



ALLIANCE FOR
MICROBICIDE
DEVELOPMENT

MICROBICIDES:

Ways Forward

2010

Acknowledgments

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01

EXECUTIVE *Summary*

Over the past few years, there have been many changes in microbicide research and development and in the environment in which that work is pursued. The microbicide field is acutely aware of the need to understand those changes, their causes, and how the field could and should adapt to them. As a result, a number of activities and consultations have been devoted to scrutinizing long-standing ideas about the process of microbicide development and the science that informs and supports it.

This report extracts the key messages from some of the most recent and relevant of those discussions and builds on strategy exercises led by the Alliance for Microbicide Development beginning in 2005, which were designed to flag gaps in microbicide research and development, track work being done to fill them, and propose ways of accelerating progress.¹ More recently, in 2009, the Alliance conducted a structured survey involving dozens of microbicide experts, in an effort to identify areas in which progress had been made, obstacles that remain, and priorities for moving the field forward. The results of that survey are also reflected in this report.

The emphasis of the report is on the science – basic, translational, behavioral, and clinical – because that is where the largest obstacles to advancement in the microbicide pipeline were identified. Happily, there is real

promise in the learning that has occurred in all those areas of science, and the report deals with those as well. Finally, the report considers matters of funding, regulation, policy-making, coordination, and the role of advocates and civil society as sustaining factors for the scientific enterprise.

The report closes with nine integrated actions that, if implemented with clear intent and speed, could go a good distance toward overcoming the obstacles identified, narrowing the gaps, and adjusting the work of microbicide development to the ever-changing world in which it must proceed.

MICROBICIDES AND OTHER PREVENTION TECHNOLOGIES

The past few years have seen acceleration in efforts to develop a range of biomedical options for HIV prevention. Of all the HIV prevention methods in development, oral PrEP – antiretrovirals (ARVs) administered to high-risk uninfected people to reduce their susceptibility to HIV infection – has the most direct implications for the microbicide agenda. An increasing number of microbicide candidates are derived from compounds first developed as antiretrovirals for HIV/AIDS therapy and, for the first time, an ARV-based microbicide is being tested alongside two

¹ Alliance for Microbicide Development. *Mapping the Microbicide Effort*. Silver Spring, MD, USA. May 2007; MDS Working Groups. *The Microbicide Development Strategy*. Silver Spring, MD, USA: Alliance for Microbicide Development. August 2006.

orally-delivered ARVs in a single HIV prevention study, the VOICE trial sponsored by the US National Institutes of Health. The basic concept of using antiretroviral drugs for HIV prevention, whether administered vaginally, rectally, or orally, is raising a constellation of scientific and practical questions that are only beginning to be asked – not least the possibility of exacerbating the problem of HIV strains resistant to such drugs.

THE MICROBICIDE PIPELINE

The contents of the microbicide pipeline have changed dramatically in a number of ways that are already affecting the development pathway. The first generation of microbicides failed in clinical trials in different ways and for different reasons. The surfactants have essentially disappeared, as have the polyanionic sulfated or sulfonated polymers that target HIV's envelope and interfere with the virus's attachment to host cells, and an acidic buffering agent intended to enhance vaginal defenses. Next-generation candidates in the current preclinical portion of the microbicide pipeline include 35 attachment/fusion/entry inhibitors, 11 replication inhibitors, 1 vaginal defense enhancer, 1 immunomodulator, and 4 with uncharacterized mechanisms of action. In addition, there are 23 candidates in preclinical development which have multiple mechanisms of action. Despite a still-unclear regulatory pathway and other complexities, combination approaches are seen as offering a potential for synergy, reduced drug resistance, and multiple targeting that is compelling, and the existence of new funding opportunities for combination microbicides supports that perception.

The clinical pipeline, as would be expected in the normal course of pharmaceutical development, is far smaller. It is also far less varied: three out of five candidate microbicides in ongoing clinical trials as vaginal microbicides are based on ARVs – dapivirine, tenofovir, and UC-781.

These numbers tell an important part of the contemporary microbicide story. Although the preclinical pipeline contains many candidates and considerable variety, most of those candidates are early in development and the process of “translation” for the relatively few candidates which have reached late preclinical status has been cumbersome and slow.

FORMULATING MICROBICIDES

Microbicide formulation is the “hinge” between the inherent efficacy of an active pharmaceutical ingredient and its ultimate biomedical effectiveness in use as a product. It is especially determining of adherence to that use. Once limited largely to gel formulations intended for application just before every sex act – in other words, “coitally-dependent” – the formulation universe for microbicides is expanding to a greater emphasis on “coitally-dissociated” approaches. These include slow-release intravaginal rings, pre-loaded physical barriers, a variety of innovative longer-lasting topical formulations, and long-acting injectable formulations and implants. A dapivirine ring is in ongoing clinical testing.

A TIME OF LEARNING: BASIC, PRECLINICAL, AND TRANSLATIONAL SCIENCE

Considerable learning has accumulated in the microbicide field, emerging from advances in the relevant basic and applied science, experience with clinical trials, and interpretation of trial results. Yet microbicide use involves complex, multi-level biochemical and behavioral interactions among host, virus, and drug that await full understanding. There are many reasons why a microbicide that prevents HIV infection in the laboratory, in cellular, tissue, and animal systems, may not provide protection – or may even increase infection – as a result of sex with an HIV-infected partner. The list of possible explanations for the failure of laboratory tests and clinical safety trials of vaginal microbicides to predict the so-far disappointing outcomes of seemingly well-defined and well-implemented clinical effectiveness trials is long and is the focus of continuing inquiry. Unanswered questions include the nature of the infectious virus and its movement in tissues, the nature and detection of epithelial damage, distribution of microbicide in the vaginal lumen and on the mucosa, and the influence of semen, cervico-vaginal secretions, and sexual activity on microbicide concentration and potency.

These questions have also been a motivating force for innovative research in the basic science underpinning microbicide development and product formulation. As a result, it is now plausible to construct a pharmacokinetic/pharmacodynamic (PK/PD) model-based paradigm that can quantify microbicide levels, HIV movement in space and time, and the interaction of both. This, in turn, may now provide a basis for solving product development problems and for designing better clinical trials that will lead to more

orderly development decisions. A large array of new tools is available to do this work, although there remain certain needs, including for example methods specifically designed for evaluating ARV-based microbicides.

CROSS-CUTTING CONCERNS

Biomarkers

The lack of surrogate markers of protection from HIV infection imposes on microbicide development the need for large, costly screening and effectiveness trials. Clearly, the validation of such biomarkers must await the development of a microbicide shown to be protective.

Nonhuman Primate (NHP) Models

There is continuing debate around the question of NHP models as gatekeepers for transition of microbicide candidates from preclinical to clinical status. This is likely to remain a topic of controversy, and NHP models will continue to be contrasted with new murine and tissue explants that are informative, can be standardized, and are far less costly.

CLINICAL RESEARCH

The most crucial lessons had to do with those aspects of effectiveness trial design most directly linked to trial power: HIV incidence, numbers of participants enrolled, time off trial product due to pregnancy, participant retention, and adherence to trial protocol. Recent experience with Phase 2B and Phase 3 clinical trials of PRO 2000 highlights the potential risks of designing intermediate-sized trials aimed at providing preliminary data on effectiveness.

In terms of Phase 1 safety trials, there is a need to identify best practices and to standardize trial design and categorize adverse events and laboratory assays across laboratories and clinics, including the best techniques for assessing the effect of a microbicide on cervical, vaginal, and rectal epithelia. There is also a case for creating a standardized blinded panel of reagents for comparison across laboratories. The optimal duration and size of a Phase 1 study and the merits and costs of parallel, concurrent Phase 1 studies need to be considered.

BEHAVIORAL AND SOCIAL SCIENCE RESEARCH

No single measure of adherence to product use in microbicide clinical trials has proved sufficient. The approaches that have been tried and found most productive, and those that show most promise, involve

the systematic integration of several methods through the entire course of clinical studies from design through follow-up. For example, “triangulation” involves the use of multiple observers, theories, and data-collection methods to overcome the inherent biases of any single observer, theory, or method, to increase the convergence of findings, followed by reconciliation of any inconsistencies across data sets. However, progress in terms of optimizing adherence and its measurement will require the continuing improvement and validation of approaches, as well as multidisciplinary efforts to maximize and assess product acceptability.

FACTORS THAT SUSTAIN

Regulation

The US Food and Drug Administration is currently revising its guidelines for microbicides to adjust to the multitude of scientific, clinical, and political changes in and around the microbicide field. There has been so much evolution in this field in response to learning from completed trials, the rising prominence of ARV-based prevention technologies, more focus on combination microbicides and diverse delivery systems, a surge in new preclinical evaluation tools, and shifts in thinking about the clinical testing sequence, that a re-working of existing guidelines and generation of new ones is a matter of urgency. For these reasons, it is equally urgent that there are opportunities for public comment, since the influence of new regulatory guidelines will inevitably be far-reaching.

Funding

Total global investment in microbicide research quadrupled from US\$65 million in 2000 to US\$244 million in 2008; preliminary figures for 2009 also show increases in US public-sector funding as well as in funding from the G8 countries and Europe. However, going forward, attention must be paid to the funding implications of the drastically altered contents of the current microbicide pipeline, reconfiguring of preclinical and clinical research algorithms, cost increases across all of pharmaceutical development, and the many unanswered questions about the gap between microbicide product approval and access. To guide estimates of what will be required to support the advance of microbicide research and development, new, evidence-based calculations of costs would be extremely helpful, for the field and for those who contribute financial resources to its support.

Advocacy and Civil Society

There has been meaningful progress with respect to the contributions of advocacy and civil society to microbicide clinical research, and wide recognition of their centrality. Microbicide trial networks have been important in ratcheting up local health care infrastructures, expanding human capacity for research and health care delivery, and involving civil society at different levels throughout the clinical trial process. Emphasis must now be placed on conserving and strengthening those advances and ensuring the necessary corresponding financial and policy support.

Coordination

The microbicide field is much more coordinated than it has been in the past. However, a vital missing piece in the picture of coordination in the microbicide field is the lack of regular engagement of donors in learning about the field, its progress, as well as its challenges. This is acutely important now, since there is a need for common dialogue about the next round of investments in microbicide

research and development, the demands for which are still in flux. Preclinical development and clinical trials will both need to be funded, but in the absence of a coherent frame of reference and access to unbiased data, the pattern of unilateral decision-making that dominated the past is likely to be repeated. Donor involvement and participation in learning and decision-making processes that go beyond individual scientific advisory committees constitute a wide-open issue that requires immediate resolution.

What follows is a set of action areas that emerged as priorities, accompanied by a brief statement of the rationale and “next steps” for each. The most critical areas of priority have to do with the processes that, together and separately, select the most plausible candidate microbicides for advancement; expedite their progress along the development pathway; support their translation into the clinic; and employ the most informative early clinical studies to arrive at proof of concept and, eventually, pivotal effectiveness studies.

Actions REQUIRING PRIORITY

Advancement of Lead Products

The fundamentals of a rational process for selection of lead microbicide candidates are falling into place and merit strategic emphasis and investment. Lack of robust, validated markers of protection from HIV infection continues to impose on microbicide development the need to do large and costly effectiveness trials.

- Concerted efforts to develop best-practice guidance with respect to the usefulness and significance of the many new models and assays, and devise and use algorithms that incorporate the best intelligence to manage the risk inherent in selecting compounds for advancement
- Intensified research on the detailed processes involved in sexual transmission of HIV and mucosal immunity, including the role of cell-free and cell-associated HIV and the significance of “founder” viruses, in the context of both microbicide and vaccine development
- More detailed examination of the effects of male and female genital and rectal secretions on microbicide activity
- New pharmacokinetic and pharmacodynamic studies as a basis for solving product development problems, making orderly development decisions, designing better

Phase 1 and Phase 2 clinical trials, and integrating those fully into current development approaches

- Steady attention to the pursuit of biomarkers that correlate with safety, product use, and potential efficacy, and their structured integration into human studies to enhance potential for validating those biomarkers that show promise
- Creation by product developers of targeted product profiles that identify a product’s best characteristics, and articulation of a plan for its advancement into clinical testing

Optimization of Clinical Trial Design and Management

There is consensus that the suite of clinical trials needs to be re-thought. A number of important first steps have been taken toward that objective, with some areas meriting prioritization and prompt strategic attention.

- Safety trials: Decisions about the size and duration of Phase 1 trials, about the most relevant parameters to include for identifying biomarkers of safety, and the potential of mounting parallel, concurrent trials

- Effectiveness trials: Focused discussions and, where possible, decisions about more efficient and cost-effective trial designs and about all major determinants of trial power

Building Strategically on Behavioral and Social Science Research

A number of methods of particular relevance to those aspects of clinical trials that have major impact on trial power have shown promise and merit priority support.

- New techniques for preclinical research that may optimize prospects for participant adherence to trial protocol
- Strategic combinations of several methods for optimizing and measuring adherence to product use across the entire course of clinical studies
- Multidisciplinary approaches for optimizing the acceptability of product formulations

Coordinating Functions

In order to develop a rational bridge across the translational gap, tools are required for organized relationships.

- Identification of and support for new targeted, flexible, agile coordinating functions to meet specific needs in the development pathway, including multidisciplinary aspects and industry involvement

Regulation

The US Food and Drug Administration is currently revising its microbicide guidelines to adjust to the many changes in the fields of microbicides and HIV prevention.

- Pursuit and exercise of opportunities for public comment on guidelines currently in draft, since their influence will be far-reaching

Donor Engagement and Education

Involvement of funders of microbicide development is uneven and incomplete at a critical time.

- Strategic engagement of donors in common, well-informed, open dialogue and learning about the status, progress, and prospects of the microbicide field as a whole

Costs

Existing analyses of what it costs to develop a microbicide, test it clinically, and make it available are outdated, and estimates of the time required are poorly understood – matters of highest

import for the funders of microbicide research, trial designers and implementers, the countries and communities in which those trials are conducted, and the advocates who are critical to the advancement of microbicide research.

- Revision of cost profiles for microbicide development
- Preparation of estimated budgets associated with timelines for manufacture, commercialization, and access

Advocacy and Civil Society Engagement

Systematic, ongoing involvement of civil society and furtherance of science literacy will continue to be critical to testing prevention technologies.

- Explicit inclusion of support for site-level advocacy and civil society engagement in trial budgets

Evaluating Progress

Planning and implementation of each of these priority actions could be undertaken immediately, given consensus that they are truly of priority.

- Review and evaluation of all these priorities 12 months hence.

IN CONCLUSION

There is no single, simple, perfect model for navigating the development pathway for microbicides. This report has attempted to synthesize ideas derived from a range of discussions over the past year around how that pathway might be clearer, how the growing content of the early preclinical pipeline might advance from discovery through all the necessary points along that pathway, how translation into the clinic might more expeditiously and confidently occur, and what sequence of clinical research would be most likely to achieve proof of the microbicide concept and advance it through to a pivotal effectiveness trial.

Nothing in this report is intended to convey a sense that simply having those discussions and reporting their gist is sufficient. What will be essential is strategic, focused, prompt, coordinated action on what the microbicide field might best do next and to what purpose, in full recognition of the place of microbicides among all of the HIV prevention approaches that will be needed to outwit a very wily foe.

BY WAY OF INTRODUCTION: WHY *This* DOCUMENT *Now*

The idea of using microbicides to prevent the sexual transmission of HIV has been around for some 20 years. Efforts to develop microbicides that are both safe and effective have, however, been confronted by numerous challenges, and the urgent need for such products so far remains unmet.

Over the past few years, there have been many changes in the approach to microbicide research and development and in the environment in which that work has been pursued. There have also been numerous consultations and conversations about those changes, what they mean, and how the microbicide field could and should adapt.

This report distills those discussions and builds on strategy exercises led by the Alliance for Microbicide Development beginning in 2005, which were designed to flag gaps in microbicide research and development, track work being done to fill them, and propose ways of accelerating progress. These exercises resulted in the publication by the Alliance of the *Microbicide Development Strategy* in 2006 and *Mapping the Microbicide Effort* in 2007. More recently, in 2009,

the Alliance conducted a structured survey involving dozens of microbicide experts, in an effort to identify, first, areas in which good progress had been made and, second, priorities for moving the field forward.

Substantive issues highlighted by these exercises are embodied in this report. The report also reflects views derived from many other sources and individuals, so while we should not presume consensus, it is fair to say that many voices have been heard and have greatly enriched the contents of this document.

What follows is a snapshot of the microbicide field as of spring 2010, with some retrospection on where it has been and what has been learned, what progress has been made, what opportunities have arisen and await, what seems to matter most, and what priorities might best focus the field in the months to come. The report emphasizes the science – basic, translational, behavioral, and clinical – because that is where the largest obstacles are found and must be overcome if there is to be, sooner rather than later, a safe and effective microbicide to add to the world's armamentarium against disease.

MICROBICIDES: *What and Why*

What

While the idea of using something called a “microbicide” as a topical application to help prevent sexual transmission of the human immunodeficiency virus (HIV) has been around for some 20 years, intensive and extensive clinical development really began just 10 years ago. Microbicides were first proposed as a potentially critical component of a multifaceted approach to HIV prevention, whose primary clientele would be the multitude of the world’s women who lack both the power and the means of protecting themselves from HIV infection.

Hopes were pinned on a seemingly safe and straightforward concept: modifications to existing spermicides, formulated for vaginal application and available over the counter without prescription and at low cost. Yet, experience with a relentlessly crafty virus and the realities of microbicide development revealed unanticipated

challenges, underlying assumptions came to be questioned, new understandings were acquired, and other HIV prevention technologies evolved. As a result, the definition of “a microbicide” has expanded and become more complex, and the list of characteristics required for microbicide development shifted accordingly (*Table 1*).

These new and expanded criteria with their complexities have re-shaped the entire microbicide vocabulary. Once simply thought of as a discrete category of “low-tech” over-the-counter products that women could apply vaginally at time of coitus, microbicides are now being developed preferentially as products for use at more distance from time of coitus. They are no longer just for vaginal application or just for women; vaginal microbicides are now tested to assure safety in rectal use, and rectal microbicide development for use by both women and men is a reality. The notion of using antiretrovirals

TABLE 1 | RE-DEFINING MICROBICIDES: EARLY AND EVOLVED CHARACTERISTICS

EARLY CHARACTERISTICS	EVOLVED CHARACTERISTICS
Safe for repeated use	Same
Toxicity offset by potential efficacy	Low <i>in vitro</i> toxicity and no systemic toxicity
No effect on vaginal environment/microflora/reproduction	Same
Designed for vaginal application	Designed for rectal and vaginal application
Efficacious with no systemic absorption	Efficacious with no or little systemic absorption
Safe and efficacious in presence of semen and cervico-vaginal secretions	Safe and efficacious in presence of semen and cervico-vaginal and rectal secretions
Broad spectrum of activity; anti-HIV and other STIs; contraception as desired	Targeted activity; potency against multiple HIV strains and relevant non-HIV-STIs, contraception; breadth to be achieved by combinations
Fast-acting for an appropriate duration after application	Longer period of activity, before and after coitus
Designed for coitus-associated use	Designed for coitus-associated and coitus-dissociated use and long effect windows
Combination-compatible with different targets, co-infections, excipients, other STIs, reproductive health	Same
Combination-compatible with mechanical barriers and various formulations	Combination-compatible with mechanical barriers and various formulations, expanded to intravaginal rings and injectable formulations
Acceptable, affordable, available without prescription	Acceptable, affordable, prescription requirement unresolved

A MICROBICIDE IS DESIGNED TO BE . . .

A safe, effective, acceptable, affordable product delivered as a single agent or multi-component strategy in a stably-formulated gel, tablet, film, injectable, and/or device (i.e., ring, diaphragm) to both HIV-negative and HIV-positive individuals. Its purpose is to prevent, or at least significantly reduce, the acquisition and transmission of HIV (and possibly other sexually transmitted infections) at the genital (vaginal and/or penile) and/or gastrointestinal (rectal) mucosa.

presumptively for “pre-exposure prophylaxis” as well as for therapy is being pursued in many clinical trials in different populations, and an increasing number of microbicide candidates are derived from compounds developed as antiretrovirals. Microbicides are now no longer just topical; they may be oral or injectable or delivered in some device that may be “applied” but remains *in situ* for varying

amounts of time. The result is that the definition of a microbicide, once a straightforward statement of about a dozen words, has become long and complicated. When all is said and done, microbicides are biomedical members of an HIV prevention family, none of whose members can do the prevention task all by itself.

Why

The term “microbicide” has expanded to encompass many different things, yet painfully little has changed in what drove microbicide development in its earliest days – the numbers. Just last year, a World Health Organization (WHO) report confirmed AIDS as the number one cause of death and disease in women of reproductive age globally, with women in developing countries bearing the brunt of the epidemic at a rate of ~7,000 new infections every day.

This is especially, though not exclusively, the case in sub-Saharan Africa, where women and girls, many married or in long-term presumably monogamous relationships, constitute almost two thirds of all new infections, most often acquiring HIV through sex with an infected male partner. In fact, in a number of countries of the region, the youngest groups of women are three to five times more likely to be infected than are males in those same age groups.

The causes of this burden are a toxic blend of biology, physiology, culture, and socioeconomic realities that leave so many women worldwide powerless against the threat

of HIV infection. For many women and girls, particularly those in abusive relationships or commercial sex work, it may be close to impossible to negotiate condom use or refuse demands for sex. Sexual and physical violence are key contributors to the HIV epidemics in a number of countries and the tools available to women for dealing with this state of affairs are few, in most cases none. Male condoms are simply unrealistic options for women who cannot persuade a partner to use condoms, especially in settings where women generally have no right to refuse sex with their husbands or boyfriends. And, while condoms are effective when used, they are obviously impractical for women and couples who want children.

The implications of these realities are clear. Women worldwide need to be empowered by having a technology whose use they determine and that will allow them, proactively and independently, to protect themselves from infection by a virus that will, sooner or later, prove lethal – for them, often their children, and sometimes their partners.

03

Where ARE WE?**MICROBICIDES IN A CHANGED AND CHANGING LANDSCAPE**

As in any scientific endeavor, microbicide research proceeds in an environment marked by advancements in science and by economic, social, and political factors, some positive, some not. For microbicides, the main factors in their recent developmental lifetime have been, and remain:

- Evolution in other HIV prevention technologies
- Evolution in the relevant sciences, including recognition of the need for integration of behavioral and social science
- Failures and disappointments in clinical research
- Global economic realities
- Persistent myths and resistant obstacles.

Each of these plays its own distinct role and interacts with all the others, producing sometimes loud reverberations in:

- Microbicide pipeline evolution
- Basic scientific and practical assumptions
- Clinical trial design, and
- Advocacy focus.

EVOLUTION OF OTHER HIV PREVENTION TECHNOLOGIES

Efforts to advance other biomedical options for HIV prevention have not stood still. Research proceeds on male circumcision; HIV vaccines; prevention, suppression, and treatment of sexually transmitted infections involved in HIV transmission or progression; female barrier methods; increasing the number of HIV-infected individuals on antiretroviral therapy; and oral pre-exposure prophylaxis with antiretroviral drugs (PrEP). Despite disappointing effectiveness trials of herpes simplex (HSV-2) suppression, a diaphragm, and HIV vaccines in the past three years, programs are accelerating scale-up of two available options, male circumcision and female condoms.

These approaches to prevention are progressing at different speeds and each will have major implications for HIV prevention strategy overall and for implementation of microbicide trials in particular. None will be sufficiently efficacious to be a stand-alone strategy and all will face challenges of attitudes and behavior, sociocultural “fit”, side effects, and perceived risk. But, most importantly, all, including microbicides, are part of an expanding prevention agenda that, together, could meaningfully alter the epidemic.

Male Circumcision Multiple randomized studies in Africa have shown that male circumcision (MC) can significantly reduce a man's likelihood of acquiring HIV through heterosexual vaginal sex – a major and unique triumph in HIV prevention. Still, there are unanswered questions about its potential protective benefit for women generally, men and women who engage in anal intercourse, and men who have sex with men (MSM). Research in Canada, the Netherlands, and the United States found no difference in risk of HIV infection between circumcised and uncircumcised MSM. Evidence of effect from MC on non-ulcerative sexually transmitted pathogens is inconclusive, though observational studies suggest that circumcised men and their partners have lower rates of infection with human papillomavirus (HPV). A recent prospective study found the risk of contracting HIV to be 40% lower for the female partners of circumcised men as compared to uncircumcised men, but the reduction was statistically insignificant. Other prospective studies show conflicting results and studies in larger samples will be needed. Despite the practical challenges of implementing medical male circumcision programs, they are being actively promoted in many countries with generalized HIV epidemics and low MC rates.

HIV Vaccines An anti-HIV vaccine is still seen by many as the best hope of ending the AIDS epidemic. Its long-awaited advent seemed a bit closer when in late 2009 it was announced that a Phase 3 trial of a prime-boost regimen in Thailand showed a 31% reduction in HIV incidence compared to placebo. There is continuing dialogue about the meaning and implications of that effect, but there is consensus that an anti-HIV vaccine at that level of efficacy would not justify large-scale manufacture and distribution and that a sufficiently effective, licensable product is still some years away. Much work remains around how that vaccine might have worked and about possible correlates of protection, and there remain critical basic scientific questions around HIV pathogenesis; humoral, innate, and cellular immunity; host genetics; animal models; trial design; degree of efficacy; and, eventually, access and use.

STI Prevention, Suppression, and Treatment HIV-infected individuals are also commonly infected with herpes simplex virus type 2 (HSV-2), often reactivated in association with higher plasma and genital levels of

HIV. The fact that HSV-2 suppressive therapy, specifically acyclovir, reduces HSV-2 reactivation and HIV levels suggested that HSV-2 suppression might also reduce HIV transmission. Even though recent trials testing this assumption in HIV-discordant heterosexual couples in Africa were disappointing, the core hypothesis is still compelling, so that the potential of higher-dose regimens, acyclovir's effects on HIV progression, and the meaning of persistence in HSV-2-infected individuals of cells susceptible to HIV infection, are all being explored.

Female Barrier Methods A recent effectiveness trial in southern Africa of a diaphragm with lubricant gel found no additional effect on HIV transmission over the standard prevention package. It is not clear whether this lack of effect was due to the fact that the diaphragm itself does not provide protection, or whether it was due to risk compensation and/or low adherence to the trial protocol, or some combination of those factors. Approval in 2009 by the United States Food and Drug Administration (FDA) of a new female condom, "FC2", with lower cost and improved design, has reinvigorated this technology as the only "female-controlled" method that permits women themselves to initiate protection against sexually transmitted diseases, including HIV. Evidence for its effectiveness against STIs is strong, and a meta-analysis of female-condom research showed anti-HIV efficacy similar to that provided by male condoms. Other female condoms are in various stages of development.

Increasing the Number of HIV-infected Individuals on Antiretroviral Therapy (ART) Efforts to facilitate universal access to antiviral drugs according to individual viral load levels have driven up global numbers of infected individuals on ART dramatically. Even so, the rate of new infections in developing countries outpaces the rate at which individuals are started on treatment. Recent mathematical modeling proposed a new strategy of "Universal Test and Treat" that would seek to have everyone tested for HIV once a year and treated immediately with ART if found infected. The model assumes that treating all infected individuals in a given community with ARVs would reduce their viral loads to less infectious levels and thus lower overall sexual transmission of HIV in that community. The strategy is evoking vigorous debate, primarily about its feasibility, potential cost, and the threat of explosive development and transmission of drug-resistant strains of HIV.

Ongoing clinical research and new operations research should provide real data to take this model beyond theory.

Oral Pre-exposure Prophylaxis with Antiretroviral Drugs (PrEP) Of all the HIV prevention methods in development, PrEP – antiretrovirals administered to high-risk uninfected people to reduce their risk of HIV infection – has the most direct implications for microbicide development. The rationale for PrEP comes from several sources:

- Effective therapeutic medications can be used by healthy people to prevent infections, for example, chloroquine to prevent malaria or isoniazid to prevent tuberculosis.
- Oral ARVs have proven generally safe and effective for long-term use as therapy in HIV-infected individuals and reducing the risk of mother-to-child transmission of HIV. Observational studies indicate that ARVs used post-exposure (PEP) can prevent HIV infection from a needle stick.
- Systemic pre-exposure rectal or vaginal administration of the ARV combination Truvada® provided high levels of protection against HIV-like infection in macaque monkeys and humanized mice.

MICROBICIDES AND PrEP: WHAT IS THE CONNECTION AND WHAT IS NEW?

TOPICALS AND ORALS

The evolution of ARV-containing microbicides and the harnessing of HIV therapeutics for HIV prevention have proceeded on roughly parallel paths; two ongoing trials, CAPRISA-004 and VOICE/MTN-003, have brought these paths closer together. Both trials are testing Gilead Sciences' tenofovir, a nucleotide analogue reverse transcriptase inhibitor (NRTI), for HIV prevention. Tenofovir was developed for oral delivery as HIV treatment and, later, in experimental gel form for topical application as a microbicide. CAPRISA is testing the gel form of tenofovir and VOICE is testing that same gel as well as two oral tablet formulations, tenofovir alone (branded as Viread®) and tenofovir combined with emtricitabine (branded as Truvada®). Tenofovir is also being formulated for delivery via a vaginal ring. CAPRISA and VOICE are not alone: as of April 2010, there are over 30 additional planned or ongoing clinical trials of ARV-

based PrEP and microbicide candidates, during which more than 30,000 participants will be enrolled. The fact that many of these trials involve the same agent, tenofovir, has raised concerns that are the focus of ongoing discussion.

WHAT NEEDS TO BE KNOWN ABOUT ARV-BASED PROPHYLAXIS (PrEP)

Topical or oral, gel, ring, or pill, many of the same questions apply to ARV-based prophylaxis (PrEP) in general and all belong in one big box as issues for all.

- Is it safe to give ARV drugs to healthy uninfected people?
- What are the most important and durable side effects?
- Do those who get infected while taking these drugs acquire or develop virus that is resistant to the ARVs being studied or, perhaps subsequently, to drugs in the same class?
- What happens if resistance does develop?
- Will those using ARV prophylaxis in any form be more inclined to risky sexual behavior because they presume themselves protected?
- Will PrEP in any form be affordable and practical?
- Which dosing (daily/intermittent/coitally-related) will be safest, most efficacious, and elicit most faithful adherence?
- Will PrEP be feasible for use by discordant couples, injection drug users, high-risk women, and men who have sex with men, and in different regions of the world?
- Will there be significant differences in the pharmacokinetics (PK) of these ARVs in women compared to men?
- What are the implications of use of PrEP by pregnant women or adolescents?
- What would be the cost and cost-effectiveness implications of generalized use of PrEP?

THE MICROBICIDE PIPELINE EVOLVES

The Alliance has monitored the microbicide pipeline steadily since the organization was founded in 1998. Though there were many fewer candidates in that pipeline

in those early days, the total number over the past decade has hovered between 50 and 60. As microbicide science advanced, funding expanded, new scientists became engaged, and clinical trials brought new insights and disappointments, the structure and content of that pipeline shifted as well (*Figure 1*).

WHAT CHANGED? THE FIRST MICROBICIDE GENERATION

SURFACTANTS

The most dramatic change in the microbicide field has been the shift away from surface-active, nonspecific, broad-spectrum agents with spermicidal and anti-microbial activities that disrupt the outer envelopes or membranes of an invading pathogen before it can bind with host cells. Two such products, COL-1492 and C31-G (Savvy®), were the first microbicide gels to enter Phase 3 trials but both failed: the former because of lack of effectiveness and evidence of harm, the latter because the trial was stopped for futility. Work with similar candidates has declined precipitously, amid consensus that they cannot be safely delivered at a dose level sufficiently toxic to the infectious agent without being toxic to host cells or tissues. The prevalent view is that it would be difficult for an anti-HIV microbicide candidate in this category to attract funding for late-stage clinical testing.

THE SECOND MICROBICIDE GENERATION

ATTACHMENT, ENTRY, AND FUSION INHIBITORS

The next pipeline shift also followed trial failures and disappointments, this time with respect to trials of large-molecule, polyanionic sulfated or sulfonated polymers that target HIV's envelope and block viral attachment, fusion, and entry into host cells. Of the

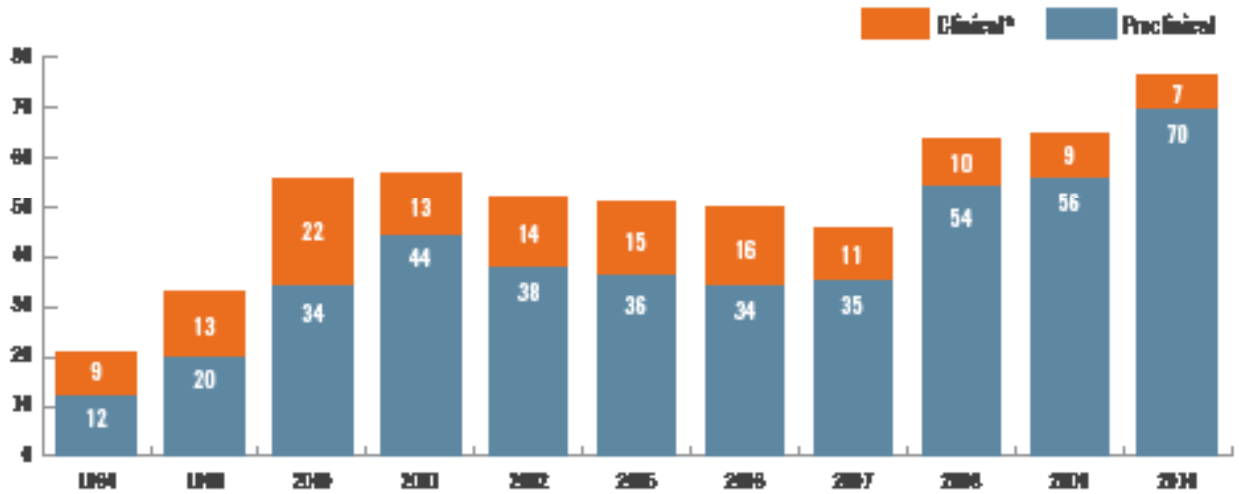
three such candidates that reached late-stage testing, none proved effective:

- **2007** The Phase 3 trial of cellulose sulfate (CS/Ushercell) (which had also shown contraceptive potential in preclinical testing) was halted when an interim analysis found a higher number of HIV infections in the active trial arm compared to its placebo arm, signaling potential for harm. Trial participants expressed desire to keep trial gel for continued use.
- **2008** The Phase 3 trial of Carraguard®, a non-contraceptive gel containing the sulfated polysaccharide carrageenan derived from seaweed, showed no efficacy against HIV but found the product to be safe, though its safety in frequent use is unclear. Its future use in combination with other mechanisms of action is under consideration.
- **2009** PRO 2000, a naphthalene sulfonate polymer also known as PRO 2000/5, was reported in early 2009 to show a tantalizing 30% level of effectiveness in a Phase 2/2B trial (HPTN-035). Those hopes were dashed in late 2009 when a larger Phase 3 trial (MDP-301) found no efficacy. Both trials found PRO 2000 to be safe and apparently liked by trial participants.

ACID BUFFERS AND VAGINAL DEFENSE ENHANCERS

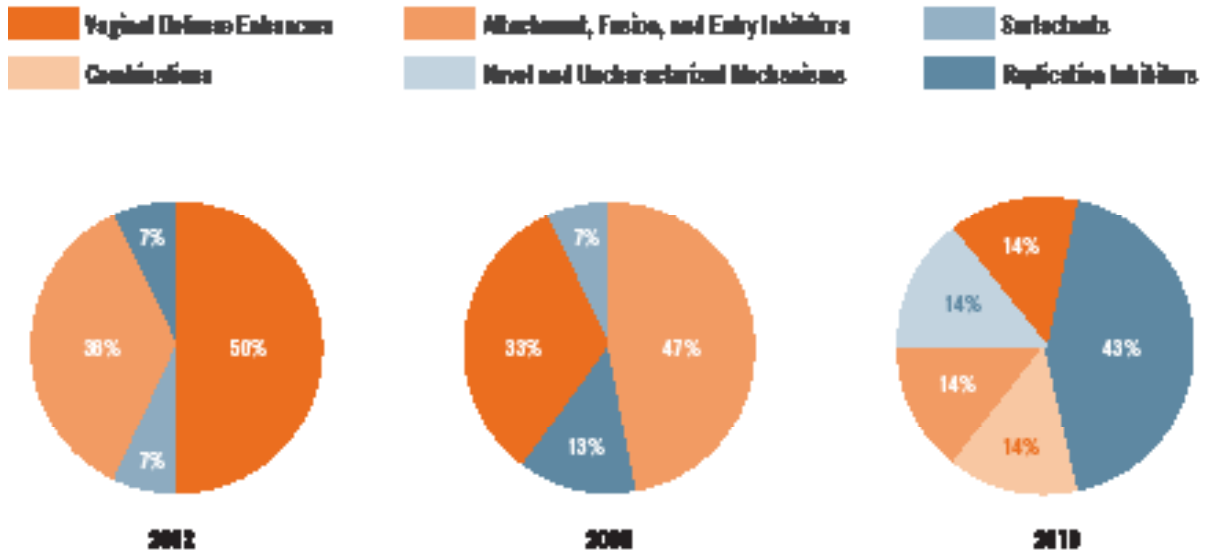
The HPTN-035 trial also tested a member of a third microbicide class, the acid-buffering agent BufferGel®. A goal of microbicides in this class is to maintain the natural acidity of the vagina in the presence of the alkalizing effects of semen, thereby inactivating acid-sensitive pathogens that cause sexually transmitted infections, including HIV. BufferGel® was the first of these agents to reach effectiveness testing but was found ineffective against HIV or any other sexually transmitted pathogen; it is continuing in testing as a contraceptive and possible component of a combination strategy. Work in a related category that uses different approaches to maintaining or enhancing inherent vaginal defenses continues.

FIGURE 1 | NUMBERS OF TOPICAL MICROBICIDE CANDIDATES IN DEVELOPMENT 1994-2010



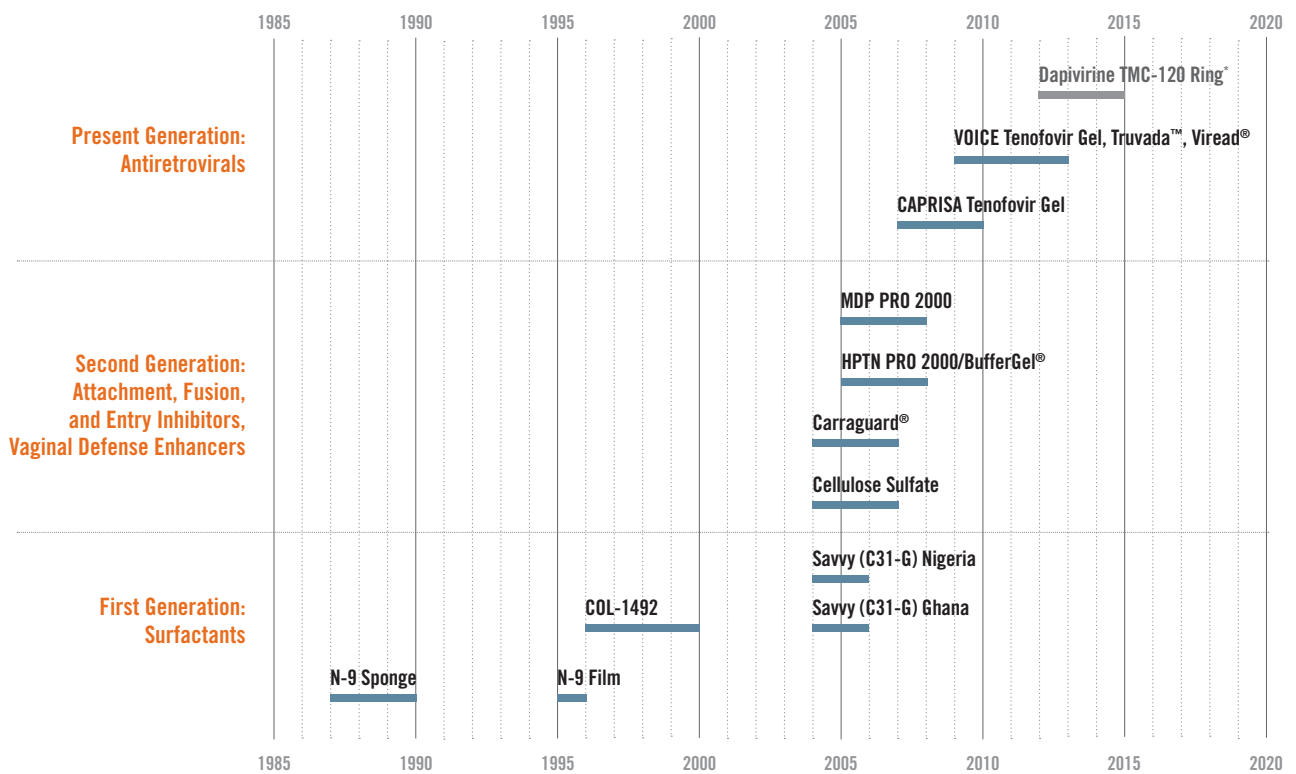
* Includes candidates in ongoing and planned clinical trials

FIGURE 2 | MICROBICIDE PRODUCT CLASSES IN CLINICAL DEVELOPMENT: THEN AND NOW*



* Includes candidates in ongoing and planned clinical trials. Totals may not add to 100 percent due to rounding

FIGURE 3 | TIMELINE OF MICROBICIDE EFFECTIVENESS TRIALS (PHASE 2B AND PHASE 3) 1987-2020



* Planned trial, dates approximated for illustrative purposes

The NEXT MICROBICIDE GENERATIONS

CANDIDATES IN CLINICAL DEVELOPMENT

ARV-BASED MICROBICIDES

These include three reverse transcriptase inhibitors (RTIs): the nucleotide analogue (NRTI) tenofovir (TFV), alone and in Truvada®, a combination with the nucleoside emtricitabine; and two non-nucleoside inhibitors, dapivirine (TMC-120) and UC-781. These specifically target HIV's earliest intracellular step, reverse transcription of its RNA genome to make a DNA copy and thereby multiply and disseminate itself throughout the human system. The ARV-based microbicide

candidates also include maraviroc, the first of a new class of therapeutics to be approved by the US FDA and marketed as Selzentry™/Celsentri®. Maraviroc prevents HIV from infecting by blocking the virus's co-receptor (CCR5) on the surface of susceptible cells used by those HIV strains mainly responsible for sexual transmission.

The CAPRISA and VOICE trials cited above are the first to investigate the clinical effectiveness of the RTIs as microbicides, work based on tenofovir's years of use in anti-HIV therapy. Dapivirine (TMC-120) and UC-781 are in early clinical development, with

dapivirine in different delivery systems furthest along. Despite the volume of data on maraviroc as a therapeutic, considerable testing is required for its use in prevention, either as an oral or a topical microbicide; two recent studies, in macaques and in male volunteers, show promise but much work remains.

That these clinical candidates are all ARV-based does not mean that they are equivalent. In fact, they display real diversity in their potential for generating resistance; bioavailability, solubility, potency, and memory effect; what is known about their pharmacokinetic and pharmacodynamic characteristics in general; potential for combination with other compounds and/or devices; and what is known about their safety and acceptability. These distinctions are critical to further discussion of whether all or some of these candidates should proceed to effectiveness testing, a conversation that will become essential as the results from trials of tenofovir start to become available later in 2010.

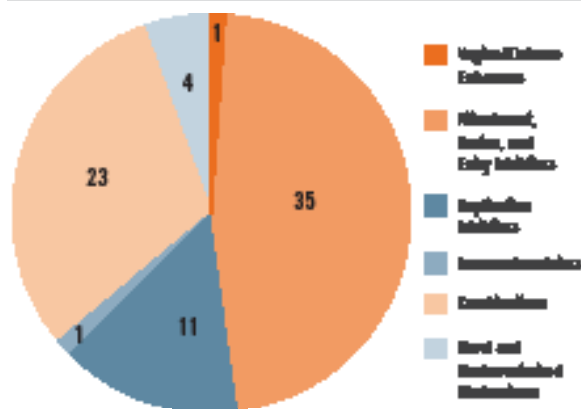
THE PRECLINICAL PIPELINE

The preclinical microbicide picture is far more diverse than the clinical part of the pipeline with respect to the mechanisms of action and origins of the candidates it contains. Like dapivirine, maraviroc, MIV-150, and UC-781, some preclinical candidates were created by pharmaceutical companies as potential therapeutic agents but proved unsuitable, primarily on grounds of poor systemic uptake. That characteristic was, however, seen as advantageous for topical microbicide use and these compounds were licensed in by nonprofit developers (e.g., CONRAD, International Partnership for Microbicides [IPM], Population Council) for that purpose. Other preclinical candidates were identified by screening large numbers of existing compounds, some through NIH-sponsored screening programs. Still others were specifically designed on the basis of new knowledge about HIV infection and progression.

In chemical terms, the list of preclinical candidate microbicides (*Appendix 2*) is dominated by an array of naturally-occurring proteins and peptides, synthetic peptides, and antibody-based inhibitors intended to interfere with viral attachment/fusion/entry processes or, in a few cases, viral replication and, in two cases, viral integration. It also includes a few compounds aimed

at enhancing vaginal defenses, lactobacilli genetically engineered to produce and secrete anti-HIV substances, and combinations of compounds and compounds with devices for coital and non-coital vaginal use and/or rectal application. As this report was being written, news was expected on exploration of protease inhibitors as potential microbicides and the results of a “first” in microbicide development – a nonhuman primate study of an integrase inhibitor being developed as a topical microbicide.

FIGURE 4 | MICROBICIDE CANDIDATES IN PRECLINICAL DEVELOPMENT* 2010



* Includes candidates in parallel preclinical and clinical development

Yet given the intrinsically high risk of attrition in pharmaceutical development, this seemingly expansive array of candidates and new concepts is, in terms of readiness for entering clinical testing, limited. The classic calculation for drug development and approval is that it takes ~15 years to move an experimental drug from laboratory to patient. On average, of ~10,000 compounds entering preclinical testing, only 5 make it to human testing, and only 1 of those is approved for distribution. A recent review sponsored by the Alliance found that only a small proportion of the substances listed in *Appendix 2* could be defined as being in the “advanced preclinical” part of the pipeline. The rest of that list are still early in development and are new and still highly experimental; have not yet undergone the necessary GLP toxicology studies or produced to GMP standards; and/or have been unable to attract sufficient confidence in their prospects to command sufficient funding for further advancement. This means that screening programs and efforts to acquire more candidate compounds from the pharmaceutical industry for development as microbicides should be awarded high priority.

As discussed later in this report, there are no agreed criteria for decisions on entry and advancement of new preclinical candidates and there seems to be no firm consensus on what candidate characteristics would best contribute to a vibrant pipeline. One thought is that the *in vitro* properties of new candidates should distinguish them from the currently leading class. Another is that novelty for the sake of novelty is risky, absent criteria and standards about what emphasis makes the most scientific and practical sense. Yet another is that the baggage associated with candidates derived from ARV therapeutics should be considered disqualifying, so that the wiser course of action would be to focus on specific entry targets that would avoid unexpected off-target effects and competition with existing therapeutic regimens.

RECTAL MICROBICIDES

Beyond the assumption that microbicides would be topical was the commitment to women as their primary, essential user population. It was assumed that men, heterosexual, bisexual, or homosexual, had the male condom for their protection and could determine its use in any sexual encounter. As microbicide research advanced, it became apparent that microbicides might also be used for lubrication in unprotected receptive anal intercourse (RAI) by both heterosexual partners and by men having sex with men. This had safety implications since the particular vulnerability of the rectal mucosa to HIV transmission results in a per-act exposure risk that can be approximately 20-fold greater than in unprotected vaginal intercourse. This is due to several factors, including the fragility of the single-layered columnar epithelium lining the rectum and the high prevalence of HIV-sensitive lymphocytes beneath it. It became clear that rectal safety testing would have to be added to the existing array of preclinical and clinical studies whether or not a given product is labeled for anal application.

The final steps toward the concept of “rectal microbicides”, that is, microbicides specifically designed for not only safe but effective use in anal intercourse, were supported by more epidemiologic data and analysis. A growing body of multicountry research indicates that RAI is more commonly practiced in heterosexual intercourse than once believed, suggesting that at least some women will be at double risk of infection. Most recently, data from sub-Saharan Africa highlighted the role of sexually active

MSM who often have both male and female partners, sometimes concurrently, and thus may play an important bridging role in disseminating HIV infection. In addition, the level of RAI being practiced by participants in clinical trials of vaginal microbicides may significantly diminish effect size in those trials.

Development of rectal microbicides has advanced rapidly over the last few years, benefiting greatly from experience in vaginal microbicide development in characterizing mucosal injury and inflammation, assessing product distribution across the mucosa, and evaluating user preferences. Adapted and new explant, mouse, and macaque models are being applied to establish baseline values for the parameters that may be affected by a rectal microbicide. Informative safety and dosing studies of ARV-based products have been completed and others are ongoing or actively planned, and the development portfolio for work on rectal microbicides includes single-agent and combination ARV-based and non-ARV-based products for development between 2011 and 2020. Despite many similarities between rectal and vaginal HIV transmission, these new studies are signaling the possibility of differences, especially in the earliest steps of mucosal infection and dissemination, which should inform the design of clinical trials that will ultimately measure the effectiveness of various prevention regimens against sexual HIV transmission.

As for efficacy, studies in mice and macaques have shown that rectal application of ARV microbicides can prevent infection from a rectal challenge with a simian/human hybrid virus (SHIV), and studies using multiple rectal biopsies show promise as a possible *ex vivo* assay for investigating the abilities of microbicides to prevent HIV infection in human rectal tissue.

COMBINATION MICROBICIDES

The notion of “combination microbicides” was part of the early vision of an “ideal microbicide” with a broad spectrum of activity that would prevent both HIV and other sexually transmitted infections, with possibilities for including contraceptive activity. In the case of microbicides, combinations of judiciously-selected ARV-based components – for example, an NRTI plus an NNRTI, or one of those plus an attachment/fusion/entry blocker, or an engineered protein integrated with a naturally-occurring defensive agent such as lactobacillus,

or an agent targeting HIV combined with one targeting pathogens acting as co-factors in HIV infection or progression – could:

- Act synergistically, resulting in greater efficacy, lower toxicity, and either greater antimicrobial specificity or a broader spectrum of activity
- Reduce risk of drug resistance, since the chance of HIV strains emerging with resistance mutations to two agents is smaller than the chance of developing resistance to a single agent
- Address challenges posed by entry inhibitors that favor a single co-receptor, since combinations could permit simultaneous blockade of more than one transmission pathway, thus increasing efficacy
- Target different steps in the HIV life cycle and provide protection against other STIs known to facilitate HIV infection
- Possibly reduce viral shedding in those unaware of their HIV status.

For all these good reasons, work on combination microbicides is advancing in several areas in various permutations:

- **Multivalent microbicides with multiple actives all targeted at HIV**
Examples: UC781/KP17, UC-781/tenofovir gel, tenofovir/dapivirine gel, mAb12 and CV-N
- **Multivalent microbicides with actives that target HIV and another relevant STI**
Examples: mapp166, PPCM
- **Combination strategies integrating one or more anti-HIV actives and a device** such as a barrier device, intravaginal ring (IVR), gels and capsules specifically designed to deliver one or more actives
Examples: dapivirine/maraviroc or tenofovir/maraviroc gel and intravaginal ring, UC781/progestin gel and IVR
- **Platform technologies** designed for delivery of multiple or multivalent actives
Examples: genetically-engineered lactobacilli, SILCS diaphragm with drug-releasing spring.

Although combinations may prove critical to achieving high levels of effectiveness, except for feasibility studies of the SILCS diaphragm with a drug-releasing spring, no combination microbicide has advanced beyond *in vitro* preclinical studies and early proof-of-concept testing

in non-human primates. This is partly because of the historical need to prove the microbicide concept with single agents; because combining biophysically diverse compounds is inherently difficult; because the intellectual property involved is generally owned by distinct entities; and because the regulatory pathway for microbicide combinations is unclear and its implications complex.

Nonetheless, the work proceeds. There are 23 “combination microbicides” in the preclinical microbicide pipeline (*see Appendix 2*), a list that does not include device combinations. Several groups (e.g., CONRAD, IPM, Population Council) are committed to at least one combination strategy. The NIAID Microbicide Innovation Program encourages submissions of proposals for combination strategies and supports a combination program for development of Combination HIV Antiretroviral Rectal Microbicides (CHARM). A large-scale five-year project funded under the European Commission 7th Framework has just been launched that will support collaborative work among 31 institutions in 12 countries for development of “Combined Highly Active Antiretroviral Microbicides (CHAARM)”; its research focus will be on combinations of inhibitors of reverse transcriptase and/or integrase and/or fusion for vaginal and rectal application.

Finally, a broader concept of combination strategies is represented by a new collaborative initiative organized in 2009 as a project of the California Microbicide Initiative (CaMI) and the Public Health Institute. Its goal is to galvanize evidence-based advocacy to increase support for accelerating development of and access to multi-purpose prevention technologies (MPT) for sexual and reproductive health. In this context, a multi-purpose technology is defined as one that would prevent HIV, other STIs and reproductive tract infections, unplanned pregnancy, or at least two of those results. The driving notion is that such products would be significant improvements over products with separate indications, for reasons of greater efficiency, economy, convenience, and appeal to users and providers.

FORMULATING & DELIVERING MICROBICIDES: AT THE HEART OF THE MATTER

Formulation is the hinge between the inherent efficacy of any active pharmaceutical ingredient (API) and its

ultimate biomedical effectiveness in use as a product. For topical microbicides, formulation is especially determining of that use because it is so immediately palpable and thus so easy to accept or reject on the basis of feel, appearance, and ease of use. The way a microbicide is formulated also influences its shelf life, its distribution and retention in the vagina or rectum, and the bioavailability and bioactivity of the APIs.

Microbicide formulation was first limited to gels, creams, and films, mostly due to familiarity with spermicidal contraceptives. Other than early trials of a nonoxynol-9 film and a vaginal sponge loaded with the same surfactant, all microbicide candidates clinically evaluated so far were delivered in semi-solid, aqueous-based gel dosage forms; used similar pre-filled plastic disposable applicators; and were intended for application just before every sex act, in other words “coitally-dependent”. Use at time of coitus seemed to make sense, given experience with spermicides which, despite low effective use rates as contraceptives, were inexpensive, readily available over the counter, and presumed unobtrusive and manageable by women. Interaction between drug and virus was expected to occur quickly on the epithelial surface, and systemic uptake was expected to be unlikely, another perceived advantage.

These assumptions, reasonable in those early days, have all come into question as clinical trials were implemented and failed and the influence of formulation on adherence, efficacy, and safety was highlighted and questioned. As trials unfolded and concluded, it was found that if all users did not like the test gels, many did; that discreet use at time of coitus was often not possible or desired; and that confidently measuring adherence was just plain difficult. Studies using new explant models and quantitative imaging techniques raised other questions: for example, were there subclinical effects that had not been identified earlier or had gel not been optimally distributed in the cervicovaginal environment or present long enough to adequately deal with invading virus?

In response to these findings, advances in formulation and delivery are expanding the microbicide pipeline beyond topical gels packaged in individual prefilled applicators for use shortly before coitus, to non-coitally-associated methods for use independent of the time of sexual activity. Much as contraceptive technology evolved, research on microbicide formulation and delivery now includes new formulation platforms for strategies able to provide protection against HIV infection even during unanticipated sex:

- Slow-release intravaginal rings made of silicone or thermoplastic urethane, loaded with API within the ring matrix or in a reservoir at its center, that could remain *in situ* for weeks or months
- Pre-loaded physical barriers
- Long-acting injectable formulations and implants
- New topical formulations that are longer-lasting, more bio-adhesive, less “messy” and detectable, more flexible in timing of use, such as:
 - Quick-dissolve polymeric films, vaginal tablets, soft-gel capsules
 - Nanoparticle encapsulation
 - Hydrogels that change conformation reversibly at varying pH
 - Potentially safe components (HEC universal placebo, Carraguard®, PRO 2000 formulation).

Whatever the formulation and delivery option, all must deal with similar issues:

- Balance between residence of active formulation *in situ* and exacerbation of local or systemic toxicity
- Ease and cost of manufacturing, packaging, distribution, and cost to consumer
- Accuracy of dose
- Stability/shelf-life, disposability
- Applicability to macromolecules as well as small diffusible molecules (e.g., ARVs)
- Side effects
- Preferences in different user populations that affect product use: access and cost, comfort, and convenience; contraceptive properties; efficacy; hygiene and sexual pleasure; and potential for covert use.

So many delivery formats are being pursued that some ask: is it time to prioritize? That may not be so easy. Each formulation and delivery method has advantages and disadvantages for researchers, trial participants, and users. For example, a slow-release vaginal ring that enhances adherence to product use and assessment of product efficacy may be ideal for use in a clinical trial aimed at proof of concept, but may not end up being the product a majority of women can or will choose to use. In contrast, coitally-dependent gels, notoriously subject to reporting biases that confound data analysis even in a well-designed, well-implemented trial, may be more popular among many users for various reasons.

04

A TIME OF *Learning*

Considerable learning has accumulated in the microbicide field, emerging from advances in the relevant basic and applied science, experience with clinical trials, and interpretation of trial results. Some examples:

- Even absent recognizable clinical findings, subclinical effects of the microbicide and/or its formulation (perhaps even GRAS components) on the genital epithelium can lead to potential harm and increase HIV transmission (e.g., by disrupting the tight junctions between epithelial cells or inducing proinflammatory responses).
- Candidates within the same class (e.g., the polyanions) may have different properties, so will not necessarily show the same behavior, in the laboratory or in the clinic.
- The microbicide may be insufficiently active against HIV R5 strains.
- Lack of established surrogate markers of safety and protection severely constrain decisions on product selection for effectiveness trials and interpretation of their results; non-human primate models used to assess the safety and potential protective effect of candidate microbicides have so far not been predictive of effects on human transmission.

POSSIBLE EXPLANATIONS FOR FAILURES IN PREDICTION

Microbicide use involves complex, multi-level biochemical and behavioral interactions among host, virus, and drug that await full understanding. There are many reasons why a microbicide that prevents HIV infection in the laboratory, in cellular, tissue, and animal systems, may not provide protection or may even increase infection as a result of sex with an HIV-infected partner. *Box 1* lists possible explanations for the failure of laboratory tests and clinical safety trials to date to predict the outcomes of seemingly well-designed and well-implemented clinical effectiveness trials of topical microbicides.

These scenarios are speculative: we do not know with certainty why the vaginal microbicides evaluated in effectiveness trials did not protect women from infection. Possibly it was some combination of the factors listed in *Box 1*, each partly responsible for reducing the benefits of a given microbicide, that resulted in its overall failure to protect. Whatever the reasons, these observations highlight serious discrepancies between expectations flowing from preclinical and early clinical assessments

on the one hand and, on the other, actual trial findings. They raise important questions about preclinical methods for assessing product safety and potency, the usefulness of the data they provide for choosing among candidate microbicides, and the appropriateness of the design and implementation of Phase 1 and Phase 2 clinical trials.

What we do know is that drug development is inherently a process of risk management, for which the

best available tools and tests must be used. Preclinical data can be useful for navigating decision points needed to narrow an array of candidates for more intense testing. The questions now for microbicide researchers are: how should existing testing strategies be modified to capture new information learned? How can the use of existing tools and/or new ones be improved so that they can reveal more relevant information as our knowledge expands?

BOX 1 POSSIBLE REASONS FOR FAILURE OF LABORATORY STUDIES AND PHASE 1/2 TRIALS TO PREDICT PHASE 2B/3 TRIAL OUTCOMES

IN THE LABORATORY

1. Limited understanding about the movement of HIV in tissues in relation to microbicide distribution capable of outdistancing and outlasting it
2. Inadequate information about the role of cell-associated HIV in mucosal transmission
3. Insufficient assessment of the effects of semen on microbicide potency, local immunity, and vaginal microflora
4. Standard, well-accepted *in vitro* and animal tests not sensitive enough to detect subtle damage to genital epithelia that could allow HIV easier access to sub-epithelial target cells
5. Current techniques unable to detect enhanced infection due to microbicide interference with local immunity or vaginal microflora, causing sub-clinical inflammation or facilitating HIV binding to host target cells
6. Dependence on symptom assessment and visual inspection of vaginal tissue, which imposes persistent uncertainties about safety implications of observations

IN THE CLINIC

7. Microbicide may not be well distributed in vaginal lumen or on mucosa, either initially or after redistribution as a result of sexual activity.
8. Some product may be lost in leakage from the vagina, spontaneously or as result of sexual activity, so exposure is to only a fraction of the expected dose.
9. Microbicide potency may be reduced by semen and/or cervico-vaginal secretions, either as a result of specific interactions or dilution.

10. A microbicide designed to be active in the vaginal lumen may not mix with ejaculate quickly and thoroughly enough to enable the active ingredient to block HIV before it targets cells in the genital epithelium.
11. Microbicide levels at sites of HIV-cell interaction within the epithelium may not reach and maintain concentrations sufficient to inhibit such interaction.
12. The microbicide may be insufficiently active against HIV R5 strains, “founder” viruses now thought responsible for vaginal transmission, cell-associated virus, and/or the particular HIV strains or clades prevalent at the trial sites.
13. Some infection may be occurring in anatomical regions (e.g., external genitalia, uterine epithelium, rectal epithelium) perhaps not adequately protected by the microbicide.
14. Phase 1 and 2 trials may involve too few participants, not include enough women who use product frequently enough, or proceed for too short a duration to reveal minor local adverse effects that could promote HIV infection.
15. Inadequate adherence to product use in Phase 2/2B and Phase 3 trials may have concealed either or both protective and adverse effects of the microbicide.
16. Women in trials may have experienced subtle but significant adverse effects of the microbicide on the genital mucosa that were not detected by the methods used.
17. Risk of infection may be increased by: effects of the microbicide or of semen components on the mucosa (e.g., increased permeability to virus and/or recruitment of HIV-sensitive cells); suppression of recruitment of immune cells that might control virus; or reduction in innate factor production.
18. The strains of non-HIV STI pathogens that are transmitted to women may be less sensitive to microbicides than laboratory-adapted strains.

05

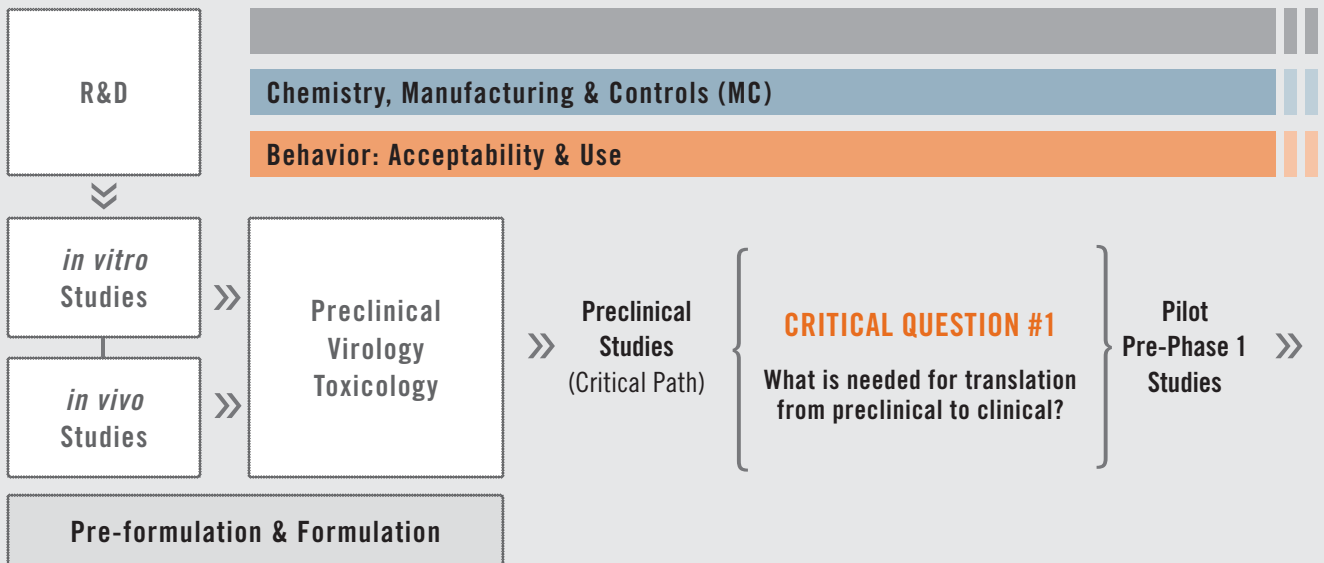
Navigating THE DEVELOPMENT PATHWAY

THE PATHWAY

A theme reverberating in and around the microbicide field over the past few years is that the field is hampered by a dearth of algorithms, plans, tools, fundamental knowledge, and – most of all – lack of a rational process

for advancing leads. This criticism reflects the early landscape of microbicide research, a time when plans, selection functions, and coordinating mechanisms were rudimentary. Microbicide development rested largely in the hands of individual researchers advancing single surface-active agents and polyanions and having

FIGURE 5 | THE MICROBICIDE PATHWAY



to overcome the challenges of securing financial and technical support. They, and the funders they approached, were confined by the continuing mysteries of heterosexual HIV transmission, caught up in the dynamics of competition, and lacking concepts and tools that might have empowered their respective assessments. And all – researchers, funders, and advocates alike – were beguiled by the belief that microbicide development would be simpler, easier, and faster than it turned out to be.

ALGORITHMS, PLANS, AND PROCESSES: WHAT IS MISSING, WHY, AND WHY IT MATTERS

By building on experience, fresh scientific insights, problem-solving in dedicated working groups, and regulatory dialogues (see Section 5), several microbicide groups have developed product- and organization-specific algorithms to help them manage the risk of developing compounds and make informed decisions. The key needs are:

- Targeted product profiles that identify products' best potential characteristics and unique properties, and focused plans to get them to clinical testing
- Systematic, unbiased processes for deciding which candidate microbicides warrant advancement at critical

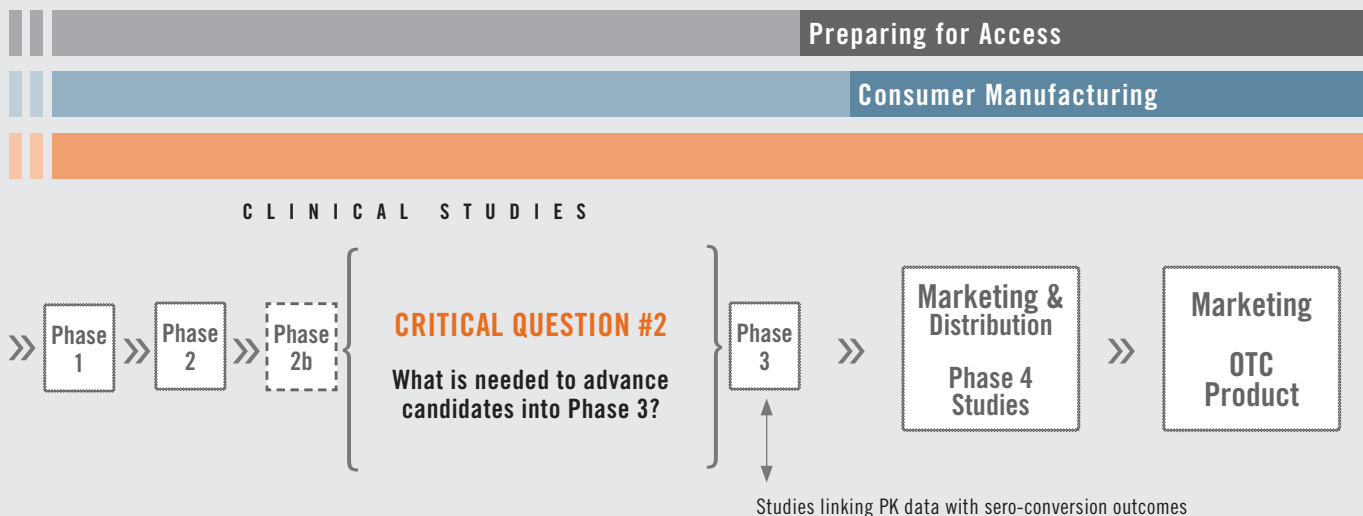
junctures in the development pathway

- A common model-based paradigm based on a harmonized minimum set of comparable assays and endpoints for making those decisions
- A strategic framework for obtaining and integrating/distilling the knowledge needed to continually inform that paradigm.

There are three areas in the microbicide development pathway that must get dedicated, systematic attention if the field is to grow and prosper (Figure 5):

1. Stages between and including discovery and preclinical studies
2. Advancement from preclinical status into the clinic
3. Advancement from early clinical studies into full-fledged effectiveness studies.

Figure 5 presents an idealized scheme. It does not tell the real story of drug development. The path from lead compound to clinical drug candidate is not a straight, tidy sequence of modular activities and milestones. Setbacks and failures are frequent and findings may seem to make no sense, perhaps due to inadequate biological understanding. There may be uncertainties about the studies that will be required by regulatory agencies before they will approve advancing a product into the clinic, and



these studies must meet a stringent level of quality, with documentation that may be beyond the investigator's laboratory capacity, and with higher costs that may be hard to predict. Funding to support this critical transitional period is hard to find: funders must be persuaded of the wisdom of such investment and must also have the competence to make the corresponding decisions. While product development plans may not guarantee funding, without them, sound funding decisions may become close to impossible.

Analyses performed for this report found that proportions of candidates in the preclinical part of the pipeline have changed radically. In 2000 and 2005, the proportions of candidates in preclinical development were 61% and 70%, respectively; that proportion is now 91%. This underscores the picture of the preclinical pipeline presented earlier (*see Section 2*), with so few candidates assessed as close to entering the clinic. The 2010 percentage could be interpreted in several ways, but two possibilities stand out: 1) intensified scrutiny

of the candidates drawing nearer to later-stage clinical development and/or 2) lack of confidence both in the processes for selecting microbicide candidates for advancement and the tools available to support those processes. The fact that clinical failures of other HIV infection strategies – herpes simplex suppression, female diaphragm use, and HIV vaccine candidates – occurred in that same period has not diminished the general air of skepticism about the failures in microbicide clinical testing.

The expanse between Phase 1 safety studies and pivotal Phase 3 clinical trials of microbicides is vast. It is well known that each successive stage along any drug development pathway is more costly than the last, not just in monetary terms but in the human resources and risks involved (*see Section 5*). For microbicides, the vastness, costs, and risks are exacerbated by factors discussed later in this report: lack of a robust surrogate for HIV infection, the demands of current effectiveness trial designs, and concerns around participant adherence to protocol.

There can be no single, simple, perfect model for a common conceptual framework for microbicide research and development, if only because of differences among candidates and because science is fluid and iterative by nature. Yet enough commonalities have accumulated to justify synthesis of proposed algorithms, best practices that will foster comparability of assays and models, and a structure for sharing and comparing that will support go/no-go decisions and translation of the findings of preclinical science into the clinic. There is more reason

than ever before to believe that the lessons and the science – basic, translational, clinical, and behavioral – can now illuminate the product development pathway well enough to make the journey possible.

Each section that follows reflects 1) conclusions from a survey of microbicide experts conducted by the Alliance in 2009 about progress in the microbicide field, enduring obstacles, and ideas about what should receive priority attention, and 2) those concepts explored and refined in subsequent analyses, key meetings, and reviews (*see References*).

BASIC, PRECLINICAL, & TRANSLATIONAL RESEARCH

PROGRESS

The microbicide field has progressed significantly in basic science, preclinical development, and formulation despite stubborn gaps in the understanding of HIV-drug distribution in sexually receptive body compartments. New assays and models for carrying out a wider range of experimental studies to address key scientific questions have proliferated. Much more has been learned about how to measure levels of drug in the female genital tract,

how gels deliver drugs in a way that could block HIV, and the impact of product on the rectal and cervicovaginal mucosae. It is now possible to use pieces of tissue in the laboratory to evaluate product safety, drug penetration, and activity against HIV. Research on the influence of the properties of formulated products on product safety, efficacy, and acceptability can now inform logical, data-based iteration between product design and evaluation. Advancements in formulation design have expanded the

original microbicide concept beyond a vaginal-only target and coital dependency.

All this said, HIV is a wily foe with many tricks in its bag and new HIV tricks keep emerging with disconcerting frequency as science digs deeper into that bag. HIV's partners in crime, notably herpes simplex, are similarly wily. Current knowledge suggests that HIV may sometimes be able to disseminate beyond the reach of a topical microbicide, persist beyond the time of microbicide action, and induce mucosal changes that pave the way for future infection; take advantage of the long-lasting effects of co-existing sexually transmitted diseases; and acquire drug resistance. Each of these abilities may or may not vary between anatomical sites and may or may not be a property of the microbicide being applied.

NEW KNOWLEDGE, NEW TOOLS: WHAT IS POSSIBLE NOW

It is now plausible to construct a pharmacokinetic-pharmacodynamic (PK/PD) model-based paradigm that can quantify microbicide levels, HIV movement in space and time, and the interaction of both. This can provide a basis for solving product development problems, for designing better Phase 1, Phase 2, and Phase 2B trials that will allow assessment of biologic effect in the clinic, and for making orderly development decisions. The new tools which make this feasible urgently need to be refined, validated, and systematically shared. They include:

- **More sensitive *in vitro* and animal tests**, including assessment of epithelial permeability and cytokine release patterns, to detect subtle damage and other local microbicide effects on genital and rectal epithelia
- **Novel organ culture models** of human tissues obtained from surgeries to provide a snapshot of immune cells in their theoretical natural environment
- **Updated publicly-available toxicity tables** for grading adverse events observed in protocols involving topical application of products to the genital and rectal epithelia
- **New animal models for assessing vaginal safety** (sexually-active pigtail macaque) **and protection** from intravaginal and rectal HIV infection (BLT humanized mouse)
- **Methods to evaluate microbicide potency in *in vitro* and animal models** that include cell-free/-associated HIV; CXCR4 and CCR5 strains; strains/clades prevalent at prospective trial sites; and, for other STIs, primary rather than laboratory-adapted strains
- **New toxicity assays** that can distinguish the relative toxicities of active microbicide ingredients, vehicles,

excipients, sexual lubricants, douches and enemas, and seminal fluid

- **Methods to assess kinetics of changing drug and virus concentrations** at mucosal target sites, effects of semen and cervico-vaginal secretions on drug potency at different concentrations, and whether drug/ejaculate mix happens fast enough to disable HIV before infection occurs
- **Non-invasive optical imaging studies** (optical coherence tomography, low-coherence interferometry, confocal microscopy, magnetic resonance imaging, and single photon-emission computed tomography) to ascertain distribution/retention of microbicide at target sites
- **Simpler, lower-volume cervico-vaginal lavage** sampling methods with intrinsic biomarkers to assess 1) microbicide concentrations at different times after insertion, with and without unprotected sexual intercourse, and 2) potency against cell-free/-associated virus *ex vivo* in the same samples
- **Radio-labeled cell-free/-associated HIV surrogates** in simulated semen to map viral migration and drug/cell interactions that could expand understanding of early HIV transmission events, measure HIV in tissue based on *in vivo* human exposures, inform formulation and dosing, and provide a base for proof-of-concept dose-ranging studies that could in turn underpin decisions about proceeding to large Phase 2B/3 studies
- **Brush sampling and mucosal tissue biopsy studies** that can track virus and provide information bridging macroscopic and microscopic drug distribution
- **Multidisciplinary, integrated explorations** of the rheological properties of different formulations (that is, changes in their form and flow), and their acceptability to users
- **Collection, storage, and utilization of clinical specimens** to explore factors predicting seroconversion
- **Enhanced Good Laboratory Practice (GLP)** at reference laboratories
- **Reliable multi-center laboratory assessments** of anti-HIV efficacy of microbicide candidates
- **Increased resources and greater integration into the microbicide development process** of preformulation, formulation, and analytical assay development.

NEXT STEPS

NEW TOOLS, NEW KNOWLEDGE: WHAT IS STILL NEEDED

Specific Areas of Need

- **Methods specifically designed to assess the intracellular pharmacokinetics** of ARV-based microbicides, since those will require different and more complex multi-compartment models
- **Studies of the optimal distribution of microbicides** with different mechanisms of action *in vivo* before and after sex with and without a condom, including study of the upper as well as the lower genital tract
- **Pharmacokinetic studies that integrate time/distance parameters and concentration** for quantitative assessment of gel distribution as that varies with formulation, coital simulation, presence of ejaculate and, in the case of studies of the rectal lumen, preparatory enemas
- **Pharmacokinetic studies with formulation types other than gels**, e.g., microbicide-releasing rings; genetically-modified microbicide-secreting lactobacilli; novel formulation approaches such as films, phase gels, and gels that incorporate nanotechnology
- **Approaches to integrating PK and seroconversion data** from large efficacy studies with seroconversion endpoints, e.g., nested small sub-studies with more intensive collection of data from many compartments to provide initial parameter estimates
- **Formulation comparison and optimization for both vaginal and rectal use.**

All of these are technologically feasible but all confront the same two challenges: their integration into the current development approach, and increasing resources so that they can be brought into that process adequately.

Cross-cutting Concerns

- **Biomarkers for Efficacy and Use and Their Validation** Lack of robust validated surrogate markers of protection from HIV infection imposes on microbicide development the need for large, costly screening trials and/or larger, even more costly effectiveness trials. Thus, pursuit of biomarkers that correlate with safety, use, and potential efficacy, and validating those, justifies steady effort, investment, and structured integration into human studies.

- **Use of Nonhuman Primate (NHP) Models** Different NHP models have been utilized to assess the safety and efficacy of vaginal and rectal microbicides and are also being used for studies of PrEP. Their use is nevertheless contentious with respect to dosing, type of challenge, and biological relevance. Their predictive power is repeatedly questioned, recently in connection with the failure of PRO 2000 to show efficacy even though an NHP study had shown protective effect. One view is that current NHP models should be refined, further validated by testing compounds failing to show efficacy in large human trials, and only then used to their fullest potential as decision tools to determine if investing human and financial resources into a large clinical trial is warranted. Given their high costs and funding constraints, the question of whether NHP models should serve as gatekeepers for transition from preclinical to clinical status for microbicide candidates is likely to remain a topic of controversy. These models will need to continue to be contrasted with new murine and tissue explants that are informative, can be standardized, and are far less costly.
- **Knowledge Access and Management** Since the days of little microbicide research and limited coordinated communication, there has been an explosion in research and the number of tools for pursuing it. Incorporation of microbicides into the HIV prevention “tool box” has further enlarged the zone of relevance for microbicide researchers and there is a danger of overwhelming abilities to read, absorb, integrate, and apply. There is also a perception that the microbicide field has not taken sufficient advantage of expertise and experience outside the field, especially early in the product development pathway. The pharmaceutical industry has begun to cope with information tsunamis through purposeful “knowledge management”, an established discipline that comprises strategies to identify, create, represent, distribute, and enable adoption of insights and experiences. The value of knowledge management services and methods for the microbicide field and, perhaps, the larger field of HIV prevention, might usefully be explored.
- **Tools for Organized Relationships** Well-conceived, well-supported, task-oriented groups can be highly effective in filling the various gaps along the development pathway. There is proliferation in the microbicide

field of such groups, each focused on different aspects of preclinical research and product development and problem-solving by intent, organized in different collaborative formats for different purposes, with a lead entity typically chairing and organizing conference calls and face-to-face meetings. A sampling of those follows:

Product-specific Entities

- *Tenofovir Gel Regulatory Working Group* (CONRAD, Gilead Inc., IPM, NIAID), engaged in gathering preclinical data, preparing for regulatory submission
- *UC-781 Working Group* (CONRAD)
- *Combination HIV Anti-retroviral Rectal Microbicides (CHARM) Program* (consortium; CONRAD, Johns Hopkins Medical School, University of California/Los Angeles, University of Pittsburgh)
- *Combined Highly Active Anti-retroviral Microbicides (CHAARM) Project* (consortium; 31 research groups in 9 countries in Europe, South Africa, United States, led by King's College London).

Topic-specific Groups

- *Biomarkers Working Group* (CONRAD)
- *Best Practices Working Groups* (series of groups being organized under DAIDS Comprehensive Resources for Topical Microbicides and Biomedical Prevention

contract with Advanced BioSciences Laboratories; first group focused on impact of semen in preclinical assays; others may address areas such as analysis of API release from formulated products in PK/PD assessments in animal models).

Other Integrating Functions

The most sizable integrating function across the microbicide field is the structured R&D program established by the NIH/NIAID Division of AIDS. The program consists of overlapping components, each serving a specific function along the development pathway:

- The Microbicide Innovation Program (MIP), described as an “Engine for Innovation”
- The Integrated Clinical-Preclinical Program for HIV Topical Microbicides (IPCP-HTM), described as an “Engine for Development” with “mini-pipelines”
- The Microbicide Trials Network (MTN), an “engine for licensure”.

NIH review processes are applied each time one of these programs emits a Request for Proposals, processes dependent on the extent to which the review committee understands microbicide development and is adapted to the demands of translational science, always a challenge.

Clinical RESEARCH

PROGRESS

Given their costs, it is not always consoling to simply respond that much has been learned from the late-stage trials of microbicides, despite their failure to demonstrate product effectiveness. Yet a great deal *was* learned, with some lessons being applied as trials were underway, and some as forthcoming trials were being contemplated and designed. Some of the positive outcomes from the effectiveness trials were:

- Increased site capacity and core funding, establishment of networks and centers of excellence
- Exploration of possibilities of innovative adaptive trial concepts to designing new trials
- Acceptance of the inevitability of co-enrollment and ways to address it
- Awareness of the importance of involving partners of trial participants and their communities
- Extensive dialogue, consultations, and publication of consensus guidelines around standards of health care for trial participants, and related ethical issues
- The value and complexities of thoughtful engagement of a broad cross-section of media and all key stakeholders in release of interim and final trial results
- The risks of over-optimistic time estimates for product development and access
- Numerous creative, flexible applications of participatory learning and action techniques to resolving implementation challenges as they arose

- The pivotal roles of behavioral and social science research in designing and implementing trials and interpreting their results
- Development of the *Site Capacity Database*.

LESSONS

The most crucial lessons had to do with those aspects of effectiveness trial design most directly linked to trial power: HIV incidence, number of participants enrolled, time off trial product due to pregnancy, participant retention, and adherence to trial protocol.

INCIDENCE

Several prevention trials experienced difficulties as a consequence of low HIV incidence at some trial sites, difficulties that ultimately compromised trial power. The complexities of producing estimates of HIV incidence based on data generated by currently available assays are daunting and matter greatly not only for the design and conduct of prevention trials, including microbicide trials, but for evaluating the success or failure of national programs. Each incidence assay has some kind of deficiency, such that the only solution may be a multi-assay algorithm-based approach rather than the use of any single assay. Many research groups are working toward evaluating such a strategy. The WHO Working Group on HIV Incidence Assays with a dynamic web site continues to struggle with development of guidance, statistical and validation approaches, and even basic vocabulary. Trial planners will have to address incidence on a case-by-case basis; it will never be a trivial matter.

SIZE OF TRIAL

Recent experience with Phase 2/2B and Phase 3 trials of PRO 2000 highlights the potential risks of designing intermediate-sized trials aimed at providing preliminary data on effectiveness.

PREGNANCY

Microbicide trials enroll sexually active women of reproductive age who are thus at risk of both HIV infection and pregnancy. Addressing this twofold risk challenges design and implementation of microbicide trials in several ways. Pregnancies must be prevented or identified before a fetus may be exposed to study drug, and the trial's statistical

power and interpretation of its results can be compromised by the withdrawal of women who become pregnant or by withdrawal of product from a participant who becomes pregnant, with product use resuming after pregnancy. The answer is requiring that participants use effective contraceptives, yet neither access nor use are always assured and potential for drug interactions may be unknown. Trial implementers have had some success in motivating increased use of reliable contraceptives through on-site provision and careful counseling. The MTN is addressing this issue head on with the evaluation of microbicide safety in pregnant women and by establishing a pregnancy registry under its “EMBRACE” project, which should illuminate a range of questions as data accumulate. In this registry, study participants are offered enrollment as early in pregnancy as possible post-exposure to study drug; babies resulting from these pregnancies are also registered.

RETENTION

Retention in most microbicide trials has been high, but is an issue throughout any trial. The consequences of low retention can be drastic. A recent oral PrEP trial of the acceptability and efficacy of Truvada® in heterosexual men and women in Botswana had to be modified because of challenges in retaining participants in a highly mobile population of young adults (and also because of much lower than anticipated HIV incidence, partly due to extensive HIV prevention services for all participants). Even doubling sample size would not have produced a valid effectiveness result.

The Botswana experience points to another challenge in HIV prevention research. It is now implicit in effectiveness trials that they include a comprehensive package of safer sex counseling, treatment of non-HIV STIs, and provision of condoms. The effect is to lower the risk of HIV infection, making it harder to demonstrate effectiveness, yet access to such packages is an ethical imperative.

RECEPTIVE ANAL INTERCOURSE (RAI)

Modeling studies suggest that even moderate frequency of RAI among vaginal microbicide trial participants could substantially reduce study power. Since data on RAI frequency are hard to obtain and HIV transmission probabilities are unknown, counseling participants against RAI during trials is presently the only practicable approach to addressing this possible effect on study power.

ADHERENCE

The percentage by which a microbicide decreases HIV incidence compared with placebo in a clinical trial (i.e., its effectiveness) will depend substantially on its consistent use by trial participants. Assuring such adherence and measuring it reliably are replete with difficulties. Ensuring high adherence to product use is especially difficult with gels intended for coitally-dependent application. Once-a-day gels, IVRs, and oral PrEP are seen as the sorts of plausible solutions to this dilemma, but whatever the formulation or mode of delivery, adherence will still matter. A battery of techniques has been developed for motivating and measuring adherence; these are described in the section headed *Behavioral and Social Science Research*.

NEXT STEPS

ACCOMMODATING TO PIPELINE CHANGES AND ADDRESSING THEIR IMPLICATIONS

The growing dominance of ARV-derivatives in the microbicide pipeline offers advantages: greater potency and specificity than their pipeline predecessors, and the fact that some have accumulated large amounts of human-use data as therapeutics prior to their development as vaginal microbicides or PrEP. But ARVs also raise questions which the MTN VOICE trial will try to answer through a strategic series of parallel and sub-studies, including the very concerning question of potential for development of drug resistance.

ACCEPTING MORE PUBLIC PROFILE AND PRESENCE

The commitment of trial teams to authentic, extensive community engagement and intensified focus on educating and involving all media were necessary and productive, but have been attended with high ongoing levels of visibility for microbicides; heightened demands for information and transparency; and, in some cases, misunderstandings that are hard to repair.

RETHINKING CLINICAL TRIALS

Perhaps the most substantial consequence of experience with microbicide effectiveness trials has been achieving agreement on the need to re-think the structure and content of the clinical trial sequence, particularly the size, duration, and focus of Phase 1 trials. A December 2010

meeting convened by the NIH Division of AIDS was the first organized effort to tackle the question of how the suite of Phase 1 trials should be designed to maximally inform decisions about advancement in the microbicide pipeline. Some conclusions follow:

- Progress has been made in the following areas:
 - Standardized collection of data on adverse effects
 - Communication among investigators
 - Collaboration with basic scientists to help find biomarkers of safety.
- The “Phase 1/Phase 2” terminology is confusing and arbitrary.
- Such studies as traditionally conceptualized in microbicide development have not provided data meaningful to inform dose/schedule finding, proof of concept, or effect.
- Only with the intense pursuit of ARVs as microbicides has the relevance of pharmacokinetics/PK and pharmacodynamics/PD been recognized, resulting in the beginnings of their incorporation into the Phase 1/2 clinical development paradigm.
- Effectiveness trials took place without full appreciation of the influence of semen and vaginal secretions, the potency of the microbicides, and their effects on intravaginal distribution and persistence of drug.
- Formulation evaluation is critical in Phase 1 studies as it, optimally, should promote adherence to the test product; at the very least, it should not discourage adherence to product use.
- Acceptability assessments are now being integrated into the early clinical development framework to enhance information gained from Phase 1 studies that will enhance adherence in eventual effectiveness trials.
- Evaluation of microflora and endogenous antimicrobial activity, cervicovaginal lavage specimens, or vaginal/rectal biopsies to determine level and duration of anti-HIV activity following product application may represent promising biomarkers for safety and efficacy; efforts to optimize and standardize sample collection to assist in evaluation of these potential markers are underway.
- Conducting parallel, concurrent Phase 1 trials to facilitate more expeditious decision-making, while more costly, is likely to be more efficient and informative.
- Given that no safety signals that might have caused concern were identified in pre-Phase 2B/3 testing of

the products that advanced to effectiveness trials, the standards for establishing product safety remain elusive, despite some understanding of what constitutes an unsafe product.

The meeting flagged topics that merit resolution or at least pursuit, in other words, “next steps” toward:

- Standardization of trials, including design, collection of adverse events, and laboratory assays
- Establishing normal range data for laboratory assays
- Standardization and comparisons across laboratories
- Deciding on the amount and content of acceptability data that are necessary
- The value of colposcopy and which techniques for examination of cervical and vaginal epithelium should be considered essential
- The potential and wisdom of attempting to “standardize” a panel of priority assays and/or providing a standardized, blinded panel of reagents for comparison across laboratories/assays
- The optimal duration and size of a Phase 1 study
- The continuing need for identifying and validating biomarkers predictive of safety and efficacy, especially questions about which are the most relevant parameters to include in Phase 1 trials.

BEHAVIORAL & SOCIAL SCIENCE RESEARCH

Early in microbicide development, the value of behavioral and social science research to clinical research was, more often than not, under-appreciated. Such research was often viewed as unjustifiably burdensome in terms of time, cost, and staff demands, its contributions too complex and somewhat ethereal. Emphasis was placed on assessing potential product acceptability, typically through surveys based on hypothetical concepts and proxy products. Utilization of adherence data in trial design, implementation, and interpretation was inconsistent, perhaps because those data derived solely from self-report. That view has changed dramatically with recognition of the centrality of adherence data to determining microbicide effectiveness, providing additional evidence to support trial results, understanding safety, and comprehending acceptability and product experience.

LESSONS

Behavioral and social science research have garnered insights that altered early perceptions about microbicides, their use, and their users; reframed the concept of acceptability; and sharpened realizations about which populations would be most likely to need and benefit from microbicides. They have stimulated:

- Adjustments to the assumption that women would, could, and should use microbicides covertly
- Revision of the notion that male partners would not, could not, and should not be involved in microbicide trials
- Expansion of understandings about microbicide acceptability to a wide range of non-clinical and clinical settings, including health care providers
- Recognition of the variety of person-, product-, and context-related factors predicting willingness to use microbicides
- Extension of the view of microbicides beyond disease prevention to perceptions of microbicides as healthful, valuable to well-being, and enhancing of sexual pleasure
- Enlarged insights into product, formulation, and device perceptions and preferences in a wide range of users and providers, male and female
- Deepened understanding of partner dynamics, decision-making, and product use, and interpersonal and contextual influences on microbicide use for both men and women
- Unanticipated learning about the potential of microbicide use to enhance partner relationships
- Richer, contextual appreciation of the sociocultural norms for gender roles and sexual behavior, as well as the economic forces affecting those roles and behaviors
- Integrated biomedical and behavioral analyses of anal intercourse, and relationships among intravaginal practices, vaginal infections, and HIV acquisition, and their implications for microbicide use

- Appreciation of the relative weights of protective and contraceptive effects, risk perception, and valuing and potential use of microbicides.

OPTIMIZING AND MEASURING ADHERENCE

Adherence optimization and measurement have emerged as critically challenging, intimately connected issues for microbicide clinical trials. The main contributor to sharpened focus on motivating and measuring adherence was the fact that several Phase 2B and Phase 3 trials reported lower than expected adherence to product use and protocols. Self-reported adherence in early trials was found not only unreliable but in one case diverged so substantially from estimates using then-available verification strategies, e.g., applicator tests, that trial conclusions about effectiveness were severely compromised. As a consequence, considerable energy and creativity have been applied to development of methods to measure or serve as proxies for adherence. Each has limitations in terms of practicality or level of confidence; some have been applied and some are still being explored. They include:

Direct Measures

Respondent-independent, quantitative biological measures or “biomarkers” of adherence and incident infection that might enable unbiased, adherence-adjusted effectiveness analyses:

- Biomarkers of semen exposure
- Applicator dye tests
- Drug levels in plasma or genital tract.

Indirect, Objective Measures

Measures that are independent of individual feelings, beliefs, or desires, and do not involve self-report:

- Applicator returns and counts
- Directly Observed Therapy (DOT) or Daily Monitored Adherence (DMA)
- Manual or MEMS cap product count
- Pharmacy disbursements.

Indirect, Self-report Measures

Self-reports collected through a range of techniques and response formats and structures, typically with a time reference:

- Audio Computer-Assisted Self-Interview (ACASI)

- Diaries (including those using Interactive Voice Response [IVR])
- Face-to-face interview; in-depth qualitative, structured, or quantitative.

As critical as direct measures could be, their development, testing, and validation have been the most challenging and slowest to advance, but also highly innovative, for example, a bar-coded “Smart Applicator” to register time and date of use and a “Sexometer” to measure microbicide use during coitus. All of the indirect measures have been explored to varying extent and success, and efforts to compare and validate them are progressing. For example, applicator dye tests compared with self-report, and ACASI compared with face-to-face interview, have documented their relative informative power.

Another consequence has been downgrading of the very concept of coitally-dependent microbicides and a trend toward technologies that are coitally-dissociated at least partially, such as intravaginal rings, longer-lasting gels, or oral PrEP, or totally dissociated such as injectables.

NEXT STEPS

ADHERENCE

Mixed Methods

No single measure of adherence to product use in microbicide clinical trials has proved sufficient. Thus, the approaches that have been tried and found most productive, and those that show most promise, are combinations or systematic integration of several methods through the entire course of clinical studies from design through participant follow-up:

- *Triangulation* – use of multiple observers, theories, or data-collection methods to overcome the inherent biases of any single observer, theory, or method; increase convergence; and reconcile inconsistencies across data sets
- *Composite measures* – combinations of different measures to generate a single outcome whose value falls somewhere between outcomes from individual measures
- *Baseline adherence predictors* – measurements taken at baseline to identify women likely to be adherent prior to randomization (e.g., observed level of adherence to a comparable product collected during a study run-in)

- *Optimizing adherence in trial design and implementation* – explicit strategies for optimizing adherence prior to study initiation; a dedicated adherence coordinator; information-motivation-behavioral skills approaches; “run-in” studies to teach proper product use prior to trial start and anticipate issues that might affect acceptability and adherence (which, though often conflated, are not the same thing)
- *Optimizing adherence in response to routine monitoring* – counseling and message modification, “trajectory analyses” that reveal individual or group behavioral patterns over time.

ACCEPTABILITY

As discussed in *Section 3*, emphasis is necessarily turning to formulating more potent active ingredients for maximum efficiency in topical microbicides for HIV prevention. This is assessed in pharmacokinetic and pharmacodynamic studies, for which measurement tools are becoming more available and constantly being improved. At the same time, the associated formulation and/or drug delivery system must be designed not only to assure potency and efficiency, but to be sufficiently acceptable to assure adherent use, a highly personal and situational matter. This is the translation point in microbicide development where drug efficiency and formulation acceptability must meet, and where innovative strategies can be applied to improving understanding of acceptability, its relevance to formulating and delivering drug substance, and its

importance during and after clinical trials. What will be required are:

- A focus on evidence-based rational development and design of novel formulations and/or delivery devices using multidisciplinary approaches
- Continued design, modification, and validation of acceptability measures and factors that moderate or mediate the multi-factorial construct that is “acceptability”
- User evaluations of formulation/device prior to Phase 1. The design of dosage forms and delivery devices should take account of the sensory perceptions of potential users who interpret product properties and “behaviors” and cast judgment on their efficacy and ability to be integrated into sexual and daily lives
- Development of strategies for product introduction and long-term marketing, in anticipation of regulatory approvals.

Clearly, enhancing the basic acceptability of any microbicide product, its adherent use in a trial context and eventually in real-life use, all require multiple strategies. The purpose of these strategies, individually and together, must be specified *a priori*; well incorporated into product development, trial design, and analytical plans; and continuously tested and validated. However, also clear is that there are not enough flexible, multidisciplinary processes of review and funding for the kind of innovative translational research that is required to get this job done soon and well enough.

MANUFACTURING, COMMERCIALIZATION, & ACCESS

PROGRESS

There have been two schools of thought about when it makes the most sense to invest major time, energy, and resources in planning for microbicide manufacturing, commercialization, and access:

1. There is enough to worry about in just getting products that work so that, absent persuasive signals

of a promising product, such planning is premature and merely theoretical.

2. It is never too soon to plan: the product development pathway is an entire trajectory with critical feedback loops, and commitment to post-trial access is ethically essential.

The sharp edges between these perspectives have softened since February 2009 when tantalizing data

from the HPTN-035 Phase 2/2B trial of PRO 2000 made planning for its future seem reasonable. The World Health Organization responded by convening a meeting on “Preparing for Access” in May 2009. Its purpose was to explore possible scenarios and uncertainties in anticipation of the results of MDP-301, the much larger effectiveness trial of PRO 2000 scheduled for release in late 2009.

The meeting was able to start at better than zero, since the *Microbicide Development Strategy* had provided a useful framework for action and several groups had done important pieces of work on priorities flagged in that document:

- Development of initial demand, cost forecasting, and impact models to inform planning for manufacturing at different time points, distribution sequences, and procurement
- Acceptability research on end-user preferences and product-specific market studies of different formulations and delivery systems
- Formal commitments to post-trial access in communities participating in clinical research
- Identification of some prospective country- or regional-level manufacturers
- Clarifications of the status of relevant intellectual property
- Ongoing conversations with prospective international funders of product distribution in low-resourced settings
- Convening of international, national, and regional regulatory meetings, and dialogue with authorities in potential countries of use.

LESSONS

What surfaced early in the WHO 2009 meeting was the substantial lack of clarity about what would really have to happen to take PRO 2000 through the next critical steps and how long those steps would take. To get a handle on that, the group created a timeline for all the elements requiring attention, immediately and over a period expected to last through the second quarter of 2012, assuming positive trial results (*see Figure 6*). Although the timeline in the figure refers specifically to PRO 2000, it can continue to be useful as a reality-based template for focusing on specific commercialization and access requirements for forthcoming products, to evolve and be fine-tuned as the nature of the product and circumstances dictate.

The meeting also served to underscore vulnerabilities in key areas:

- **Determining levels of effectiveness warranting further development of a given product** This is a complex, context-specific topic requiring some sort of engagement of prospective consumers and beneficiaries; international and national regulatory authorities; scientists, providers, policy-makers, and advocates, in consensus-building processes that are barely defined.
- **The realities of product availability, manufacture, and funding** The microbicide field has been encountering difficulties in manufacture of product for use in trials and material for new delivery systems (e.g., intravaginal rings), as well as funding for such manufacture. (Indeed, challenges were anticipated around manufacture of enough PRO 2000 for further studies and scale-up.)
- **Prospective regulatory requirements following effectiveness studies** These are evolving and will vary according to the regulatory authority and product involved (*see Section 5*); this fluidity may be a good thing, given all the changes in the pipeline and the environments in which microbicides will be tested and used, but does complicate planning processes, particularly with regard to time and costs.
- **Decisions about the distribution sequence according to which a product is to become available once approved for distribution** This is another practically and ethically complex matter that raises hard questions for planning and sequencing of scale-up.
- **Knowledge levels** Academic and clinical researchers generally have little experience of product development or ready, systematic access to relevant expertise.
- **Financing** Funding for bridging the various transitions from academic and clinical research to the later stages of product development is rarely considered in proposed budgets or included in funding awards, yet its absence is likely to be responsible for large gaps between successful clinical research outcomes and consumer access to successful products.

NEXT STEPS

The vulnerabilities exposed as a result of the WHO meeting stand out as chronic deficits likely to re-appear in connection with other later-stage candidates. The question is: how much of this can be usefully anticipated

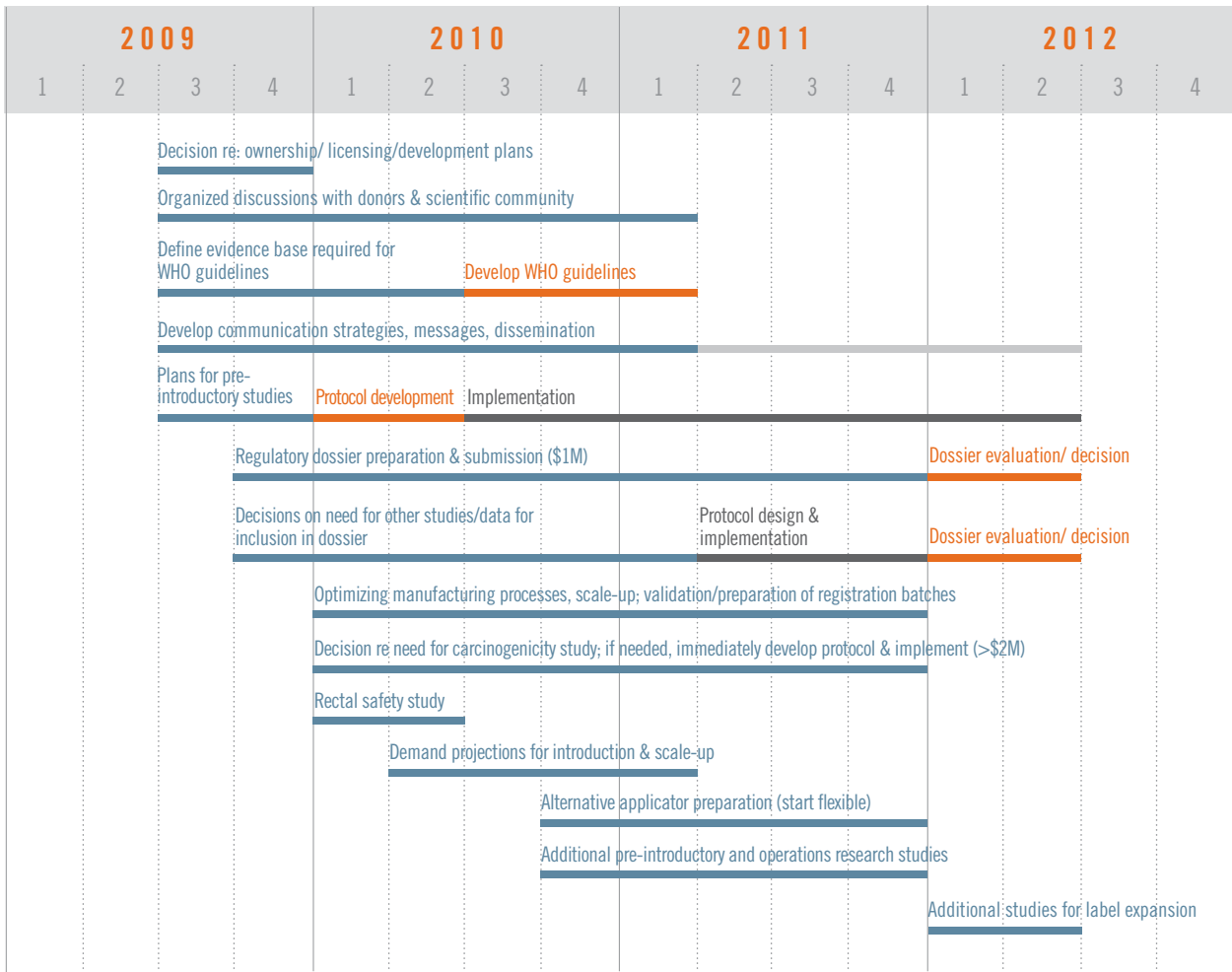
and with what level of specificity, absent specific products? The real test of planning will take place in the presence of an efficacious product. Only so much theoretical discussion can prepare the field for all the needs and processes and time that will become apparent, in some cases gradually or surprisingly.

This means that as this knowledge is accumulated, it should be systematically shared and updated, especially (although not exclusively) with new researchers and developers entering or considering entry into the microbicide and PrEP fields. Researchers and trialists should not and, in fact, cannot be expected to take on the chain of actions required for manufacturing, commercialization, and access. Additional expertise in these areas will be needed and, ideally, should be brought into planning conversations early on rather

than waiting until a product is ready for manufacturing, commercialization, and access. Funders should also be brought into these conversations so that they can at least begin to think about the financial and timing implications of eventual product roll-out.

A useful piece of work in this connection might be constructions of model budgets associated with timelines and milestones. Building a budget to take to funders for any portion of the work required under the rubric of “manufacture, commercialization, and access” is at best difficult, given that there is presently no clear picture of what costs those three areas of effort might imply and the realities of time to access. Thus, work to build or model a cost structure could be helpful and, in fact, has already proved helpful to rollout of other prevention technologies, most recently male circumcision.

FIGURE 6 | TIMELINE FOR PREPARATION FOR ACCESS: THE CASE OF PRO 2000



The FACTORS THAT SUSTAIN

For the microbicide field to have grown and for it to keep growing healthily, there is a web of sustaining effort beyond the supportive research underpinning the basic, preclinical, and clinical science:

- The **funding** required from bench to end-user
- The **regulation** that assures the safety and efficacy of what is produced
- The **policy-making and coordination** that inform and strengthen
- The essential voices of **advocacy and civil society**.

Each of these pieces of sustaining effort has seen progress as the microbicide field advances and learns from both achievement and failure, and each requires more effort, some now, some soon, some later.

FUNDING

As one of its first tasks when it was founded in 1998, the Alliance for Microbicide Development launched a series of annual tallies of investment in microbicide research and development and, soon after, a regular

sequence of detailed analyses of expenditures and allocations. This research and monitoring work would become a strong plank in the Alliance platform for microbicide advocacy that would effect real change in policy, institutional response, and resources for the microbicide field over the coming years. The results of that advocacy are well expressed in *Table 2*.

RECTAL MICROBICIDES

The figures for investment in rectal microbicide (RM) research are subsumed in the previous numbers but merit separate attention here as newly available data. Between 2000 and 2006, total RM investment was US\$34 million; the US public sector contributed 97.4% of that amount. Between 2007 and 2010, global spending on rectal microbicide research totaled US\$25 million; the estimate for global spending for 2010 is approximately US\$7.2 million. The US public sector contributed 91.6% of that global investment in rectal microbicides, European contributions constituted 5.3%, and the philanthropic sector 3.0% in that period.

TABLE 2 | ANNUAL INVESTMENT IN MICROBICIDE RESEARCH AND DEVELOPMENT 2000-2008 (US\$ millions)¹

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Public Sector									
United States	34.6	61.3	75.3	78.8	92.0	101.6	129.7	139.8	154.4
Europe	0.7	0.4	5.1	10.6	29.9	30.3	56.3	59.6	39.9
Other	0.3	<0.1	0.2	0.9	2.0	10.5	4.7	3.4	12.1
Multilaterals	<0.1	0.3	0.4	<0.1	0.2	0.2	1.4	0.2	0.2
Total Public	35.7	62.0	81.0	90.2	124.2	142.6	191.2	203.0	206.7
Philanthropic Sector									
Total Philanthropic	29.4	3.4	24.8	16.9	18.1	21.3	26.2	19.0	34.6
Total Non-commercial	65.1	65.4	105.8	107.1	142.3	163.9	217.4	221.0	241.3
Commercial Sector									
Biopharmaceutical Companies	ND	ND	ND	ND	4.5 (range 3.0- 6.0)	4.5 (range 3.0-6.0)	4.5 (range 3.0- 6.0)	4.5 (range 3.0-6.0)	2.5 (range 1.5-4.0)
Total Commercial	ND	ND	ND	ND	4.5	4.5	4.5	4.5	2.5
Total Global Investment	65.1	65.4	105.8	107.1	146.8	168.4	221.9	226.5	243.8

¹ HIV Vaccines and Microbicides Resource Tracking Working Group. *Adapting to realities: trends in HIV prevention research and funding 2000 to 2008*.

MICROBICIDES AND OTHER PREVENTION TECHNOLOGIES

According to analysis in 2009 by the HIV Vaccines and Microbicides Resource Tracking Group, there was a 3.74% increase in investment in microbicide research and development between 2000 and 2008, compared to a 2.65% increase in funding for HIV vaccine R&D (Table 3). Figures for 2009 will not be fully available until July 2010. Other HIV prevention technologies showed increases (except for cervical barriers), but levels of investment are small relative to both vaccines and microbicides (Table 3). The PrEP investment can be expected to rise, given the number of clinical trials that are ongoing and planned; male circumcision investment is likely to shift away from biomedical research into program investment as it is rolled out and a decision will have to be made on how to track the corresponding investment.

FUNDING FOR THE FUTURE

From 2005 onward, there were steady increases in funding from the two major US contributors to microbicide R&D, NIH and USAID. Although figures for the next two fiscal years (FY) are preliminary, current estimates are as follows:

- The NIH pending budget request for microbicides for FY 2011 is US\$148 million, 19.4% over the previous year (FY 2009 level: \$128.7 million)
 - The USAID obligation rose from US\$39.6 million in FY07, to US\$44.6 million in FY08, and US\$45 million in FY09; the budget request for FY10 is evolving.
- Figures for microbicide R&D investment for 2009 for the G-8 countries and Europe are also preliminary, but are considered close to final (Table 4).

TABLE 4 | PRELIMINARY ESTIMATES OF INVESTMENT IN MICROBICIDE R&D, USA, G-8 COUNTRIES, AND EUROPE 2009 (US\$ millions)

Countries	2008	2009	Change
USA	154.5	172.6	+12%
G8 Countries*	179.0	196.9	+10%
Europe**	39.9	41.0	+3%

* Canada, France, Germany, Italy, Japan, Russia, United Kingdom, United States
 ** Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom, European Commission

THE COSTS OF MICROBICIDE DEVELOPMENT

In preparation for this report, all microbicide development groups were surveyed and asked the following question: “On the basis of your expenditures for your current clinical candidates and what you have learned from experience to date, what cost ranges would you suggest are reasonable/required for Phases 1 through 3?” All groups responded with enough real data for a set of ranges to be constructed and provided the basis for Tables 5 and 6. Table 5 presents the ranges in actual costs of microbicide trials to date and Table 6 presents estimated costs in terms of cost per participant and cost per trial endpoint.

The tables make several critical points. First, there is a great deal of variability and width in trial cost ranges. Second, the widest cost spreads are found in Phase 2B and Phase 3 trials, which are the most sensitive to the number of participants and endpoints required. Both these calculations are crucial since while cost per participant is necessary for trial budgeting, it is cost per endpoint that is

TABLE 3 | ANNUAL INVESTMENTS IN MICROBICIDES AND OTHER BIOMEDICAL HIV PREVENTION TECHNOLOGIES 2000-2008 (\$US millions)^{1,2}

	2000	2001	2002	2003	2004	2005	2006	2007	2008
Microbicides*	65.1	65.4	105.8	107.1	146.8	168.4	221.9	226.5	243.8
Vaccines*	327.0	366.0	548.0	547.0	682.0	759.0	933.0	961.0	868.0
PrEP*	ND	ND	2.2	3.4	7.9	12.5	17.0	33.5	44.4
Male Circumcision*	ND	0.5	3.1	5.9	5.9	6.8	11.2	7.7	10.6
Herpes Suppression*	ND	ND	2.6	2.9	8.0	11.9	11.5	9.6	4.4
Cervical Barriers*	ND	ND	7.0	7.0	7.0	7.0	8.0	8.0	ND

¹ HIV Vaccines and Microbicides Resource Tracking Working Group; *Adapting to realities: trends in HIV prevention research and funding 2000 to 2008.*

² HIV Vaccines and Microbicides Resource Tracking Working Group; *Sustaining the HIV prevention research agenda: funding for research and development of HIV vaccines, microbicides and other new prevention options 2000 to 2007.*

* Amounts reported include public, philanthropic, and commercial sector investments

† Amounts reported include public and philanthropic sector investments only

TABLE 5 | COST RANGES FOR MICROBICIDE CLINICAL TRIALS: 2002, 2004, 2010 (actual costs in \$US millions)

Clinical Phase	Cost Range, 2002*	Cost Range, 2004**	Cost Range, 2010†
Phase 1	1M – \$3M	\$0.3M – \$4M	\$0.5M – \$4M
Phase 2	\$1M – \$5M	\$2M – \$5M	\$3.5M – \$5M
Phase 2B	No data	No data	\$18M – \$100+M
Phase 3	\$30M – \$50M	\$9M‡ – \$50M	\$56M – \$62M

* Rockefeller Foundation. *The Economics of Microbicide Development, 2002.*

** Alliance for Microbicide Development; *Microbicide Trial Cost Survey, 2004.*

† Alliance for Microbicide Development; *Microbicide Clinical Trial Cost Survey, 2010;* costs of Phase 3 trials that were terminated early are not included in estimates

‡ Includes cost of trials that were terminated early

most important to decisions about effectiveness. Also important to note is that these costs do not invariably include the cost of other, directly related research such as ancillary behavioral, laboratory, or sero-converter studies; additional specimen collection; or such parallel activities as pregnancy registries; or critical support components such as community activities, communications, and central core requirements for study implementation and data analysis.

What is not apparent is the variability subsumed under “Phase 1 Trials” which, as discussed earlier under *Clinical Research*, is a category of effort requiring greater attention. Future Phase 1 trials are likely to be more costly than their forebears, given the prominence of ARV-based candidates. For purposes of illustration, *Table 7* provides a diverse and incomplete list of the sorts of Phase 1 trials that are likely to become necessary and, therefore, what might be in

the wings from a cost perspective. Studies that are being described as “Pre-Phase 1 studies” are not included.

COSTS GOING FORWARD

When this report was first contemplated, there was an illusion that it might also include some perspective on what the next years of microbicide R&D might cost. The evidence that accrued to the writing of the report, however, revealed that as truly an illusion. In 2002, a

TABLE 7 | ILLUSTRATIVE COSTS FOR SELECTED FUTURE PHASE 1 TRIALS (by trial type)

Phase 1 Trial Types	Per Trial Cost
Acceptability	\$300,000
Feasibility	\$500,000
Gel comparison	\$200,000
Imaging studies	\$1.5 million
Male tolerance/safety in men	\$75,000 – \$500,000
Safety in HIV-infected men and women	\$1.1 – \$1.5 million

major analysis performed by the Boston Consulting Group modeled what would be required to advance the microbicide pipeline at that time. The altered contents of today’s pipeline, reconfiguring of preclinical and clinical research algorithms, cost increases across all of pharmaceutical development, and questions about the gap between product approval and access, demand new calculations of microbicide development costs.

TABLE 6 | ESTIMATED COSTS FOR MICROBICIDE CLINICAL TRIALS (completed and ongoing as of April 2010)

Clinical Trial Stage	Estimated Trial Cost Range (US\$ millions)	No. of Trial Participants	Cost per Participants (US\$ thousands)	Cost per Endpoint (US\$ thousands)
Phase 1	\$0.5 M – \$4 M	30 – 60	No data	No data
Phase 2	\$3.5 M – \$5 M	50 – 400	\$8.8 K – \$23 K	\$438 K
Phase 2B (completed and ongoing (estimated))	\$18 M – \$100+ M	1,000 – 3,000	\$18 K – \$27 K	\$264 K – \$461 K
Phase 3* (completed and ongoing (estimated))	\$56 M – \$62 M	5,000 – 10,000	\$6.6 K – \$9.0 K	\$204 K – \$245 K

*Costs of trials terminated early are not included in estimate

REGULATORY MATTERS

If product development is not to be hindered, efforts to illuminate the regulatory landscape for microbicides must be accelerated. Developers must know 1) what requirements will need to be satisfied for the regulatory oversight of clinical research on microbicides and 2) what data will be needed to support applications for licensure.

PROGRESS

These questions have been addressed over the years as regulators have become better acquainted with microbicides as a prospective technology. For example, the US FDA has:

- Participated in the International Working Group on Microbicides (IWGM) and in the creation by that group of two major documents on preclinical (2004) and clinical (2001) recommendations for microbicide development (*see References*)
- Engaged in public dialogue on microbicide clinical trial design
- Participated in numerous technical meetings
- Interacted with developers on a case-by-case basis and reviewed their regulatory submissions.

While US FDA regulators are a critical part of microbicide review, regulation and, eventually, access, they are just one part. Beginning in 2002, regulators from the US FDA and other countries and entities with varying responsibilities for microbicide research, development, and testing, e.g., the European Medicines Agency (EMA), UK Medicines and Healthcare Products Regulatory Agency (MHRA), regional organizations such as the Southern African Development Community (SADC) and Association of Southeast Asian Nations (ASEAN), and regulatory authorities in countries where microbicide trials are held, have participated in a series of international consultations convened by WHO and other organizations. WHO has published a consolidated report on this series of meetings (*see References*). In addition, regulators and corresponding ministry counterparts in countries hosting trials have become increasingly engaged in microbicide research and challenges through deliberations during and on conclusions of effectiveness trials.

NEXT STEPS

The US FDA is in the process of revising its guidelines for microbicides to adjust to the multitude of scientific, clinical, and political changes in and around the microbicide field. There has been so much evolution in this field in response to learning from completed trials, the rising prominence of ARV-based prevention technologies, more focus on combination microbicides and delivery systems, a surge in new preclinical evaluation tools, and shifts in thinking about the clinical testing sequence, that a re-working of existing guidelines and generation of new ones is a matter of urgency. For these reasons, it is equally urgent that options be made available for public comment since the influence of new guidelines will inevitably be far-reaching.

POLICY DIALOGUE, COLLABORATION, AND COORDINATION

Microbicides have been a topic of policy dialogue for almost two decades. A landmark event in that dialogue on a global stage was the call at the 1994 International Conference on Population and Development in Cairo for the “donor and research communities [to] find a vaccine and to develop women-controlled methods, such as vaginal microbicides, to prevent HIV infection”. In the 1990s several groups were established whose primary purpose was to facilitate coordination in microbicide development (the International Working Group on Microbicides) and to press on policy-makers for response (the Alliance for Microbicide Development and Global Campaign for Microbicides [GCM]).

PROGRESS

Policy Dialogue

The major achievements of policy dialogue have been expansion of the dialogue itself; the positive effects on funding volumes described above; and, in the United States, legislative and institutional impact.

A key element in this work was the series of *Microbicide Development Acts* (MDAs) introduced in the US Congress in eight different Congressional sessions (US House of Representatives 2000, 2001, 2005, 2007; US Senate 2001, 2003, 2005, 2007). Their aim was to authorize increased funding for microbicide development; require better coordination among federal

agencies conducting microbicide research (US Centers for Disease Control and Prevention, US National Institutes of Health, US Agency for International Development); establish a branch dedicated solely to microbicides within the National Institute of Allergy and Infectious Diseases; specify a major coordinating role for the NIH Office of AIDS Research, including a Federal strategic plan for microbicides; and require annual reports to Congress.

None of these pieces of legislation was passed into law, but they had cumulative and crucial leveraging effects. They inserted the concept and the need for microbicides into the policy vocabulary and served as an educational force among legislators and their constituencies: the most recent version of the *MDA* had 74 House sponsors and 18 in the Senate, and sign-on support from over 150 organizations. The *MDA* series elevated the policy discourse to high levels, thereby effecting institutional changes, most importantly establishment in 2007 of a Microbicide Branch at NIAID, and creating the structure and constituency for establishing the Microbicide Trials Network. Finally, they were rallying points for vigorous parallel efforts in national and international public education and advocacy.

The United States was far from being the only country where the subject of microbicides was on government agendas, including decisions about investing in their development. Amounts varied widely but in 2008, a total of nine other countries plus the European Commission were providing funding for microbicide research and development, decisions typically following numerous briefings and discussions.

Collaboration and Coordination

Little of the policy work could have been achieved without major collaborative effort among a wide range of advocacy groups, led in its earliest days by the Alliance, GCM, and the IPM. With time, those initial collaborations expanded to a large number of advocacy groups working in women's health, such as the Guttmacher Institute and National Women's Health Network, and HIV prevention technologies advocacy groups such as AVAC and International Rectal Microbicides Advocates (IRMA).

Other efforts toward collaboration and coordination have been successful in other areas relevant to microbicide research: the pioneering IWGM, which in 1994 began assembling major stakeholders annually for information exchange and discussion; the "Quick" Clinical Trials

Working Group (QWG), an MDC sub-project under the Alliance, which productively convened researchers with competing products in late-stage trials for information-sharing and problem-solving; the Microbicides Media and Communications Initiative (MMCI), which convenes advocates, civil society representatives, and researchers to ensure dissemination of accurate messages and foster research literacy; and numerous MTN Working Groups.

All that said, the microbicide field has been criticized for lack of coordination in an area of maximum importance: the making of go/no-go decisions on advancement of candidate microbicides along the development pathway, with particular respect to decisions around their advancement into late-stage trials. For that to become possible, there is a need for systematic and unbiased guidelines to underpin processes for deciding which candidate microbicides warrant advancement at critical junctures in the development pathway.

There are concerns that this perceived deficiency will persist because the overall problem is structural rather than circumstantial. Suggestions have been made that this could be avoided were the microbicide field to function more like individual pharmaceutical companies are presumed to function. However, that model is not apt: the microbicide field consists of multiple entities competing for scarce resources to develop products that famously fail to attract the rich expertise or investment from large pharmaceutical companies.

Efforts have been made toward this goal, but results have been limited. The QWG was not constituted as an arbiter of go/no-go decisions. The MDC itself could have been shaped into a deliberative body, but its mandate was unclear and compromised by competing institutional agendas. The Microbicide Research Working Group (MRWG), established in 2007 under the NIH Office of AIDS Research, is expanding its membership to facilitate its ability to provide guidance to NIH and the field regarding scientific direction for microbicide research, and is coordinating a Fall 2010 workshop to outline its next steps. Finally, each individual development group has its own scientific advisory committees to help guide its own portfolio directions, and meetings of those committees typically include donor representatives.

NEXT STEPS

There is still a vital missing link: the engagement of donors in common dialogue about the next round of investments in microbicide research and development,

the demands for which are still in flux. There will be clinical trials to be funded and there will be preclinical development needs to be supported as well, but absent a frame of reference and access to unbiased data, the pattern of unilateral decision-making that dominated the past is likely to be repeated. The need for articulation of decision-making processes that may go beyond individual scientific advisory committees and the NIH-convened reviews of individual components of its program remains a wide-open issue awaiting resolution.

ADVOCACY AND CIVIL SOCIETY

The preceding section illuminated areas where advocacy has been vital – recruitment of financial resources and pressures for institutional response – and recognized groups that play combined roles by engaging in advocacy, coordination, information, and policy research.

Another area of high significance is where advocacy and civil society meet in connection with clinical research, the environments in which it is pursued, and the various populations and entities that come to be involved. The Civil Society Working Group, formed to write an additional chapter of the *MDS*, defined “civil society” as follows: “a wide spectrum of nongovernmental organizations and advocates, inclusive of both of the groups usually identified by clinical trials as ‘community members’, and stakeholders outside the parameters of the geographic locale surrounding a research site. Thus, civil society engagement refers to a broader scope of activities and a wider range of actors than is generally the case for community involvement as it is commonly understood.” In turn, community involvement or “community engagement”, as defined by AVAC, refers specifically to “a meaningful and participatory process of involving stakeholders early and continuously in the design, development, and implementation of clinical trials and distribution of their results”.

PROGRESS

There has been meaningful progress with respect to the size of the role of civil society in microbicide clinical research and in recognition of its centrality. Experience,

analysis, and dialogue over decades have persuasively concluded that conduct of clinical trials without explicit integration of community perceptions, realities, and norms is simply unethical. There is an ample literature around those conclusions and specific attention to them has been paid over the years of microbicide research and development.

In addition to the function of microbicide trial networks in ratcheting up local health care infrastructures and expanding human capacities for research and health care delivery, the networks have been crucial to the support and advancement of civil society in microbicide research by involving civil society at different levels throughout the trial process.

These contributions have been codified in different ways. For example, in 2007, AVAC and UNAIDS published guidelines for what they termed “Good Participatory Practice Guidelines (GPP)”, intended as a roadmap on community engagement in the clinical research process for use by trial sponsors, implementers, and advocates. At the field level, microbicide researchers have developed and applied models for community representation and participation in HIV prevention trials, including engagement of vulnerable at-risk sub-populations, and definitions of what comprises “community” in each trial setting. What is being learned about the development, application, benefits, and limitations of participatory methodologies and processes is being recognized as essential and more frequently shared at meetings and in publications.

A new *Communications Handbook* prepared by FHI and the GCM contains a rich body of experience that should serve to enhance research literacy and communication skills in the sites and communities where trials are being introduced and implemented.

LESSONS

Events in connection with trials of microbicides and PrEP in Africa and Asia highlighted the fact that conduct of clinical trials without explicit integration of community perceptions, realities, and norms can be devastating to trial implementation; that insufficient incorporation of stakeholders can be fatal to understanding, discussion, and accurate dissemination

of trial results; and that inadequate relations with the full range of relevant media will cost dearly.

Chronicling and interpreting these events have proved difficult and understandably contentious, but five elements stand out in a complex web of explanation:

- First, definitions of who are the relevant stakeholders and what constitutes “the community” beyond the trial participants themselves are neither clear nor simple.
- Second, the frequency and nature of stakeholder involvement, political subtleties, and personnel changes may be underappreciated and require steadier attention than is sometimes the case.
- Third, what would constitute sufficient “research literacy” may be insufficiently appreciated and tested so that core understandings simply go missing.
- Fourth, host governments themselves may not be fully committed to community involvement or even actively resist it.

Finally, despite progress, there has sometimes been disparity in perspectives about the importance of civil society engagement. One explanation for any lack of enthusiasm has to do with resources: even though a given network may be organized to support civil society’s work at the site level and committed to do so, a given site might not be so committed, be accountable for such commitment, or have the requisite financial or human resources to act on such commitment.

NEXT STEPS

Emphasis going forward may best be placed on conserving and strengthening advances in recognizing the centrality of civil society and community engagement in clinical trials of microbicides and other prevention technologies. In its conclusions, the Civil Society Working Group proposed a set of seven highest priority actions, as follows:

- Use microbicide trial site development investments as opportunities to ratchet up local health care infrastructure and expand human capacities for research and health care delivery in ways that provide durable local benefit
- Develop mechanisms to increase civil society’s engagement across the entire arc of research,

development, and product introduction and to improve communication among researchers, sponsors, developers, and civil society

- Create more structural opportunities and build capacity for civil society participation in the monitoring bodies that guide microbicide research and development
- Invest in initiatives to increase advocacy participation by microbicide scientists and expand the scientific expertise of microbicide advocates
- Improve systems for rapid and user-friendly dissemination of trial results and their implications to stakeholder groups and the general public through multiple communications channels
- Utilize the existing expertise of civil society actors in efforts to develop product introduction, distribution, and marketing plans
- Create structural opportunities and build capacity for civil society to have meaningful input into regulatory processes.

These recommendations remain valid, but there are other issues. There is a sense that funding various components of civil society engagement in network and site budgets, as well as host country support, might be the first to be cut when austerity measures are imposed. Thus, as more HIV prevention trials and global health trials are organized in the same country, all governments hosting such trials may need to be repeatedly educated on the “how” and “why” of community involvement, in and across trials and research sectors. Community engagement may need to be more clearly defined for every government to allow for full understanding of both the role of the researchers and the role of the community, bridge-building that will be essential for authentic and meaningful engagement. Clinical trial funding should be more transparent and more easily tracked in its trajectory from network to site and to the community itself, so that there is greater overall accountability and so that civil society organizations can identify gaps in funding and support and engage all relevant players, including funders, in addressing them. Finally, there will be a persistent need to create more structured opportunities and build capacity for civil society participation across the full arc of the research enterprise.

This report comes at a time when the microbicide field is scrutinizing a number of long-standing ideas about microbicide development. The report engages in that process of inquiry by asking: What has been learned, where has there been good progress, and what should happen next?

The emphasis of the report is on the science – basic, translational, clinical, and behavioral – because that is where the largest obstacles to advancement of candidates along the microbicide development pathway were identified. The report also considers factors vital to sustaining the scientific enterprise, factors which themselves must be sustained: funding, regulation, policy-making, collaboration, coordination, and the participation of advocates and civil society.

What follows is a set of action areas that emerged as priorities, accompanied by a brief statement of the rationale and “next steps” for each. The most critical areas of priority have to do with the processes that, together and separately, select the most plausible candidates for advancement; expedite their progress along the development pathway; support their translation into the clinic; and employ the most informative early clinical studies to arrive at proof of concept and, eventually, pivotal effectiveness studies.

It is tempting at a time of change and introspection to recommend that everything must be done “next” because so much has happened and there is still so much to do. However, this report endorses the notion that it is possible to assign priority to a relatively small set of specific actions or clusters of actions; support them strategically; promote increased efforts in these areas; and, in some cases, impose a sense of timing.

PRIORITIES

1. ADVANCEMENT OF LEAD PRODUCTS

The fundamentals of a rational process for selection of lead microbicide candidates are falling into place and merit strategic emphasis and investment. Lack of robust, validated markers of protection from HIV infection continues to impose on microbicide development the need to do large and costly effectiveness trials.

- Concerted efforts to develop best-practice guidance with respect to the usefulness and significance of the many new models and assays, and devise and use algorithms that incorporate the best intelligence to manage the risk inherent in selecting compounds for advancement
- Intensified research on the detailed processes involved in sexual transmission of HIV and mucosal immunity, including the role of cell-free and cell-associated HIV

and the significance of “founder” viruses, in the context of both microbicide and vaccine development

- More detailed examination of the effects of male and female genital and rectal secretions on microbicide activity
- New pharmacokinetic and pharmacodynamic studies as a basis for solving product development problems, making orderly development decisions, designing better Phase 1 and Phase 2 clinical trials, and integrating those fully into current development approaches
- Steady attention to the pursuit of biomarkers that correlate with safety, product use, and potential efficacy, and their structured integration into human studies, to enhance potential for validating those biomarkers that show promise
- Creation by product developers of targeted product profiles that identify a product’s best characteristics, and articulation of a plan for its advancement into clinical testing

2. OPTIMIZATION OF CLINICAL TRIAL DESIGN AND MANAGEMENT

There is consensus that the suite of clinical trials needs to be re-thought. A number of important first steps have been taken toward that objective, with some areas meriting prioritization and prompt strategic attention.

- Safety trials: Decisions about the size and duration of Phase 1 trials, about the most relevant parameters to include for identifying biomarkers of safety, and the potential of mounting parallel, concurrent trials
- Effectiveness trials: Focused discussions and, where possible, decisions about more efficient and cost-effective trial designs and about all major determinants of trial power

3. BUILDING STRATEGICALLY ON BEHAVIORAL AND SOCIAL SCIENCE RESEARCH

A number of methods of particular relevance to those aspects of clinical trials that have major impact on trial power have shown promise and merit priority support.

- New techniques for preclinical research that may optimize prospects for participant adherence to trial protocol
- Strategic combinations of several methods for optimizing and measuring adherence to product use across the entire course of clinical studies
- Multidisciplinary approaches for optimizing the acceptability of product formulations

4. COORDINATING FUNCTIONS

In order to develop a rational bridge across the translational gap, tools are required for organized relationships.

- Identification of and support for new targeted, flexible, agile coordinating functions to meet specific needs in the development pathway, including multidisciplinary aspects and industry involvement

5. REGULATION

The US Food and Drug Administration is currently revising its microbicide guidelines to adjust to the many changes in the fields of microbicides and HIV prevention.

- Pursuit and exercise of opportunities for public comment on guidelines currently in draft, since their influence will be far-reaching

6. DONOR ENGAGEMENT AND EDUCATION

Involvement of funders of microbicide development is uneven and incomplete at a critical time.

- Strategic engagement of donors in common, well-informed, open dialogue and learning about the status, progress, and prospects of the microbicide field as a whole

7. COSTS

Existing analyses of what it costs to develop a microbicide, test it clinically, and make it available are outdated, and estimates of the time required are poorly understood – matters of highest import for the funders of microbicide research, trial designers and implementers, the countries and communities in which those trials are conducted, and the advocates who are critical to the advancement of microbicide research.

- Revision of cost profiles for microbicide development
- Preparation of estimated budgets associated with timelines for manufacture, commercialization, and access

8. ADVOCACY AND CIVIL SOCIETY ENGAGEMENT

Systematic, ongoing involvement of civil society and furtherance of science literacy will continue to be critical to testing prevention technologies.

- Explicit inclusion of support for site-level advocacy and civil society engagement in trial budgets

9. EVALUATING PROGRESS

Planning and implementation of each of these priority actions could be undertaken immediately, given consensus that they are truly of priority.

- Review and evaluation of all these priorities 12 months hence.

CODA

There can be no single, simple, perfect model for a common conceptual framework for microbicide research and development. Nor is it possible that microbicides, by themselves, will solve the problem of HIV/AIDS. As a component of comprehensive and integrated prevention strategies, however, they could play a vital role, complementing the benefits of behavioral interventions, male and female condoms, barrier methods, male circumcision, treatment of STIs, antiretrovirals to prevent mother-to-child transmission and, in due course, oral PrEP, antiretroviral therapy to reduce viral transmission, and anti-HIV vaccines.

While it must be conceded that the outcomes of the microbicide effectiveness trials completed so far are disappointing, the field has succeeded in demonstrating

the feasibility of designing and implementing large-scale microbicide trials and bringing them to a meaningful conclusion. This has been achieved despite the immense logistical, financial, organizational, and scientific challenges of working with an international network of sites in low-resource settings, recruiting and examining many thousands of volunteers, and retaining them for the duration of the trial. And all this has been done while meeting ethical imperatives such as regular counseling to promote safer sex behaviors, providing supplies of condoms, treating STIs, and engaging the communities to which trial participants belong. The approaches developed and the experience gained will pave the way for successful trials in the future, not just of microbicides but other prevention approaches as well.

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TABLE 8 | ONGOING AND PLANNED CLINICAL TRIALS OF MICROBICIDE AND PrEP CANDIDATES (as of April 2010)

Study Name	Candidate Name	Population	Location	Sponsor/Funder	Status
Phase 3					
iPrEX	Truvada®: Oral	2,499 gay men and other MSM	Brazil, Ecuador, Peru, South Africa, Thailand, United States	BMGF, NIH	Data analysis
FEM-PrEP	Truvada®: Oral	3,900 heterosexual women	Kenya, Malawi, South Africa, Tanzania, Zambia	BMGF, FHI, USAID	Ongoing
Partners PrEP	Truvada®: Oral, Viread®: Oral	4,700 serodiscordant heterosexual couples	Kenya, Uganda	BMGF	Ongoing
IPM-009	Dapivirine: Ring	TBD, women	Multiple countries, Africa	IPM	Planned
MDP-302	Tenofovir: Gel	6,320 heterosexual women	Mozambique, South Africa, Tanzania, Uganda, Zambia	MRC/UVRI	Planned
Phase 2/3					
CDC-4370	Viread®: Oral	2,400 injecting drug users	Thailand	CDC	Ongoing
Phase 2B					
CAPRISA-004	Tenofovir: Gel	900 heterosexual women	South Africa	CAPRISA, CONRAD, FHI, Gilead, LIFElab, USAID	Data analysis
VOICE (MTN-003)	Tenofovir: Gel, Truvada™: Oral, Viread®: Oral	5,000 heterosexual women	Malawi, South Africa, Uganda, Zambia, Zimbabwe	CONRAD, Gilead, MTN, NIAID, NICHD, NIMH	Ongoing
Phase 2					
TDF2 (CDC-4940)	Truvada®: Oral	1,200 heterosexual men and women	Botswana	CDC	Data analysis
CDC-4323	Viread®: Oral	400 gay men and other MSM	United States	CDC	Data analysis
MTN-001	Tenofovir: Gel, Viread®: Oral	144 women	South Africa, Uganda, United States	CONRAD, Gilead, MTN, NIAID	Ongoing
ATN-082	Truvada™: Oral	99 young MSM	United States	NICHD, NIDA, NIMH	Ongoing
MTN-010	UC-781: Gel	150 women	TBD	NIAID, MTN	Planned
Phase 1/2					
IAVI-E002	Truvada™: Oral	72 serodiscordant couples (men and women)	Uganda	IAVI	Data analysis
IAVI-E001	Truvada™: Oral	72 men and women	Kenya	IAVI	Data analysis
IPM-014A	Dapivirine: Gel	320 women	South Africa, Rwanda (ongoing), Kenya, Malawi (planned)	IPM	Ongoing
IPM-014B	Dapivirine : Gel	320 women	South Africa	IPM	Ongoing
IPM-020	Dapivirine : Gel	180 women	United States	IPM	Ongoing
IPM-015	Dapivirine: Ring	280 women	South Africa (ongoing), Kenya, Malawi, Rwanda, Tanzania, Zambia	IPM	Ongoing
PrEP TMC-278LA	Rilpivirine (TMC-278LA): Injectable	100 men and women	United Kingdom	St. Stevens AIDS Trust	Ongoing
Phase 1					
IPM-024	Dapivirine: Ring	16 women	Belgium	IPM	Data analysis
A04-095	Tenofovir: Gel	49 women	Dominican Republic, United States	CONRAD, IPM, USAID	Data analysis

Study Name	Candidate Name	Population	Location	Sponsor/Funder	Status
MTN-002	Tenofovir: Gel	16 pregnant women	United States	CONRAD, MTN, NIAID, NICHD	Data analysis
TFV-010	Tenofovir: Gel	30 women	United States	NIAID	Data analysis
MTN-004	VivaGel® (SPL7013): Gel	61 women	United States	MTN, NICHD	Data analysis
AF-020	Amphora™/ACIDFORM™: Gel	36 women	United States	AECOM, NIAID	Ongoing
IPM-013	Dapivirine: Ring	48 women	Belgium	IPM	Ongoing
RMP-002/ MTN-006	Tenofovir: Gel, Viread®: Oral	18 men and women	United States	CONRAD, Gilead, MTN, NIAID	Ongoing
Pilot Study	UC-781: Gel	15 women	United States	CONRAD	Ongoing
IPM-010	Dapivirine: Gel	TBD	TBD	IPM	Planned
MIV-150/Zinc Salt Gel Study	MIV-150/zinc acetate Gel	TBD	TBD	Population Council	Planned
MTN-007	Tenofovir: Gel	60 men and women	United States	CONRAD, MTN, NIAID	Planned
MTN-008	Tenofovir: Gel	230 mothers and their infants	United States	MTN, NIAID	Planned
Vaginal Applicator Study	Tenofovir: Gel	25 women	Dominican Republic	CONRAD, PATH	Planned
PK/PD, Mucosal Safety Study	UC-781: Gel	50 women	Dominican Republic, United States	CONRAD	Planned
Zinc Salt Gel Study	Zinc acetate: Gel	TBD	TBD	Population Council	Planned
Ancillary Studies					
IPM-011	Placebo ring, safety, acceptability	220 women	South Africa, Tanzania (ongoing); Kenya (site closure)	IPM	Last participant visit completed
MTN-003B Bone Mineral Density Substudy	Truvada™: Oral, Viread®: Oral	300 women (enrolled in oral arm of MTN-003)	Malawi, South Africa, Uganda, Zambia, Zimbabwe	MTN, NIAID	Ongoing
MTN-015 Seroconverter Protocol	No Product	HIV-positive women	Malawi, South Africa, Uganda, Zambia, Zimbabwe	MTN, NIAID	Ongoing
EMBRACE (MTN-016) Pregnancy Exposure Registry	No product	Pregnant women (exposed to microbicide/PrEP study agents) and their infants	Malawi, South Africa, Uganda, Zambia, Zimbabwe	MTN, NIAID, NICHD	Ongoing
Adherence Simulated Trial	Placebo: Gel	Female sex workers	India	Population Council	Ongoing
IPM-007 Seroconverter Protocol	No product	HIV-infected women	Kenya, Malawi, Rwanda, South Africa, Tanzania, Zambia	IPM	Planned
MTN-009 Substudy	No product	350 HIV-infected women	Various	MTN, NIAID	Planned
MTN-003C Study Product Adherence Substudy	N/A	1,375 trial participants, male partners, CAB members, key stakeholders	Malawi, South Africa, Uganda, Zambia, Zimbabwe	MTN, NIAID	Planned
MTN-005	Placebo: Ring	252 women	India, United States	IPM, MTN, NIAID	Planned
Adherence Simulated Trial	Placebo: Gel and Ring	TBD	Zambia	Population Council	Planned

ARV – antiretroviral; ATN – Adolescent Trials Network; BMGF – Bill and Melinda Gates Foundation; CAB – community advisory board; CAPRISA – Centre for the AIDS Programme of Research in South Africa; CDC – US Centers for Disease Control and Prevention; FHI – Family Health International; IAVI – International AIDS Vaccine Initiative; IPM – International Partnership for Microbicides; MSM – men who have sex with men; MTN – Microbicide Trials Network; N/A – not applicable; NIAID – US National Institute of Allergy and Infectious Diseases; NICHD – Eunice Kennedy Shriver National Institute of Child Health and Human Development; NIMH – US National Institute of Mental Health; PrEP – pre-exposure prophylaxis; RMP – Rectal Microbicide Program; TBD – to be determined; TDF – tenofovir disoproxil fumarate; TFV – tenofovir; USAID – United States Agency for International Development

TABLE 9 | MICROBICIDE CANDIDATES IN PRECLINICAL DEVELOPMENT* (as of April 2010)

Mechanism of Action	Candidates in Preclinical Development
Vaginal Defense Enhancers (N=1)	Unipron
Surfactants (N=0)	
Attachment, Fusion, and Entry Inhibitors (N=35)	5P12- RANTES Actohivin C52L CADA (cyclotriazadisul fonamides) Cyanovirin-N (CV-N) (including bioengineered Lactobacillus expressing CV-N) CMPD167 D-peptides DS001/ L-860,167 DS003/BMS-599793 DS004/L-860,872 DS005/L-860,882 DS007/L'644 peptide EBd peptides Flavonoids (EGCG) Griffithsin ISIS 5320 K5-N, OS(H), K50SH LMBL (Lactobacillus mannose-binding lectin) Maraviroc Nanobodies™ Optimised dendrimers PEHMB PIE 12 trimers PPCM (polycarboxylated aryl oligomer, poly[1,4-phenylene-(1-carboxyl)methylene]) PSC-RANTES RANTES peptides (including bioengineered Lactobacillus expressing RANTES) REP 9C, REP 9AC Retrocyclins (RC101) sCD4-17b Single-chain ICAM Sodium rutin sulfate (SRS) Soluble DC-SIGN Syndecan T1249 Talactoferrin

Mechanism of Action	Candidates in Preclinical Development
Replication Inhibitors (N=11)	Dapivirine (non-nucleoside reverse transcriptase inhibitor) Darunavir (protease inhibitor) EFdA (nucleoside reverse transcriptase inhibitor) GS9160 (integrase inhibitor) Lopinavir (protease inhibitor) MIV-150 (non-nucleoside reverse transcriptase inhibitor) Raltegravir (integrase inhibitor) Ritonavir (protease inhibitor) Saquinavir (protease inhibitor) Tenofovir (nucleotide analog reverse transcriptase inhibitor) UC-781 (non-nucleoside reverse transcriptase inhibitor)
Immunomodulators (N=1)	Glycerol monolaurate (GML)
Combinations/Multiple Mechanisms (N=23)	Dapivirine and DS003 Dapivirine and maraviroc Diterpene HHA, KR2110, T20 combinations KP1, KP17 LNG and MIV-150 in a vaginal ring mapp66 (combination of anti-CCR5 and anti-HSV antibodies) Maraviroc and tenofovir MIV-150, zinc acetate, and carrageenan (carrageenan is an excipient) NCp7 Thioesters (SAMTs) Nisin Novasomes Opuntia spp (Osp) Pyrimidinediones Pyrimidinediones and ISIS 5320 siRNA SJ-3991 UC-781 and KP17 UC-781 and progesterin UC-781 and tenofovir x-REPLAB Zinc acetate and MIV-150 in a vaginal ring Zinc tetra-ascorbo-camphorate derivative "C14"
Novel and Uncharacterized Mechanisms (N=4)	BASANT C5A (virucide) Zinc acetate and carrageenan (carrageenan is an excipient) Zinc

* This list of preclinical candidates includes those in published literature and/or recent conference abstracts, and subsequently confirmed by the researcher/developer; it also includes candidates in parallel preclinical and clinical development; many other products exist in preclinical development, without verification by personal correspondence

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