targeted research; product formulation and manufacturing of research product; capacity for Phase 1 clinical trials; and ultimately, adequate staffing levels for this work.

Current US legislation

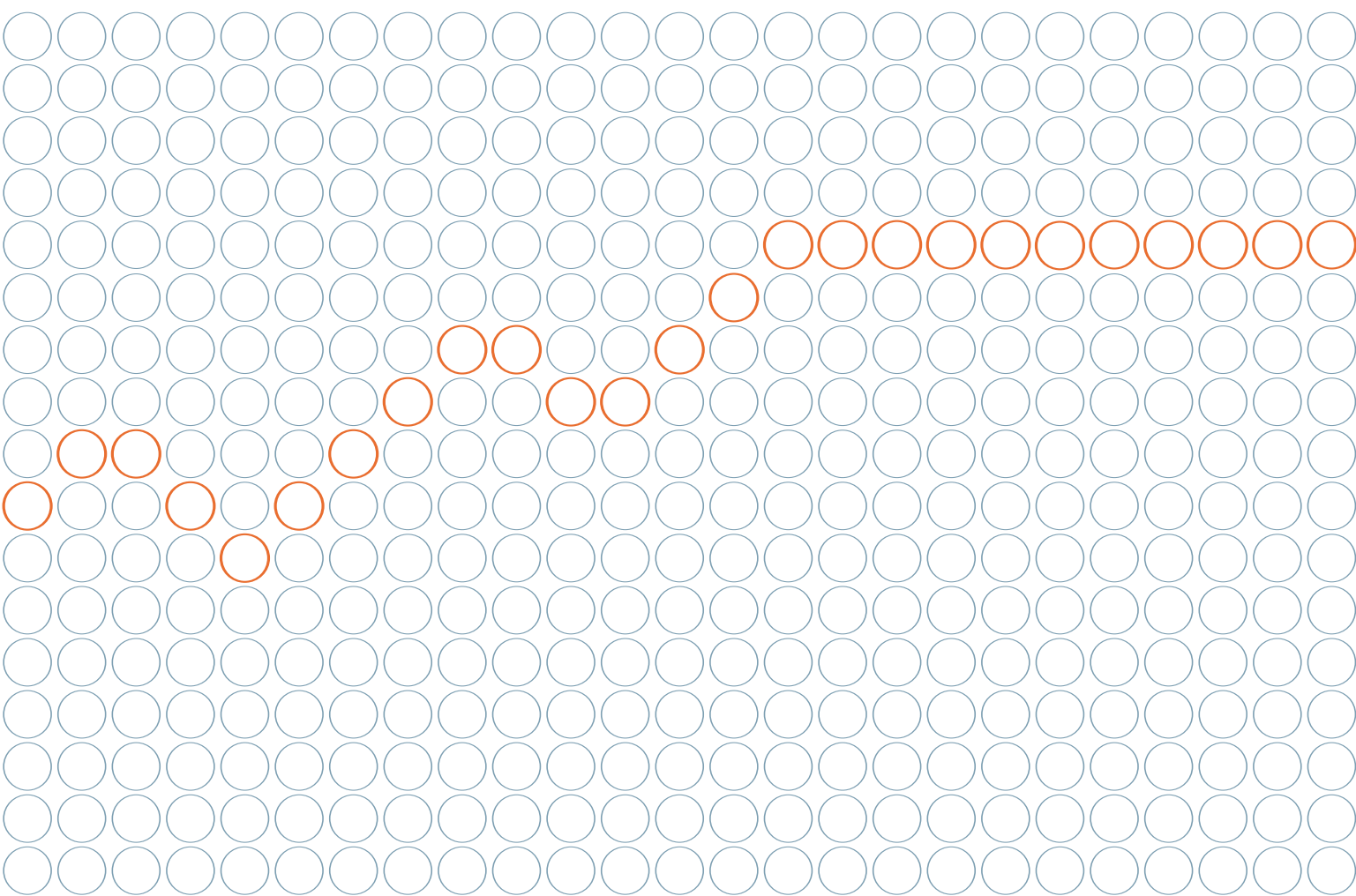
Encouraged by growing public attention and support for microbicides, US legislators are increasingly focused on the expansion and coordination of US government research efforts. The ***Microbicide Development Act***, most recently introduced by Jon Corzine (D-NJ), Barack Obama (D-IL), and Olympia Snowe (R-ME) in the Senate, and Jan Schakowsky (D-IL) and Christopher Shays (R-CT) in the House, would establish a clearly

defined organizational unit at NIH dedicated to microbicide research. The Microbicide Development Act would also strengthen microbicide activities at USAID and CDC.

Another promising policy effort is to encourage PEPFAR, the government's coordinating entity for international HIV/AIDS funding, to support prevention research, perhaps through provision of ARVs and related medical care to people enrolled in microbicide and other clinical trials. Language to this effect was added to a congressional report accompanying the Fiscal Year 2006 ***Foreign Operations Appropriations Bill.*** This accomplishment has opened the opportunity for advocates and researchers to work with officials at PEPFAR, USAID, NIH, and CDC to move this idea forward to implementation.

06

IMPROVING THE REGULATORY TERRAIN



Regulators walk a tightrope between approving products too quickly (and later discovering they do harm) and being overly cautious on safety concerns (and thus holding up approval of products that would be powerful public health tools). When they are in relatively new territory, as with microbicides, regulators understandably tend to err on the side of safety. Several regulatory issues need attention to accelerate research and, eventually, product licensure.

- surrogate endpoints and trial designs related to HIV prevention, STI prevention, and contraception.

Key factors in accelerating microbicide development and reducing development costs will be early and ongoing consultation between regulatory agencies and product sponsors, and greater clarity from regulatory agencies.

The FDA and EMEA can do more to define clear and appropriate standards, and to support regulatory capacity of high-burden regions and countries.

DEFINING (AND RE-EVALUATING) GUIDELINES

In consultation with product sponsors, the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA) can do more to define clear and appropriate standards for the evidence needed from clinical trials. This includes defining guidelines for:

- microbicide safety and use, including acceptable evidence of participants' adherence with product use instructions, and acceptable models for trial design that incorporate these measures of use; and

Moving beyond the research requirements of a condom-only control

FDA currently suggests that microbicide effectiveness trials should include three groups of trial participants: one receiving the active microbicide gel, a second using a placebo gel, and a third control group receiving no gel. (Participants in all groups receive extensive risk-reduction counseling and advice to use condoms and are provided with condoms and routine STI testing, treatment, and other health care.) Of the five large-scale trials currently being conducted, one (HPTN 035) is following this type of study design.

FDA's goal in setting the "two control groups" requirement is to try to understand behavioral changes related to microbicide use. The main question is whether the provision and use of a gel that might be protective has any effect on sexual behavior and risk-reduction, such as number of partners or condom use.

Inclusion of a condom-only group in microbicide trials might not provide meaningful data and could act as an impediment to Phase 3 trials by greatly increasing sample sizes and research costs and delaying clinical results for months or years. Recognizing this, FDA has recently indicated that it may remove the requirement for a condom-only group after results are seen from the one current microbicide trial with a condom-only arm (HPTN 035). These results are not due until 2008.

BUILDING NATIONAL AND REGIONAL CAPACITY

Traditionally, many low- and middle-income countries have looked to regulators in the United States and Europe (FDA and EMEA, respectively) to determine whether a product should be approved for local use. Such reliance on industrialized-country regulators can mean that the unique characteristics of national epidemics are not sufficiently attended to in regulatory decision making. For example, a risk/benefit analysis of a product's acceptability may be different in a country with 0.5% HIV incidence from one with 5% incidence.

One solution is development of regulatory capacity in high-burden countries and regions. In 1996, the World Health Organization (WHO) initiated an ongoing effort to review and support regulatory capacity in less-developed countries. WHO is also now assembling an international group of regulatory experts who can provide guidance to national regulatory authorities. Four global and regional meetings, spearheaded by WHO, have already been convened. This is an important new effort to support in-country regulatory decision-making—and it deserves far greater support from outside funders.

In June 2005, representatives of 14 national regulatory authorities in southern Africa met with officials from WHO and IPM to discuss regulatory issues for reviewing clinical trial applications and registration of microbicide products. Meeting attendees identified the need for development of regulatory capacity in national agencies and regional harmonization of product registration and licensing requirements for microbicides.[11] The effort within the Southern Africa Development Community (SADC) to develop regional regulatory guidelines is an important model for other regions of the world.

Together, the FDA and EMEA can play a more supportive role in helping high-burden countries consider licensing of microbicides and other HIV prevention technologies. A nod from either agency would help countries that are still developing their regulatory capacity to make judgments about licensing microbicides without facing criticism based on the fact that

US or European regulators rejected the product for prevention of HIV infection.

The European Union has already endorsed the idea of its EMEA providing guidance on product licensing for interventions that may not be licensed in Europe. EU Article 58 states that EMEA "…may give a scientific opinion...for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community." Importantly, the EMEA has already acted on Article 58 to provide guidance on licensing of a new pediatric vaccine. FDA has said that it is willing to share technical opinions on microbicides and other products with regulators in other countries, even when the agency might not be approving the product for use in the United States.

PLANNING FOR PHASE 4

Phase 4 studies have become an important tool for the pharmaceutical industry to speed the approval process. They were first authorized in 1993, when FDA instituted regulations allowing accelerated approval of drugs that significantly improve treatment outcomes for patients suffering from life-threatening illnesses. Such approvals are based on data from trials that use a surrogate endpoint that reasonably suggests clinical benefit, rather than conventional clinical endpoints that are needed for full marketing approval. Phase 4 studies are then done to confirm the effectiveness and safety of the product in use. Phase 4 trials can also be used to evaluate safety and effectiveness in populations that may not have been well represented in Phase 3 trials; the risks and benefits of longer-term use of products; and comparisons with other similar products.

The microbicide community should explore possibilities and strategies for a microbicide safety and effectiveness reporting system that is appropriate for microbicide end-users.

LOOKING AHEAD

The past decade of efforts to develop microbicides and other technologies to prevent HIV and other STIs have brought great potential and promise. Much progress has been made, yet the terrain ahead is complex, undefined, and only partly explored.

Through many collaborative efforts, the microbicide field has found new clarity of direction and commonality of purpose. But the future landscape is likely to contain many challenges, including the need for adequate research capacity, many paths of scientific inquiry to follow, and plenty of ruts and roadblocks for all to overcome.

To avoid reversals or loss of momentum, our best recourse is to regularly review markers of progress and anticipate challenges. Advocates and policy makers are increasingly finding a shared voice and mutually-agreed expectations. Although this research and development effort may take many years, the goal is in sight.

ENDNOTES

1 Rough annual incidence projections derived from country incidence statistics in the UNAIDS 2004 Report on the Global AIDS Epidemic. Geneva, December 2004, with supplemental information from national country reports and from UNAIDS. *AIDS epidemic update*. Geneva, December 2005. At www.unaids.org

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3 *Microbicide Research and Development Database (MRDD)*. At www.microbicide.org

4 Alliance for Microbicide Development. Data compiled and updated March 2006.

5 HIV Vaccines and Microbicides Resource Tracking Working Group: the AIDS Vaccine Advocacy Coalition (AVAC), Alliance for Microbicide Development (AMD), International AIDS Vaccine Initiative (IAVI), and Joint United Nations Programme on HIV/AIDS (UNAIDS). *Tracking funding for microbicide research & development: estimates of annual investments, 2000–2005. August 2005.*

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8 *Ibid.*

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10 *Ibid.*, plus calculations performed by IPM.

11 Malonza, I, Farley, T, and Coplan, P. Strengthening regulatory capacity for microbicides in Southern Africa, *The Microbicide Quarterly*, Alliance for Microbicide Development, April–June 2005.

ACRONYMS

AMAG: African Microbicide Advocacy Group

AMD: Alliance for Microbicide Development

ARV: antiretroviral

AVAC: AIDS Vaccine Advocacy Coalition

CDC: Centers for Disease Control and Prevention (US government agency)

CONRAD: Contraceptive Research and Development Program

DFID: Department for International Development (UK government agency)

DSMB: Data Safety Monitoring Board

EC: European Community

EDCTP: European and Developing Countries Clinical Trials Partnership

EMEA: European Agency for the Evaluation of Medicinal Products

EMPRO: European Microbicides Project

EU: European Union

FDA: Food and Drug Administration (US government agency)

FHI: Family Health International

G8: Group of Eight

GCM: Global Campaign for Microbicides

GFATM: Global Fund to Fight AIDS, Tuberculosis and Malaria

HIV: human immunodeficiency virus

HPTN: HIV Prevention Trials Network

HPV: human papilloma virus

HSV: herpes simplex virus

IAVI: International AIDS Vaccine Initiative

IND: investigational new drug

IPM: International Partnership for Microbicides

MCB: Microbicide Coordinating Board

MDP: Microbicides Development Programme

MHRA: Medicines and Healthcare products Regulatory Agency, United Kingdom

MRC/ZA: Medical Research Council, South Africa

MRC/UK: Medical Research Council, United Kingdom

MSM: men who have sex with men

NDA: new drug application

NGO: non-governmental organization

NHVMAG: Nigerian HIV Vaccines and Microbicides Advocacy Group

NIAID: National Institute of Allergy and Infectious Diseases (US government agency)

NICHD: National Institute of Child Health and Human Development (US government agency)

NIH: National Institutes of Health (US government agency)

PEPFAR: US President's Emergency Plan for AIDS Relief

PPP: public-private partnership

Q/CTWG: "Quick" Clinical Trials Working Group

R&D: research and development

STI: sexually transmitted infection

TMQ: The Microbicide Quarterly

TOPCAD: Topical Prevention of Conception and Disease (Rush University, United States)

UNAIDS: Joint United Nations Programme on HIV/AIDS

USAID: US Agency for International Development

WHO: World Health Organization

THE ALLIANCE FOR MICROBICIDE DEVELOPMENT

The Alliance for Microbicide Development is a global, multidisciplinary, multisectoral coalition of scientists, product developers, advocates, and public health experts. The Alliance was founded in 1998 to accelerate development of safe, effective, and affordable microbicides to prevent the ongoing spread of HIV and other sexually-transmitted infections. The Alliance works through advocacy, communication, convening, monitoring progress, addressing critical problems in practice and policy, and providing a neutral platform for dialogue on key issues.

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