A Field on the Verge of Change

What it will take to find new prevention options for women

For nearly two decades, the search for female-initiated HIV prevention options has taken place at a unique intersection of research goals and reality. Unlike vaccine studies, which administer the strategy at the clinic site, trials of microbicides and oral pre-exposure prophylaxis (PrEP) ask participants to use a product on their own—in their homes or other private spaces. But even if the product is used in the real world, the trials are still a controlled environment. Trials provide better health care and more rigorous counseling and adherence support than almost all public health prevention programs. In the real world, people have some idea of how effective a strategy is; in a clinical trial participants are told repeatedly that they may have received a placebo and that the preventive benefit of the experimental product—if any—is uncertain. Some trials compensate participants for their time and/or provide transportation refunds; few clinics compensate their patients in the real world.

The research, with its artificial conditions, seeks a simple solution for a highly complex problem. Women and men are at risk because of a wide range of factors including epidemic levels of gender-based violence, restricted access to education and secure income, enduring cultural barriers to shared sexual decision making, homophobia, discriminatory laws. No single product will eliminate these issues, and these issues will affect women's and men's ability to use any product.

And yet this array of issues is exactly why women and men need biomedical strategies that they can use easily and safely. While the struggle to address structural drivers of the epidemic continues, biomedical strategies can help people reduce their risk of HIV infection. The solutions may be imperfect—offering partial levels of protection—but the impact can still be significant. It is the fundamental conundrum of biomedical HIV prevention research: the real world both defies and requires simple HIV prevention strategies.

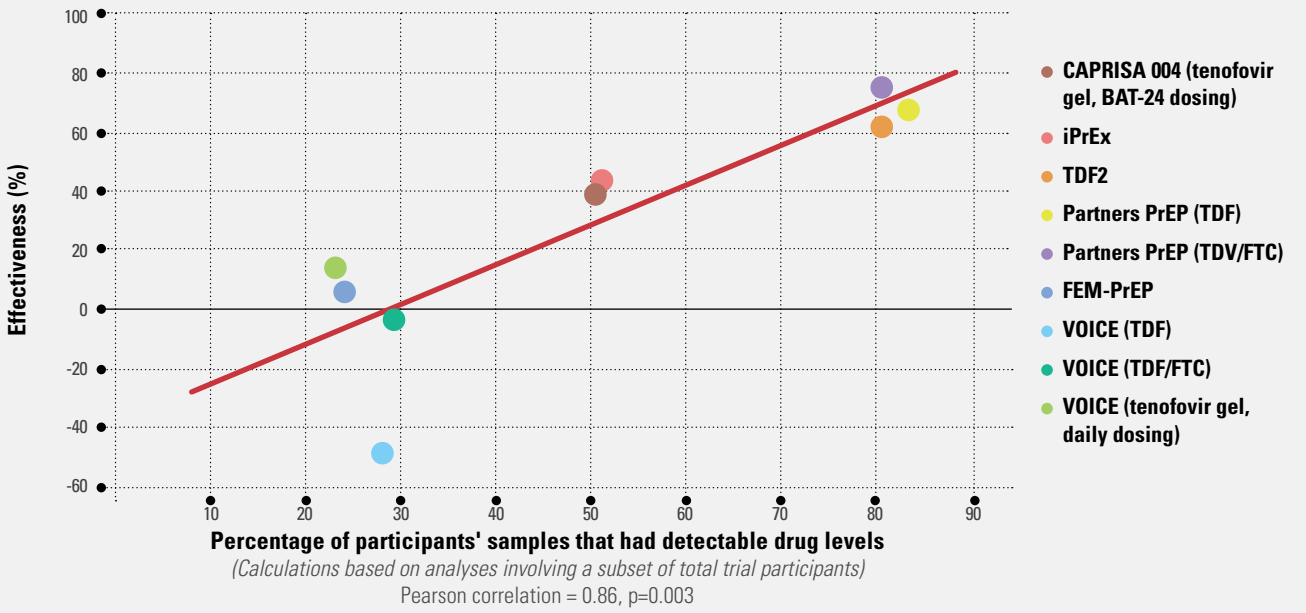
Today the field of female-initiated prevention research is grappling with a range of data. Some of the findings are positive, some disappointing, and all are intimately related to questions about how research impacts women's lives—and vice versa.

The CAPRISA 004 trial showed proof of concept that tenofovir gel can reduce women's risk of acquiring HIV. In the VOICE trial, which tested a different dosing strategy of the same gel, participants had such low rates of adherence that it was impossible to evaluate the effectiveness of the gel at all. In FEM-PrEP, young African women had very low rates of adherence to daily, oral tenofovir-based PrEP. In Partners PrEP, women in serodiscordant couples had high rates of adherence, and high levels of protection. Daily oral tenofovir also reduced men's and women's risk via sexual transmission in the Botswana TDF2 trial, and via injection drug use in the Bangkok Tenofovir Study (see page 16 for a review of data to date).

There are many interpretations of these varied data. Some stakeholders say that the low levels of adherence in VOICE and FEM-PrEP show that women don't want specific products or dosing strategies; others say that adherence was so low that the issue must be with how women relate to research and not a given product. A vast majority of the women in these trials reported using the product correctly and consistently—and there are multiple proposed explanations of the discrepancy between what women said, and what they actually did. There is also the persistent question of whether a female-initiated strategy that requires regular use is a realistic goal at all.

The current challenge for the field of female-initiated prevention is to move past these sometimes-competing perspectives and towards a new, cohesive agenda for addressing the issues raised by trials to date. If plans are guided by incorrect assumptions about the lessons from past trials, the field may end up with yet more confounding and disappointing results. By the same token, decisive, informed action

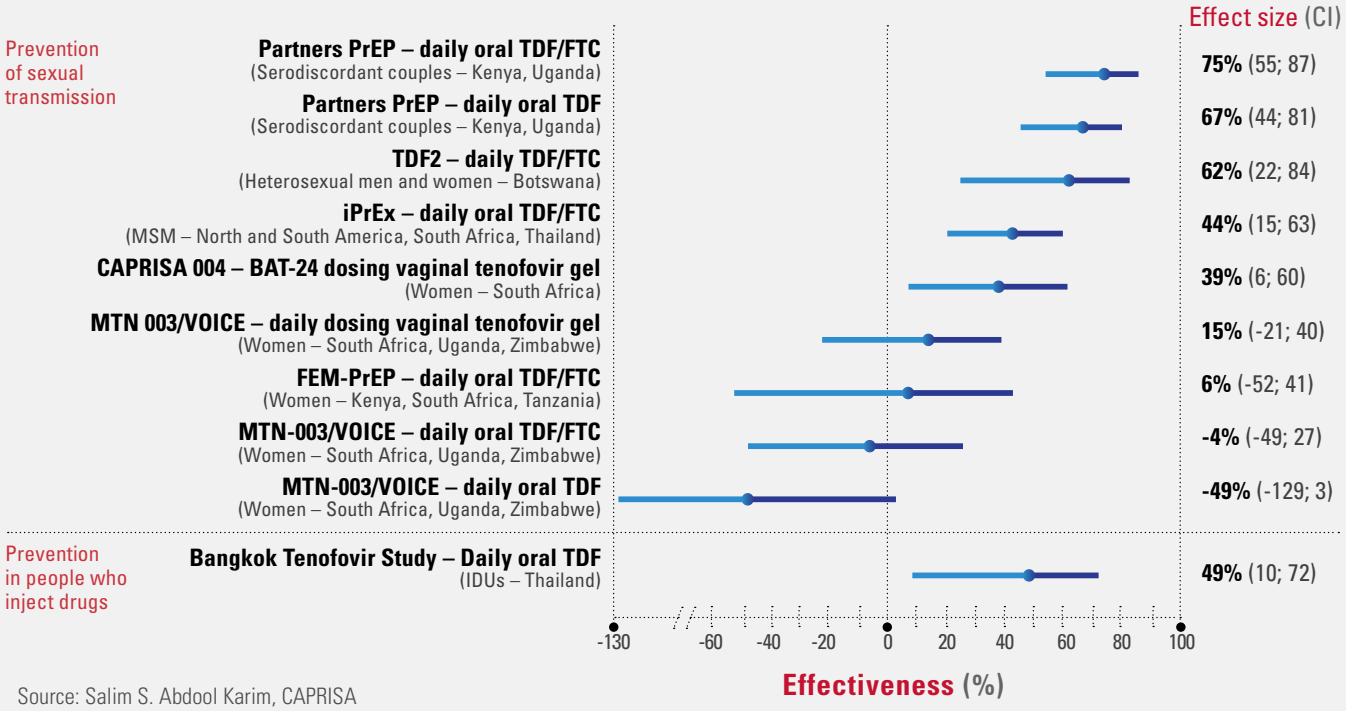
Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention



Trials of oral and topical tenofovir-based PrEP show that these strategies reduce risk of HIV infection if they are used correctly and consistently. Higher adherence is directly linked to greater levels of protection.

Source: Salim S. Abdool Karim, CAPRISA

Clinical Trial Evidence for Oral and Topical Tenofovir-Based Prevention (December 2013)



Source: Salim S. Abdool Karim, CAPRISA

based on an accurate understanding of where things went wrong in the past could transform a field whose goal—reducing the rate of new infections in women—is at the heart of the effort to bring the AIDS epidemic decisively under control.

Moving past the "make-or-break" moment

The field of women's HIV prevention requires a clear, forward-looking analysis and plan of action that is shaped by the lessons learned to date. Many of the issues that need to be addressed have come up in the context of two recent trials—VOICE and FEM-PrEP. VOICE was a five-arm trial designed to evaluate daily use of tenofovir gel, daily oral TDF and daily oral TDF/FTC. FEM-PrEP evaluated daily oral TDF/FTC. Both trials enrolled African women at high risk of HIV, and both evaluated daily dosing of products that contain an antiretroviral (ARV) whose presence can be detected in the blood. Participants in both trials reported high rates of adherence. Yet, neither trial showed evidence of benefit. What's more, very few participants in the active arms of either trial had detectable drug in their blood.

These were not the first trials of female-initiated options to show no evidence of benefit. Efficacy trials of the microbicide candidates Carraguard, PRO2000 and BufferGel all found no evidence of benefit. All of these trials used multiple strategies to support and evaluate adherences. What set VOICE and FEM-PrEP apart from previous trials was that each tested products that had shown benefit in other efficacy trials. The trials analyzed participants' blood samples for presence of tenofovir—an indication of adherence. (The graphics above and on page 10 summarize efficacy data and the impact of adherence.)

Oral and topical tenofovir-based prevention is also different from previous products in that it has an active antiretroviral component that can be detected in the blood. This allows for objective analysis of product use. In VOICE and FEM-PrEP, it was possible to test for presence of the drug in participants' blood samples and determine that there was very low adherence. If women aren't using a product, then it isn't possible to tell whether it works or not. This is the likely explanation for the lack of observed efficacy—even though participants reported high rates of adherence throughout the trial. It's possible that previous microbicide trials which also had high reported adherence rates but no direct measurement of product use could have had very low adherence as well. Effective products might even have been discarded.

Top-Line Recommendations

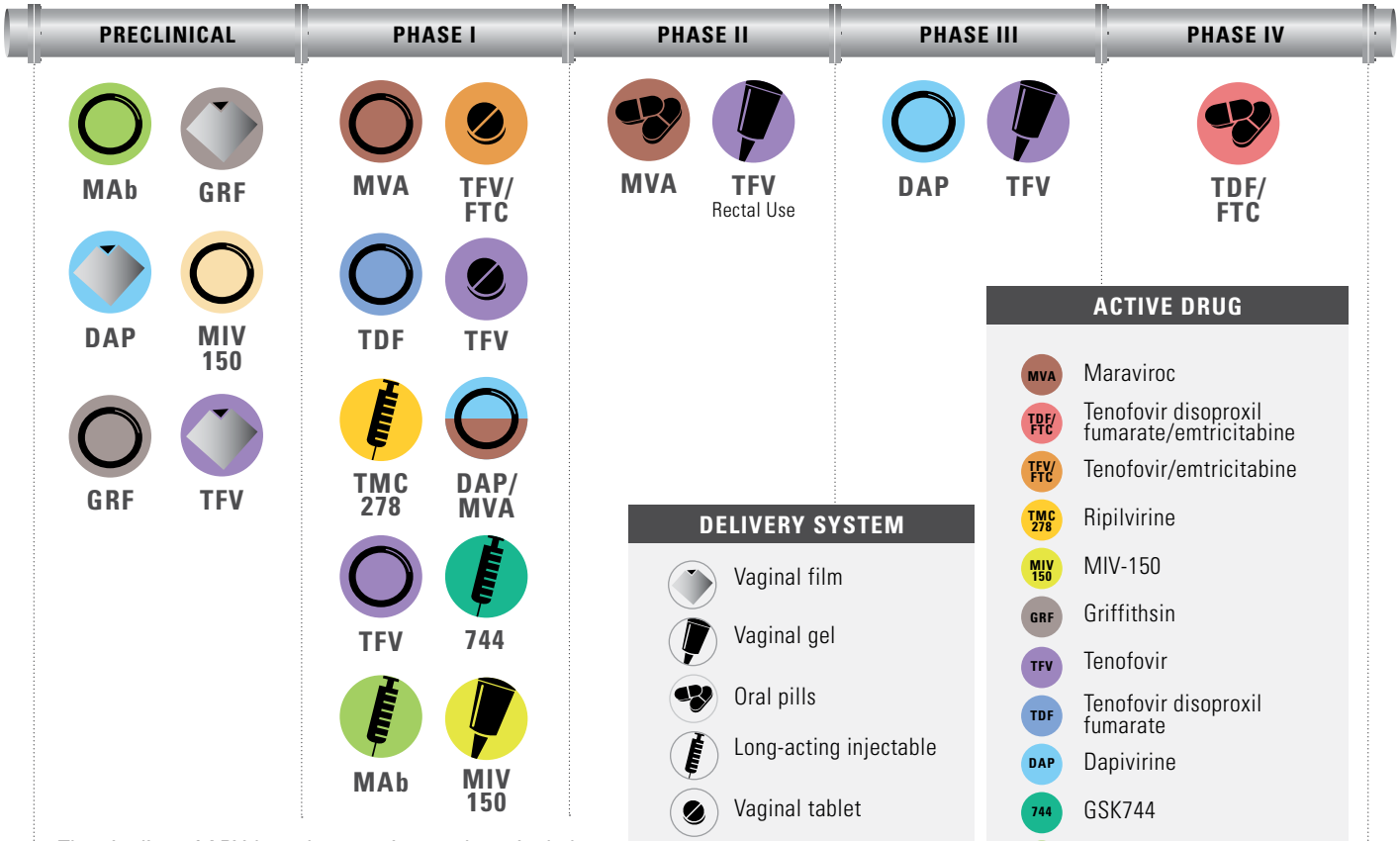
- Prepare for additional efficacy trials of user-dependent methods
- Invest in studies of why women participate in research
- Differentiate between trial participants and end users
- Measure methods to improve adherence
- Plan for success, applying lessons from oral PrEP
- Prioritize informed civil society involvement

VOICE and FEM-PrEP have been interpreted as evidence that women don't want or won't use certain types of products, or perhaps certain dosing strategies. (VOICE tested daily dosing, while CAPRISA 004 used BAT-24.) To the chagrin of some microbicide advocates, the results from these two trials have cast a shadow of doubt that encompasses all products requiring regular dosing including vaginal gels and rings. They point out that FEM-PrEP and two of the VOICE arms involved daily oral PrEP, a strategy that hasn't traditionally been positioned as a female-initiated method by the microbicide field. But such distinctions probably won't mean much in the real world, where different women will need and prefer different strategies—and the same woman may want to use different methods at different times in her life. A more productive approach may be to embrace a broad definition of female-initiated prevention that encompasses rings, gels and pills, as well as long-acting injectable ARVs and multipurpose prevention technologies (MPTs) which are being developed to prevent both pregnancy and HIV (see table page 18 for a list of MPTs in development).

Today much of the skepticism about user-dependent methods is focused on the three ongoing biomedical prevention efficacy trials evaluating female-initiated options. The Ring Study and ASPIRE are testing a vaginal ring containing the antiretroviral drug dapivirine. The ring is designed to be worn for 28 days. Women don't have to remember to use the product on a daily basis or around the time of sex; they just have to decide to leave the ring in. FACTS 001 is a trial of 1% tenofovir gel, using the BAT-24 dosing schedule that showed modest protection in the CAPRISA 004 trial.

The data from these trials will shape the future of the field. If one or more of these trials has the same type of adherence issues seen in FEM-PrEP and VOICE, there will almost certainly be calls to abandon user-dependent methods like pills, gels and even monthly rings and move to long-acting methods that require even less adherence: a long-acting injectable antiretroviral, for example. Long-acting ARVs are likely to be preferred by some women—they will remove burdens of adherence and could be delivered on the same dosing schedule as long-acting contraceptives. But they should not be the only option available—just as women also need and want a range of family planning options (see page 26 for more on this topic.)

ARV-Based Prevention Pipeline (December 2013)



The pipeline of ARV-based prevention products includes oral pills, vaginal rings, vaginal and rectal gels, vaginal films, long-acting injectable ARVs. Not pictured are a range of multipurpose technologies in development that aim to reduce women's risk of HIV and STIs, and provide effective contraception.

For up-to-date information on the ARV-based prevention pipeline, visit the HIV Prevention Research Database at *www.avac.org/pxrd*.

Even if there is evidence of efficacy from the ring trials or from FACTS 001, there are bound to be questions as to whether women will use product correctly and consistently in the real world, without the intensive support provided in the research setting. (It is also possible that adherence will be higher in the real world—where people know that a product works—versus in a clinical trial where efficacy is unknown.)

In reality, these trials are not "make-or-break" endeavors. The search for additional female-initiated methods will continue, and there are a range of steps being taken to build on the lessons to date. But it is time to put these activities into a comprehensive, prioritized agenda. Ideally, this approach will shift from a focus on moving a given product through efficacy trials to a broader engagement with questions about product choice and use, adherence and non-adherence, and participants' relationship to research itself. This work also impacts on gay men and other men who have sex with men (MSM) who could use a rectal microbicide. There is an ongoing Phase II trial of a rectal formulation of tenofovir gel in MSM. Efforts to support adherence in this trial and in future efficacy trials should be included as part of a comprehensive approach to microbicides.

Top-Line Recommendations for Women's Prevention Research

Prepare for additional efficacy trials of user-dependent methods

If one or more of the ongoing trials also has major adherence challenges, the field should prepare for a "last-hurrah" trial that would test an existing product—or another user-dependent product—with a design that is optimized to obtain an answer about efficacy. Preparations for such a trial should begin now, so that the field has a cohesive plan of action in place. We hope this plan won't be needed, but it's important to anticipate all scenarios.

One option would rely on a biomarker that could be detected in samples from participants in both the placebo and active arms of a trial. (By definition antiretrovirals are only detectable in participants in the active arm of the trial.) Participants' samples could be analyzed for the presence of this biomarker, which would give an indication of adherence. Non-adherent participants in both the active and the placebo arm could be discontinued from the trial. A similar approach could be used in a run-in phase, providing all women with an identical, inert product containing the biomarker, then randomizing adherent participants into active and placebo arms. Both of these approaches would preserve blinding.

These may seem like extreme measures—and they are, in many ways, a departure from a more traditional enrollment strategy focused on identifying people at high risk of HIV. (The factors that contribute to HIV risk can also complicate adherence, so participants at highest risk may have more difficulty adhering.) However, it should be possible to develop improved approaches that identify individuals who are at risk *and* likely to adhere. The priority for the field must be to get an accurate measurement of product efficacy among participants who use it as prescribed. If this means using a design that feels like an artificial scenario, it is well worth it. It is only after efficacy (e.g., benefit measured in the context of a clinical trial setting) has been determined that stakeholders can begin to strategize about implementing a product in the real world.

Key next steps include:

- **Discussion of what the next-generation trial of a user-dependent method might look like**—in terms of design, budget and location—so that there's a clear way forward if the field is faced with adherence issues in current trials.
- **Achieving consensus on which user-dependent product (whether a type, category or specific intervention) might be best suited for this effort.**

Invest in studies of why women participate in research

Right now, there's no single, clear explanation for the low levels of adherence seen in VOICE and FEM-PrEP. One possibility that is important to consider is that low adherence isn't a measure of a woman's attitudes about the product or an inaccurate perception of her risk of HIV but an indication of her relationship to research itself. The research agenda related to this topic might once have been considered something of a luxury—it is social science well beyond the scope of what is built into most product evaluations. But it's clear that this work is not incidental but

rather fundamental to the next phase of research on both female-initiated methods and related work on a rectal microbicide in men who have sex with men.

Some questions that must be explored include: How is the research enterprise perceived by a woman and the people in her community? What influences these perceptions, and how do they change when a given trial site conducts multiple trials over the years? How do a trial site's non-research activities impact on its reputation and relationship with the community? What are the dynamics among participants and site staff in the waiting room, counseling rooms and clinical exams—and how do they impact participants' decisions about product use and the veracity of the information they provide about adherence?

Some of this work is underway, and there are various theories about what has worked in the past. For example, in Vulindlela, South Africa, one of the sites of the CAPRISA 004 trial, the site has been an active partner in community development for years—building schools and forging strong, joint ownership of the research agenda. Several stakeholders AVAC spoke to mentioned this approach one factor potentially influencing adherence in women participants at that site.

It's critical to follow these clues and take a systematic approach to funding studies of why women participate in research. Given the realities in many places where trials take place, women may enroll in trials even if they do not trust or have concerns with the research establishment. They may have no intention of using the product to begin with—and perhaps enroll because of benefits such as high-quality health care, transportation refunds or other financial compensation.

A woman who decides not to use a given intervention before she enrolls in a trial has different issues and motivations from a woman who enrolls with the intention of using the product and stops later on. The end result is the same—low or no adherence—but important distinctions about the causes of non-adherence are lost.

Studies that seek to understand more about how women view and experience research can guide approaches to eliciting more honest communication from participants. They can also help shape tailored approaches to supporting adherence in different categories of women, based on an emerging taxonomy that distinguishes between non-adherers who never initiate use of a product, and those who do initiate it and then stop later on (see box, right).

This work requires financial resources and multi-disciplinary collaboration with anthropologists, behavioral scientists and clinicians. It also requires acknowledgement that some social scientists have identified this gap in the biomedical prevention research agenda for many years. Whether the work is overdue or merely responsive to lessons that have emerged to date does not matter in the long term. What is important is that it is undertaken now.

Dimensions of Adherence

Adherence to product: Participant's use of study product(s) as instructed

Initiation: Time point for the first dose/time participant uses study product

Execution: Extent to which participant's actual dosing corresponds to the instructed dosing regimen, from initiation until discontinuation

Persistence: Time period between initiation and discontinuation of study product use

Discontinuation: Time point for the last dose/time participant uses study product

Adapted from: van der Straten et al Curr HIV/AIDS Rep (2013) 10:89–102.

TRIALS OF TENOFOVIR-BASED PREVENTION METHODS: AT A GLANCE

DAILY ORAL TENOFOVIR-BASED PREP

Four trials found protection with oral PrEP

- The **Partners PrEP** trial studied daily PrEP using TDF/FTC or TDF in HIV-negative women and men aged 18 to 65 with HIV-positive partners or spouses (serodiscordant couples) in East Africa. The trial found high rates of adherence at 81 percent for TDF/FTC and 83 percent for TDF. Protection in Partners PrEP was also high at 75 percent [CI*=55–87] for TDF/FTC and 67 percent [CI=44–81 percent] for TDF for both HIV-negative women and men. The US CDC–sponsored **TDF2 trial** in Botswana also found that daily oral TDF/FTC reduced risk of HIV infection by 62 percent [CI=22–83] in female and male participants. The **iPrEx** study tested daily oral TDF/FTC in MSM and found 42 percent risk reduction [CI=18-60]. The **Bangkok Tenofovir Study** tested daily oral tenofovir in men and women who inject drugs and found a 49 percent risk reduction [CI=9.6-72.2].

Two trials found no protection with oral PrEP in women

- The **FEM-PrEP** trial found no effect with daily oral TDF/FTC among a group of African women aged 18 to 35 from Kenya, South Africa and Tanzania, who were at risk of HIV through sexual transmission. Analyses from the FEM-PrEP trial reported that less than half of the women in the trials had any drug detected in their blood. Adherence was too low for the trial to determine whether the intervention provided any protection.
- The majority of participants in the **VOICE** trial were single, young women aged 18 to 45. The trial took place in South Africa, Uganda and Zimbabwe. VOICE participants were similar in age and relationship status to the women enrolled in FEM-PrEP. Like FEM-PrEP, VOICE found that none of the interventions tested—daily oral TDF, daily oral TDF/FTC and daily 1% tenofovir gel—reduced the risk of HIV infection. In the VOICE trial, an analysis of blood samples from a subset of participants showed that drug was detected in less than 30 percent of women in all product groups. Analysis of adherence in the VOICE trial is ongoing and includes examination of drug levels in vaginal fluid samples and two qualitative behavioral studies.

TENOFOVIR GEL

One trial to date has shown evidence that a microbicide—1% tenofovir gel—reduces HIV risk in women

- The **CAPRISA 004** trial in 889 South African women found that 1% tenofovir gel reduced women's risk of HIV infection via vaginal sex by 39 percent overall. Women in the trial were counseled to use the gel within 12 hours before and after sex, a regimen known as BAT-24. There is an ongoing open-label study (where all participants are offered the product being tested and there is no placebo) of 1% tenofovir gel, called CAPRISA 008. This study will look at effective ways to deliver the gel in communities where the CAPRISA 004 trial took place.

One trial to date has shown that 1% tenofovir gel does not reduce HIV risk in women

- The **VOICE** trial, which was designed to test both oral (pill form) and topical (gel form) ARV-based prevention, found that 1% tenofovir did not reduce risk in women counseled to use it on a daily basis. The tenofovir gel arm was stopped early, after an interim DSMB review in 2011 found it to be safe but not effective in the study population.

One trial of 1% tenofovir gel is ongoing in women

- **FACTS 001** is a large-scale trial of tenofovir gel in South African women, which began enrolling in October 2011. The trial is testing the same BAT-24 dosing strategy evaluated in CAPRISA 004. FACTS 001 results are expected in late 2014.

One trial of a rectal formulation of 1% tenofovir gel is underway

- **MTN-017** is the first-ever Phase II trial of a rectal microbicide candidate, a rectal formulation of 1% tenofovir. It will enroll nearly 200 MSM at sites in Peru, South Africa, Thailand and the United States.

* CI stands for Confidence Interval, a statistical measure of the reliability of a finding, which is given as a point estimate, such as a 35 percent reduction in risk of infection. The narrower the confidence interval around the point estimate, the more likely it is that the result is accurate.

Recommendations for learning more about women and research:

- **Invest in research at sites where adherence has been an issue.** One example is VOICE C, which was conducted while the VOICE trial was taking place and looked at factors within participants' communities, social groups and households that might have influenced participation. VOICE D, is ongoing, aims to understand why women joined VOICE, why most stayed in the study and why so few used the products (or were willing to admit to non-use).
- **Invest in research that gets at questions about attitudes toward research overall.** This sounds like a conundrum—and it may be one—but the fact is that there must be efforts to understand how trust is built or broken in different trials and at specific sites.

Differentiate between trial participants and end users

One of the conclusions drawn from VOICE and FEM-PrEP is that the women who most need a product like a microbicide may not be ideal trial participants. Women targeted for these and other trials are often young, single and come from communities where HIV is one of many pressing issues. Conducting trials in these communities has many benefits, including the ability to gather data that can guide eventual product introduction. But if participants in these communities aren't actually using the test product, then researchers can't get the data needed to bring the product to market, anyway. Ideal as it may be to involve end users in trials, it's even more crucial to involve participants who are likely to adhere to test product protocols. Pharmaceutical industry trials routinely use rigorous screening for participants who are highly likely to adhere to an experimental strategy—even if they aren't the target population for the strategy.

Many factors are being considered: age, relationship status, whether a woman has support for trial participation from her partners and family, whether she has an accurate understanding of her own risk of HIV, how she views research, and so on. A systematic approach to refining screening criteria is key. Specifically, it is important to:

- **Document approaches to selecting adherent participants**—both in terms of participant profile and effective changes in screening questions—so that we can figure out what works and what doesn't work and adapt accordingly.
- **Be prepared with bridging and demonstration project proposals** for the women who don't make it into the trials but may have the greatest need.

Measure methods to improve adherence

The importance of improving methods for measuring adherence may seem obvious enough that it needn't be listed as a recommendation, but the reality is that there has been no systematic evaluation of the interventions that different trials have used to support adherence. There are obvious reasons for this: adherence is hard to measure, so it's hard to measure whether an intervention is working or not. But with "objective" measures that give some indication of product use—e.g., presence of drug in the blood—it is easier than it once was to determine how a given strategy affects women's product use. (VOICE had revamped its adherence counseling approach just a few months prior to the DSMB recommendation that the trial stop due to futility, but there wasn't time to compare adherence among women under the new approach versus the original counseling technique.)

Vaginal Rings: Products in development for HIV prevention and multipurpose technologies

Delivery System	Active Drug	Protects Against	Status	Developer
4-week silicone elastomer vaginal matrix ring	Dapivirine	HIV	Phase III clinical trials, results expected 2016	IPM
	Maraviroc	HIV	Phase I clinical trial complete, results expected 2013/2014	IPM
	Combination dapivirine-maraviroc	HIV	Phase I clinical trial complete, results expected 2013/2014	IPM
	Combination dapivirine-darunavir	HIV	Preclinical studies underway	CHAARM; IPM
	Various triple combinations of NNRTI, progestin + anti-HSV agent	HIV	Preclinical studies underway	Queens University Belfast
60-day silicone elastomer ring	Dapivirine; levonorgestrel	HIV; pregnancy	Preclinical studies underway; Phase I clinical trial planned for 2015	IPM
4-week hollow polyurethane intravaginal ring	Tenofovir disoproxil fumarate	HIV (will be evaluated in women using injectable hormonal contraception)	Preclinical results Phase I clinical trial scheduled for late 2013	CONRAD
	Tenofovir disoproxil fumarate powder and sodium chloride	HIV	Preclinical results*	CONRAD
90-day polyurethane intravaginal ring	Tenofovir; levonorgestrel	HIV; HSV-2; pregnancy	Preclinical results; Phase I clinical trial planned for early 2014	CONRAD
	Tenofovir	HIV; HSV-2	Preclinical results; Phase I clinical trial plnned for late 2013	CONRAD
Polyurethane matrix intravaginal ring	Tenofovir; IQP-0528	HIV; HSV-2	Preclinical results	CONRAD
Silicone "POD" IVR (Versaring)	Tenofovir	HIV; HSV-2	Preclinical results	CONRAD; Auritec Pharmaceuticals
BioRing (nanoporous hydrophilic polymeric hydrogel)	Ferrous gluconate; ascorbic acid; pharmalytes; boc-lysinated betulonic acid; tenofovir	HIV; pregnancy	Preclinical studies underway	BioRing LLC
Silicone elastomer ring with 2 cores	Nestorone® and ethinyl estradiol	Pregnancy	Pending submission to the FDA	Population Council
Silicone reservoir ring	Nestorone® and estrogen estradiol	Pregnancy	Phase II	Population Council
Silicone layered ring	Ulipristal	Pregnancy	Phase II	Population Council
90-day ethylene vinyl acetate (EVA) *or* silicone intravaginal ring	MIV-150; zinc acetate; carrageenan	HIV; HSV-2; HPV	Preclinical studies underway	Population Council
	MIV-150; zinc acetate; carrageenan; levonorgestrel	HIV; HSV-2; HPV; pregnancy	Preclinical studies underway	Population Council
	Griffithsin	HIV; HSV-2	Early development	Population Council
Silicone "Ab POD" IVR	Monoclonal antibodies (Abs)	HIV; HSV-2	Preclinical NHP** studies 2014-2015	Antibody IPCP (ReProtect, Auritec, Mapp)
Reusable Duet/IVR + Ab capsules that are replaced by the end user	Monoclonal antibodies (Abs)	HIV; HSV-2	Preclinical NHP studies 2014-2015	Antibody IPCP (ReProtect, Auritec, Mapp)
TBD	Immunogens (trimeric gp140 boosts following DNA prime), and microbicides (1% tenofovir or dapivirine IVR) via an intravaginal ring. Mucosal adjuvant R848 (a TLR 7/8 agonist) to sustain mucosal memory	HIV; HSV-2	Early development	Imperial College, Queens University Belfast
TBD	L2 epitope fusion with griffithsin; intravaginal ring for burst release of HPV vaccine and sustained release of griffithsin as microbicide	HIV; HPV; HSV-2	Early development	University of Louisville

* Preclinical Results refers to those ensuing from animal testing.
** NHP refers to non-human primate studies.

Sources: AVAC PxRD, *www.avac.org/pxrd*; *Clinicaltrials.gov*, CAMI MPT Microbicides and Devices Database, *www.cami-health.org/mpt/Prevention-Targets.php*.

The Ring Study and ASPIRE trials of the dapivirine ring are using new approaches that should also be evaluated. Both trials are analyzing data—blood samples and returned rings—to get an indication of adherence. While the study investigators don't have access to individual participant results, they can access information about adherence at a given site and in the trial overall. This information can be shared with participants—the first time that information on adherence is being reported back to participants as the trial is going on—and such updates may reinforce or improve adherence.

Another approach is to follow what Microbicides Trial Network regional trial physician Patrick Ndase calls "the emotional energy path"—creating discussion groups where participants talk honestly about their product use, and site staff share their own experiences "from the heart". These discussions are a departure from adherence counseling sessions that focus on information and education—and ones in which women may not feel comfortable admitting their challenges or perceptions of the product. These and other approaches can be analyzed for their impact, so that the field has a sense of what works in clinical trials and what may be effective when it comes to introduction.

Plan for success: Learn from—and improve on—daily oral PrEP

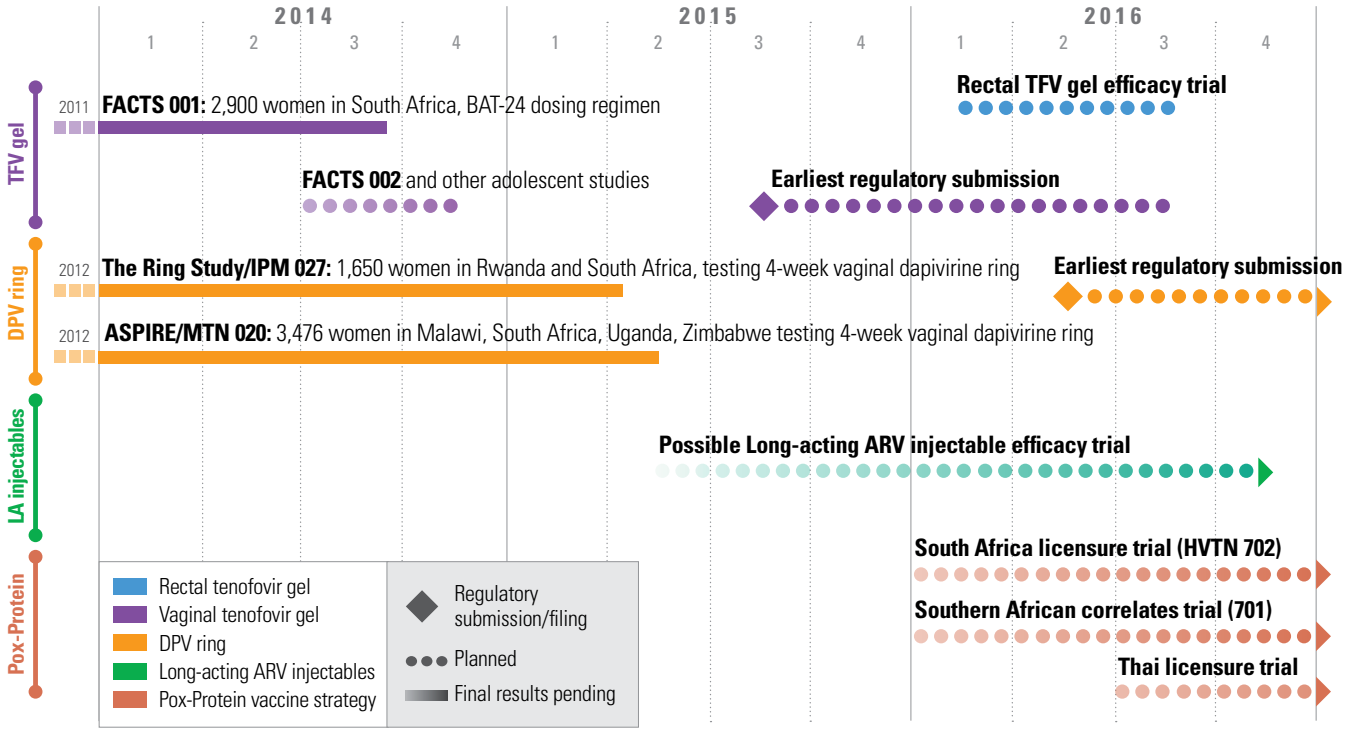
In the best-case scenario, the microbicide field will have one or more options on a licensure track in the next two years. These topical ARV-based prevention strategies will follow in the footsteps of daily oral tenofovir-based PrEP. The first microbicides will be different from daily oral PrEP for many reasons. Oral PrEP involves a drug that is also widely used as part of an effective treatment for HIV-positive people. Microbicides will require new manufacturing, licensure and approval processes. It is possible that these differences will set microbicides on a different course from PrEP. On the other hand, a ring- or gel-based form of ARV-based prevention will probably require HIV testing before use; it also will require new training for providers, extensive social marketing research and piloting, and communications and messaging campaigns that reach an array of audiences. These products will be more expensive than existing options. There will be many questions about the best way to deliver them outside of the clinical trial setting. They will, almost certainly, be accused of facilitating women's promiscuity—sexist, alarmist language that gets used in any context in which women have agency over their sexual lives.

Those involved with the introduction of tenofovir-based PrEP are already grappling with these issues (see page 30). The microbicide field can get a head start on introduction by learning from their experiences—namely, by defining demonstration projects and developing strong advocacy approaches that tackle skeptics' concerns early on.

Prioritize informed civil society demand

Right now, women outside of the immediate sphere of microbicide advocacy are confused about what conclusions have been drawn from the trials to date and when they might expect a product to become available. The various interpretations of what VOICE and FEM-PrEP mean for female-initiated prevention haven't been put in a framework that explains how the field will get greater clarity. As a result, some of the field's most important allies may think that daily gel or pills don't work for young unmarried women—and that there's little to be done except wait for other options

Biomedical HIV Prevention Efficacy Trials, 2014–2016*+



* Trial end dates are estimates; due to the nature of clinical trials, the actual dates may change. For full trial details, see *www.avac.org/pxrd.*

\+ This table only includes efficacy evaluations of biomedical strategies in HIV-negative people. There are ongoing pilot and demonstration projects of oral PrEP, an open-label evaluation of 1% tenovfovir gel in the community where CAPRISA 008 took place, and numerous Phase I and II trials of other options.

to emerge from the pipeline. The momentum that came after CAPRISA 004 has waned. There is a pervasive attitude of "wait and see".

This needs to change. Informed civil society demand is going to be essential to catalyzing action that gets products across the gap between positive trial results and eventual introduction—and this demand can't just be cultivated once there is a positive result. Advocates, funders and trial teams need to invest in sustained collaborations with civil society groups to be sure that there are allies who understand the different interpretations of the low adherence data from trials to date—and the steps that are being taken to move forward.

Engagement is needed at many levels. "Grasstops" advocates—those with access to resources and policy makers—can help make the case for continued investment in research. Women and men living and working in trial communities can have more influence over what happens in a trial than the most sophisticated adherence counseling session ever will.

All of this work depends on robust investment in stakeholder engagement from trial funders and networks. In the context of resource scarcity, stakeholder engagement budgets are often cut or scaled back. It is critical to sustain investment in a variety of activities that engage civil society groups as active partners to help ensure that the next trials of female-initiated options yield definitive conclusions regarding efficacy. It will also ensure that there is a chorus of informed, strategically minded women ready to work on innovative product introduction when that day comes.