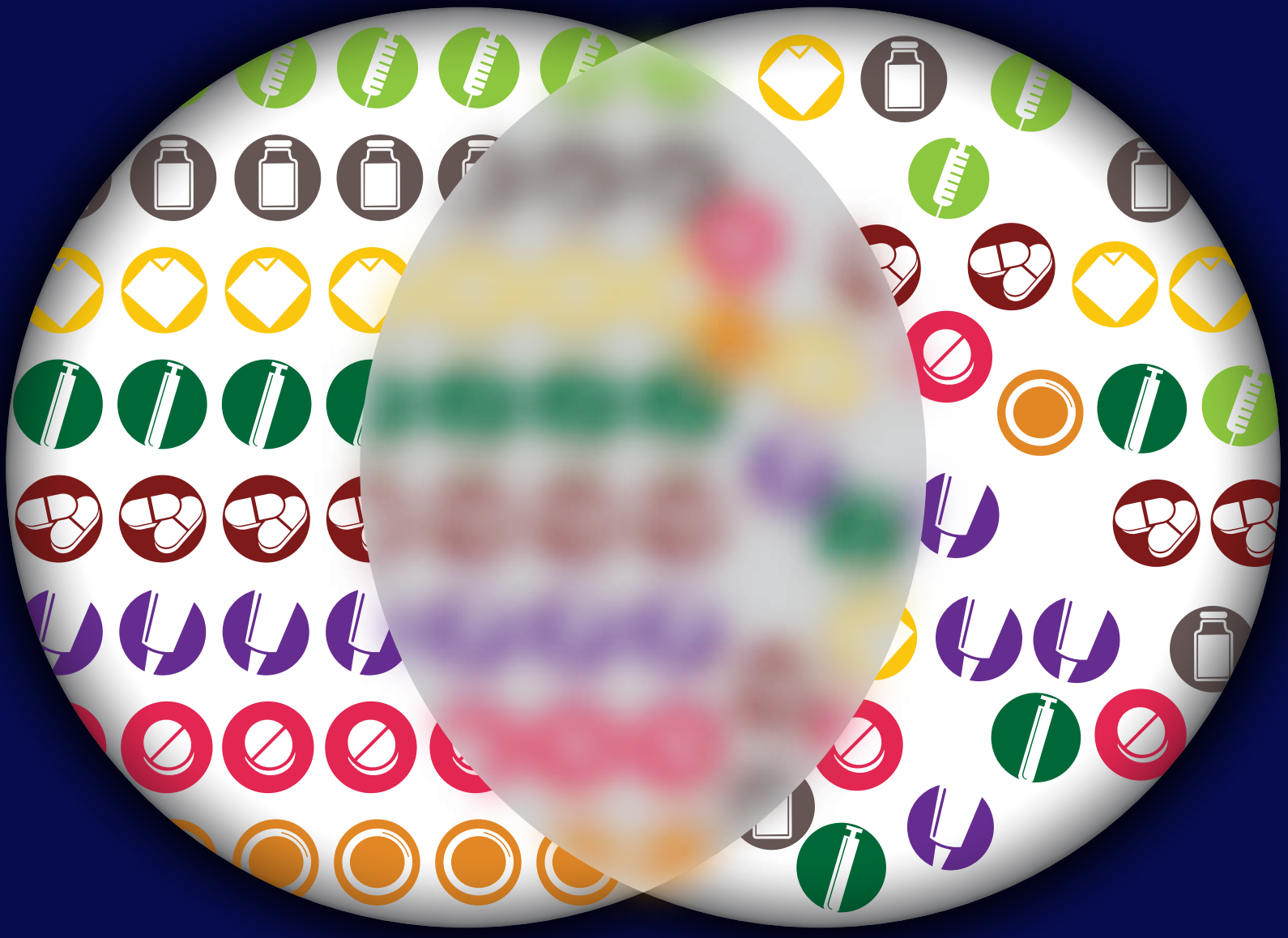
AVAC REPORT 2013: Research & Reality



AVAC
Global Advocacy for HIV Prevention

www.avac.org

Acknowledgements

AVAC gratefully acknowledges many friends and colleagues in government, industry, academia and the advocacy community who shared their expertise and advice as we researched and prepared *AVAC Report 2013: Research & Reality.*

AVAC Report 2013 was written by Emily Bass in collaboration with AVAC staff and board members. Invaluable input came from many external partners as well. Special thanks to Judy Auerbach, Jared Baeten, Matthew Barnhart, Stephen Becker, Albert Berces, Ward Cates, Connie Celum, Mike Chirenge, Lee Claypool, Mike Cohen, Barbara Friedland, Catherine Hankins, Sharon Hillier, Quarraisha Abdool Karim, Salim Abdool Karim, Johanna Kehler, Jerome Kim, Catey Laube, Donna Lomangino, Siobhan Malone, Margaret McCluskey, Liz McGrory, Nelson Michael, Nelly Mugo, Jennifer Nadeau, Patrick Ndase, Emmanuel Njeuhmeli, Karen O'Malley, Jim Pickett, Jacob Potter, Jason Reed, Helen Rees, Lisa Reilly, Robert Reinhard, Merlin Robb, Lisa Rossi, Bill Snow, Ariane van der Straten and Naomi Wax.

AVAC is dedicated to the ethical development and global delivery of new and proven HIV prevention options. This publication and AVAC's continuous policy, advocacy and outreach work is made possible by the dedicated labor of AVAC advocates and support from the Blum-Kovler Foundation, BTG Bridge via FHI 360, the Bill & Melinda Gates Foundation, the International AIDS Vaccine Initiative, the International Partnership for Microbicides, the John M. Lloyd Foundation, M·A·C AIDS Fund, UNAIDS, Until There's a Cure Foundation, the United States Agency for International Development (USAID) and many generous individuals who have become AVAC members and contributors directly and through the Combined Federal Campaign (CFC). AVAC does not accept funding from the pharmaceutical industry.

IN MEMORIUM

Spencer Cox

March 10, 1968 – December 18, 2012

Spencer Cox was an AIDS activist, a member of the AIDS Coalition to Unleash Power (ACT UP), and a founder of the Treatment Action Group. Cox was both resource and role model at a time when AIDS treatment literacy was low-tech and high stakes. Survival depended on people sharing what they knew. Cox distilled down the facts and made them accessible; he explained things until the science was simple—even when it wasn't. We also learned from his actions: from his work with the Food and Drug Administration's Antiviral Drugs Advisory Committee and his direct, uncompromising approach to working with scientists. Cox embodied the reality that people living with HIV were the experts and the leaders in the struggle to save their own lives. We're grateful for this example, and better for it.

Nelson Mandela

July 18, 1918 – December 5, 2013

"It is never my custom to use words lightly. If twenty-seven years in prison have done anything to us, it was to use the silence of solitude to make us understand how precious words are and how real speech is in its impact upon the way people live and die," said Nelson Mandela at the International AIDS Conference in Durban 2000. His remarks that day were precious indeed. It was a moment when effective AIDS treatment was out of reach of all but a handful of Africans. He spoke gently but firmly and galvanized the room. The world could change how it approached AIDS in Africa—it had to. That great man, Madiba, helped make sure that it did. We join the world in honoring his tremendous life.

Table of Contents

Boxes, Figures and Tables

A LETTER FROM THE EXECUTIVE DIRECTOR

Back to Reality: Planning for the next phase of prevention research

The phrase "research to rollout" is shorthand for the path between a positive clinical trial result and a public health program that delivers the new strategy in the real world. It's a multistep process, with many potential pitfalls. Today, there is an urgent need for smart and accelerated "implementation science" agendas that lay out strategic plans for maximizing the impact of new prevention and treatment options. Sadly, this is often lacking. As World Bank President Jim Kim said earlier this year, "I'm just asking that we bring the same kind of rigorous approach and scientific thinking to actually delivering these tools for health that we bring to creating them."[1]

But while the phrase "research to rollout" is useful, it's not perfect. It conveys a sense of linearity—suggesting that the research arena and the real world are two separate realms. In fact, there is no such distinction. Research happens in, and is affected by, the real world. The real world is impacted by research long before a result is available.

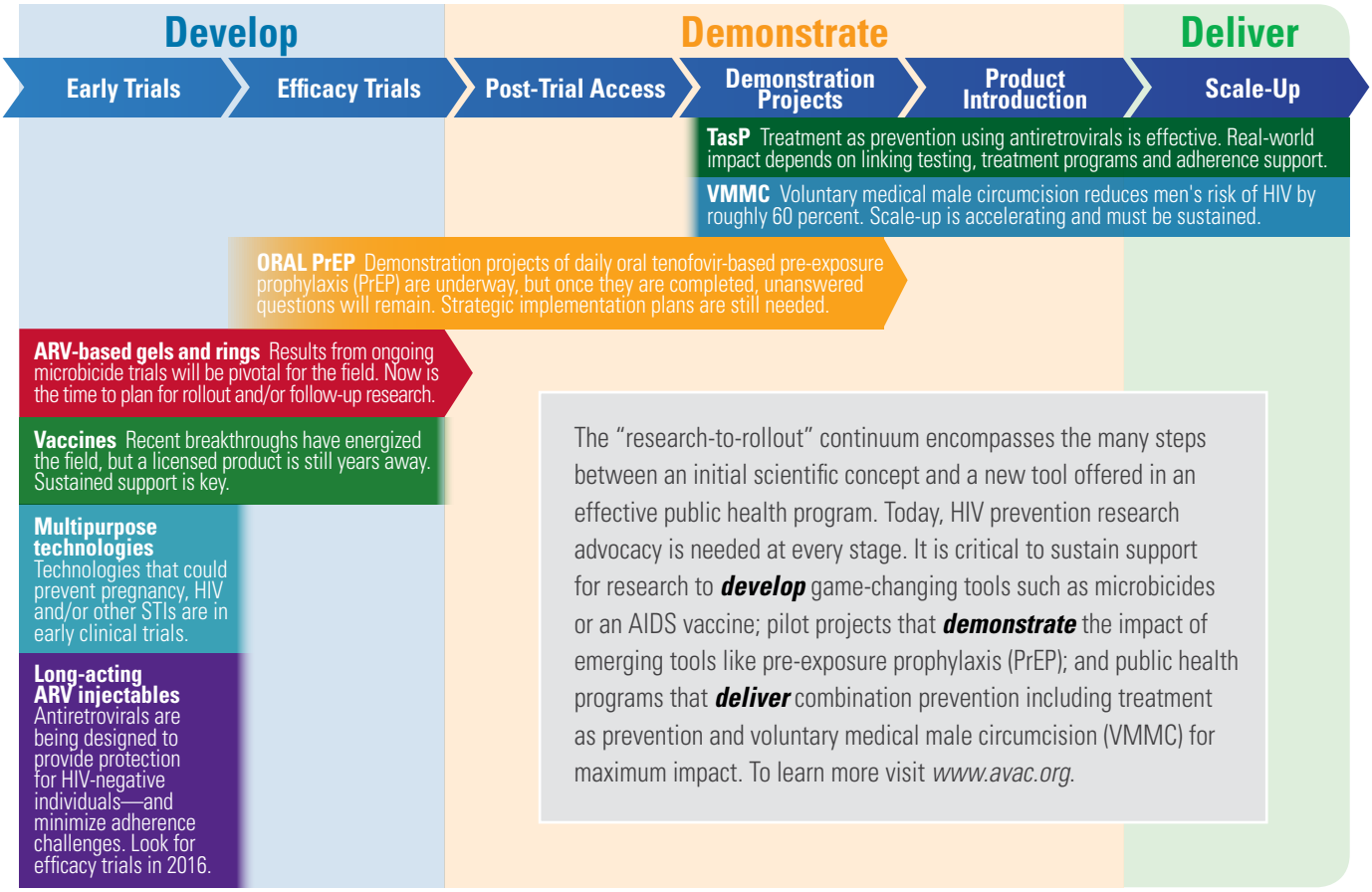
It's not research *to* reality, point "A" to point "B". Rather, it is research *and* reality overlapping and coexisting in ways that are both invigorating and chastening. Invigorating—because to understand what is happening where research and reality meet it is necessary to see things differently and use this new perspective to make better decisions. Chastening—because sometimes what comes into focus are false assumptions, missed opportunities or even, in the worst-case scenario, instances where research may have done harm.

This year's *AVAC Report* is focused on some of the key issues found where research and reality overlap. In many cases, these are issues that emerged after trial results; they involve questions about what to do next, when research does—or doesn't—go as planned.

Most of these issues were anticipated. But even so, the reality was still surprising. One leading microbicide researcher told us, "We expected adherence to be an issue—we just didn't know how much of an issue it was going to be." The vaccine field knew it would not be simple to select and manufacture a protein vaccine for RV144 follow-

[1] "A Q&A with the other banker to the poor, World Bank Prez Jim Kim," Sept 12 2013, http://www.humanosphere.org/2013/09/a-qa-with-the-other-banker-to-the-poor-world-bank-prez-jim-kim/ (Accessed November 20, 2013).

The HIV Prevention Research-to-Rollout Continuum, December 2013



on trials. But it's taken even longer than originally anticipated to complete this step, and the original trial timelines have shifted.

These developments are reality checks for the field. Expectations and predictions need to be revised based on what has actually happened. *AVAC Report 2013* seeks to inform this process.

While the field has been caught off guard by some developments in recent years, there is, in many cases, clarity about what should happen to get, or stay, on track. Future success depends on making these adjustments. Many of our recommendations are directed at funders and researchers—with the hope that they, along with other advocates and allies, will put them into practice.

Our bottom line: Success in ending the epidemic in the long term depends on prevention and, more specifically, on prevention research. Biomedical strategies alone cannot end the epidemic—but the epidemic also cannot be curbed without innovation and strategic implementation in programs that address structural barriers and biological vulnerability at the same time. Couples counseling and testing, gay-friendly health services and post-exposure prophylaxis programs for rape survivors are all examples of such initiatives.

But today's epidemic demands even more. To expand the range of tools available, and to ensure that they are delivered well, it is critical to: sustain funding for prevention research; invest in implementation science; and ensure that advocates

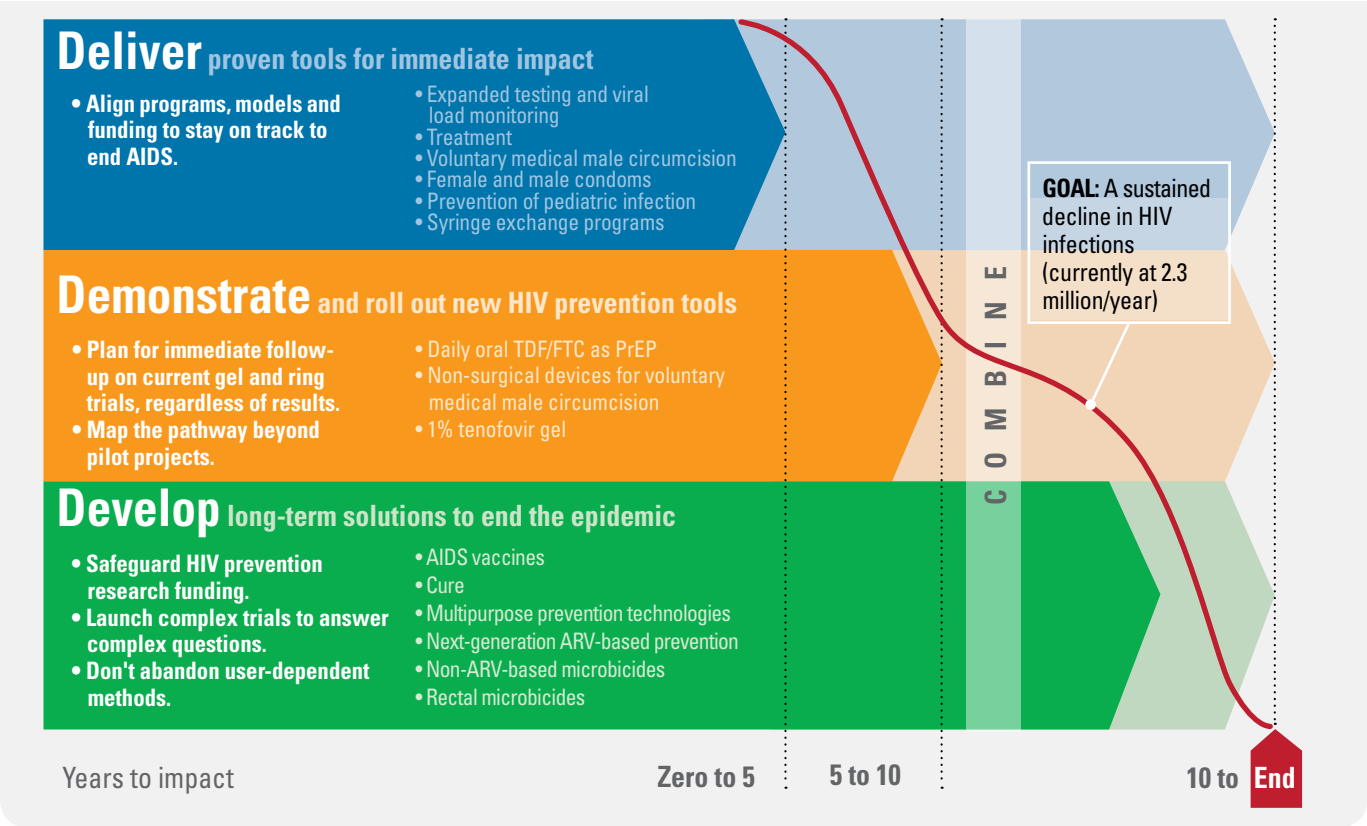
get even better at articulating what needs to happen to move a product from a clinical trial to a high-impact public health program. Success also depends on the field's ability to admit where it has gone wrong—and on being ever more attuned to the social, economic and gender inequalities that define the real world where all research and implementation takes place.

The search for new HIV prevention options for women is at the heart of this year's *AVAC Report.* The past few years have seen progress and disappointment in this field. CAPRISA 004 was the first proof of concept that a microbicide could reduce women's risk of HIV infection. Two subsequent trials—FEM-PrEP and VOICE—found major adherence challenges with daily regimens of oral and topical tenofovir-based prevention.

These recent trial disappointments have rocked the field. At times, it seems as though there is a looming question about whether it is possible to evaluate female-initiated strategies—and whether women want and will use these strategies if they become available. But at the precise moment when the notion of user-controlled methods (e.g., ones that require adherence on a daily or intermittent basis) is in question, there is more clarity than ever about what to do next.

In the second section of the Report, "Research Reality Checks", we take a brief look at several prevention research domains where the ideal conditions of research are colliding with unruly realities. We take stock of the AIDS vaccine field and the ways that data from the Step and Phambili trials—which tested a regimen that

A Three-Part Agenda for Ending AIDS



increased some participants' risk of acquiring HIV—continue to shape the field. We explore the options for dealing with the uncertainty regarding the question of whether specific hormonal contraceptives increase HIV risk. We look at the ways that demonstration projects are—and are not—being linked to plans for implementation with daily oral tenofovir-based PrEP and non-surgical devices for male circumcision.

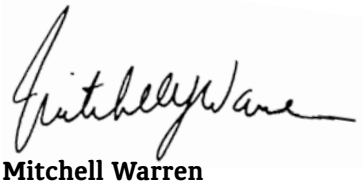
Treatment as prevention—a strategy validated by a major clinical trial over two years ago—is now a focal point of the World Health Organization's guidance on the strategic use of antiretroviral treatment (ART) for treatment and prevention. The research tells us that virologic suppression is key to achieving this benefit. As we discuss, this point that may be lost if the world focuses on ART targets, rather than the quality of adherence over the long term.

Finally, we call for a feedback loop connecting research, epidemiologic models and real-world programs. Current efforts to begin to end the AIDS epidemic depend on these linkages, and such strategic work is only possible in the context of sustained funding and strong leadership.

More than a decade ago, there was a small meeting in New York City on trial design and microbicide research. The Carraguard microbicide trial was taking place, and one of the trial participants had traveled from Gugulethu, a township outside of Cape Town, to New York City to present her experiences with the research. During her remarks, she talked about how the trial had been explained to participants and described some of the interactions between participants and site staff over the course of the trial. She was enthusiastic and honest. At the end of her talk, she said, matter-of-factly, that many women in the trial had taken the pre-filled applicators from the clinic and then emptied them out in their latrines. Her delivery didn't suggest that she intended to make a show-stopping revelation. She was just sharing the truth about how things had gone for some women in a trial.

It was one of those moments when an ordinary meeting shifts into another dimension—the script gets tossed and something intrudes that is both bracing and authentic. Something that we could call, for lack of a better word: reality.

The afternoon at the meeting has stayed vivid over the years. The point is not whether the South African participant's remarks were predictive of what has since happened in the field. It's not a matter of—did we know what was going to happen all along? We didn't. There are clear results from trials with user-controlled methods that did find efficacy. The lesson is that it is important to listen—above all, to the people participating in trials and, especially, the people who may ultimately use the products. In that listening, the field must question assumptions and be prepared to depart from the script as often as it takes—until this essential work of searching for additional strategies to help end the epidemic once and for all is done.



Mitchell Warren
Executive Director

EXECUTIVE SUMMARY

Research & Reality

This year's *AVAC Report* is about the new realities of biomedical HIV prevention research.

In the last few years we've seen major advances, but also have had sobering realizations about the difficulties of developing new HIV prevention options that can succeed both in trials and programs in the real world. Landmark vaccine, microbicide and PrEP trial results energized the biomedical HIV prevention field. Yet, follow-up work from all these trials has been slower than necessary. In the search for new prevention tools for women two recent trials have found very low rates of adherence. These trials have given rise to important questions, not only about women's willingness to use the test product, but about the research process itself.

None of the challenges is a complete surprise. But even the issues that were anticipated—e.g., adherence to daily prevention strategies and scaling up beyond pilot projects—are far more complex in reality. Today the field has a depth of experience that should be reflected in future actions. Now is the time for better problem solving, more critical thinking and coordinated action.

We argue that the field needs to take a fast, focused look at fundamental assumptions and missed opportunities across the HIV prevention research field—and retool its approaches so that the next generation of research delivers advances that women and men want and will use.

Research Reality Checks

AVAC Report 2013 looks ahead to the coming year with four key recommendations on issues that lie at the intersection of research goals and real-world conditions.

- **Launch complex trials to answer complex questions.** Clinical trials can seem like a detour from our attempt to control AIDS with the tools available today. This is especially true when the proposed trials are complex and costly—and are part of research agendas that could take years to have a concrete impact. But in many areas, including AIDS vaccines, as well as hormonal contraception and HIV risk, this research is critical and must proceed.
- **Map rollout beyond pilot projects.** Pilot projects help move clinical research findings into the real world. They are a chance to learn how to deliver a new product. But pilot projects and normative guidance don't guarantee introduction. In 2014, donors, implementers and national governments need to review progress in pilot projects of daily oral PrEP and non-surgical devices for medical male circumcision—and launch strategic implementation plans where appropriate.
- **Invest in innovative approaches to virologic suppression.** Simply starting antiretroviral therapy (ART) doesn't preserve a person's health or prevent HIV transmission. What matters is sustained treatment and suppression of HIV. Advocates need to make the case for investment in treatment adherence programs, better viral load monitoring in resource-poor settings, and sustained research into new antiretroviral treatments, therapeutic vaccines and functional cures.
- **Align programs, models and funding to stay on track to end AIDS.** Models are being used to set targets and define core interventions for high-impact prevention in many settings. In 2014, models and programs need to be connected in a feedback loop so that models are informed by research, programs are informed by models and models are improved by real-world experience. This requires sustained funding and visionary leadership at national and international levels.

Refocusing the Women's HIV Prevention Research Agenda

This Report's central focus is the search for female-initiated prevention options. Today, there are only three ongoing efficacy trials of biomedical prevention strategies—and all of them involve vaginal microbicides. These trials are being tracked with interest and concern, in large part because of adherence challenges in some recent studies. Whether positive or not, the results will shape the field. But we cannot wait until the data are in to take action. Now is the time to articulate a broad and ambitious approach to finding new prevention tools for women.

Our Top-Line Recommendations for Women's Prevention Research

Don't abandon vaginal gels and other user-dependent methods for women. There are competing interpretations of what low adherence in past trials says about the products women will and will not use—and why. Funders and research teams need to use smart research and trial design to move past competing views and generate plans for innovative trials.

Keep searching for methods to improve adherence and measure their effectiveness to determine what works. Many new adherence measures are being used in trials today. Funders and trial networks need to sustain investment in innovation and evaluation of approaches to identify ones that work—and those that don't.

Invest in research to better understand why participants—especially women—enroll in trials. It's clear that there are many reasons why people enroll in a trial and use (or do not use) a product. If these reasons are not well defined by researchers and communities, products may be discarded unnecessarily.

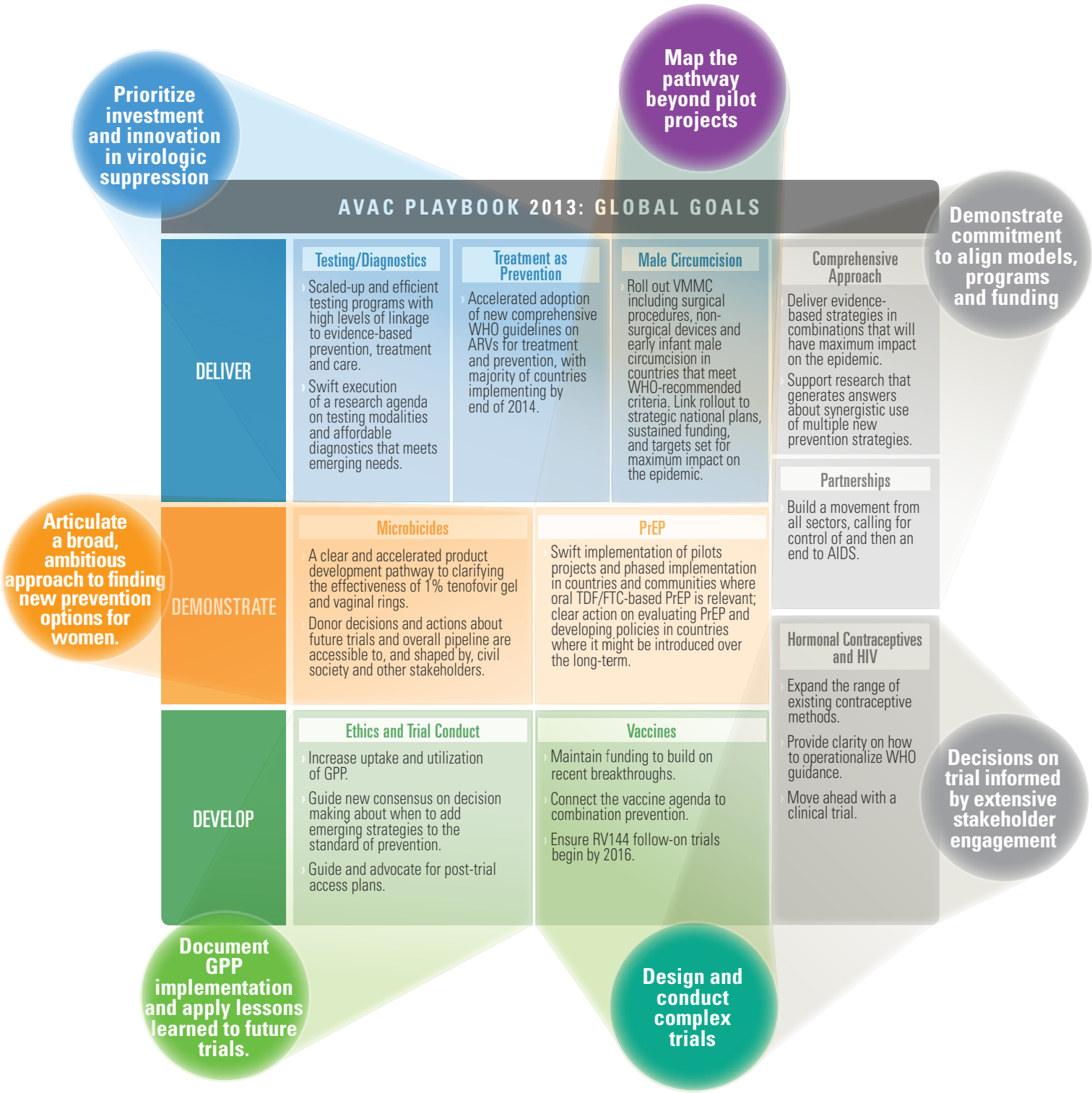
Plan for success, so that valuable time—and the opportunity to reduce new infections—isn't wasted after positive trial results. Delays experienced with the rollout of PrEP and voluntary medical male circumcision (VMMC) should not be repeated in other areas. Researchers need to begin defining a core package of demonstration projects for products that are currently in efficacy trials.

To help ensure clear efficacy findings trials should seek to select participants who are most likely to adhere to a product regimen. The women who most need new HIV prevention strategies may have difficulty adhering to a product regimen in a clinical trial. Trial designs and follow-up plans should reflect this reality.

Prioritize informed civil society involvement to build a community of champions in support of an eventual product. For new prevention options to make a difference, community support is essential—even with the most well designed trials and products.

AVAC Playbook 2013–2014: Global goals and priorities

The *AVAC's Playbook* is a concise look at global goals related to ten areas that are critical to ending the AIDS epidemic. The squares contain long-term goals; in the circles we have laid out priorities for 2014. Working with our partners, we develop and implement advocacy strategies to get us closer to these goals. To learn more about this work at global, national and community level, visit *www.avac.org/programs*.



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.

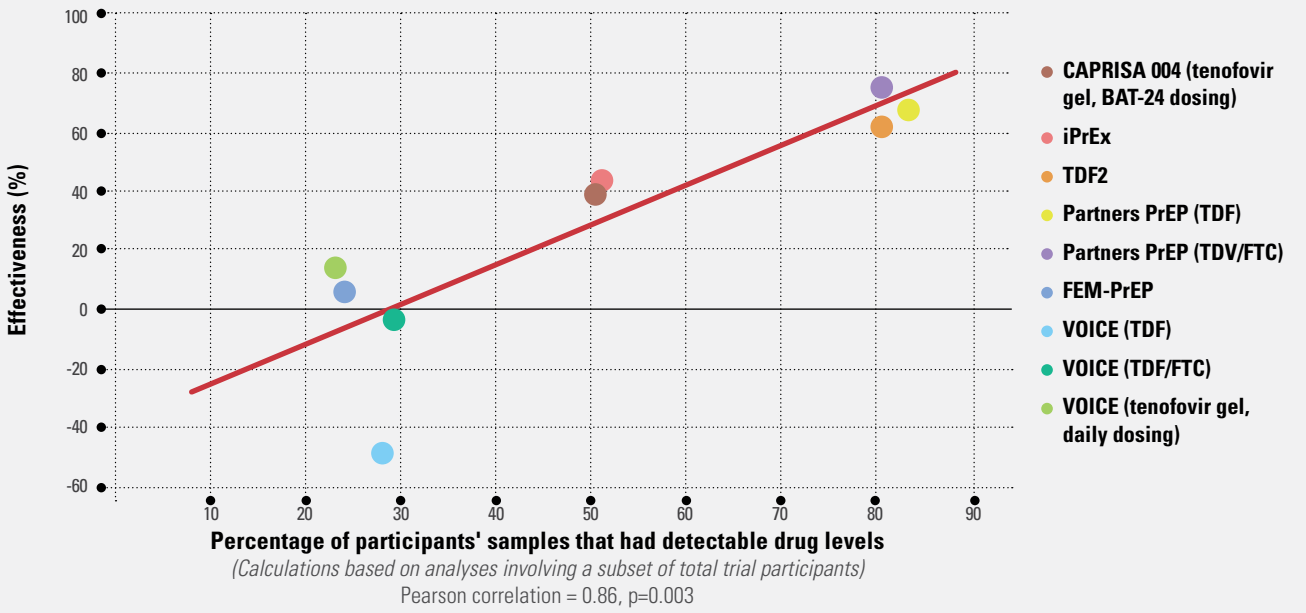
Today the field of female-initiated prevention research is grappling with a range of data. Some of the findings are positive, some disappointing, and all are intimately related to questions about how research impacts women's lives—and vice versa.

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

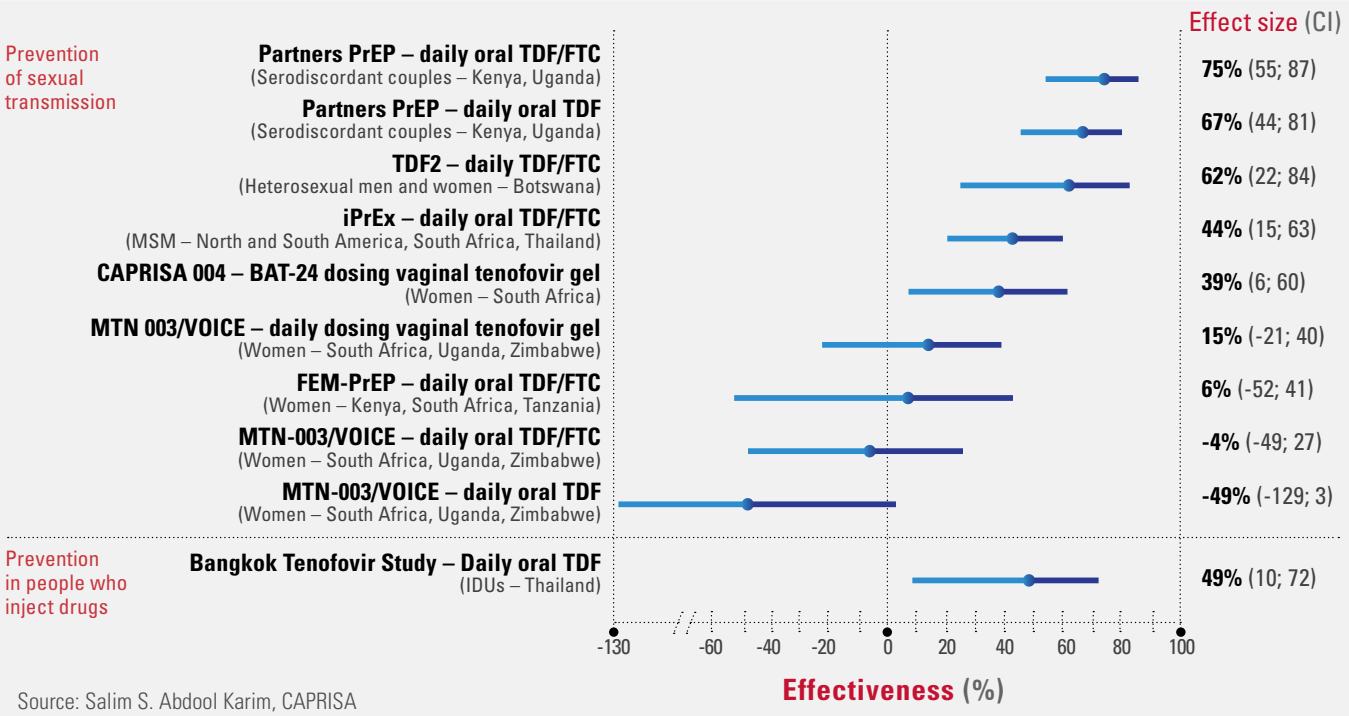
Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention



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

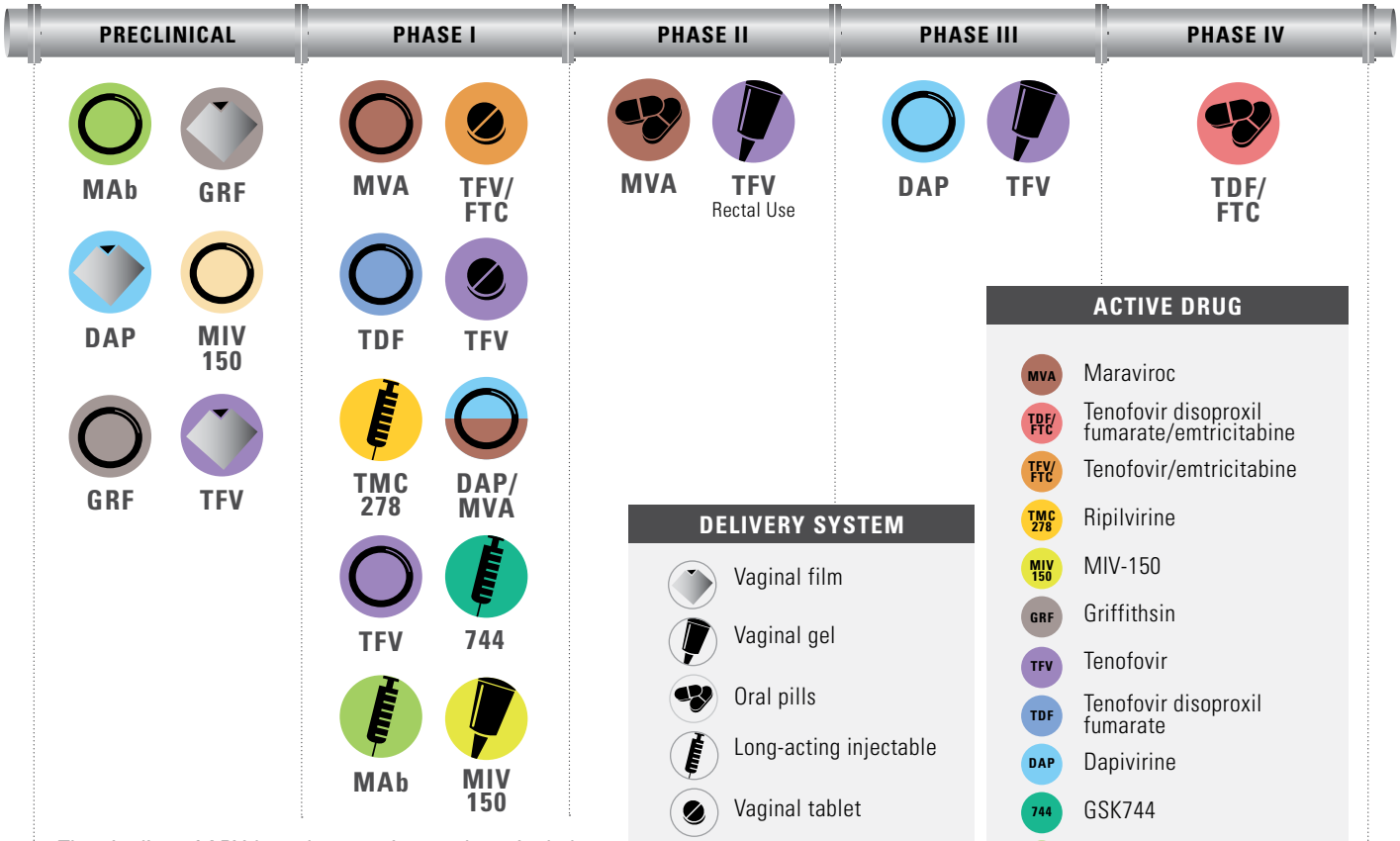
- Prepare for additional efficacy trials of user-dependent methods
- Invest in studies of why women participate in research
- Differentiate between trial participants and end users
- Measure methods to improve adherence
- Plan for success, applying lessons from oral PrEP
- Prioritize informed civil society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

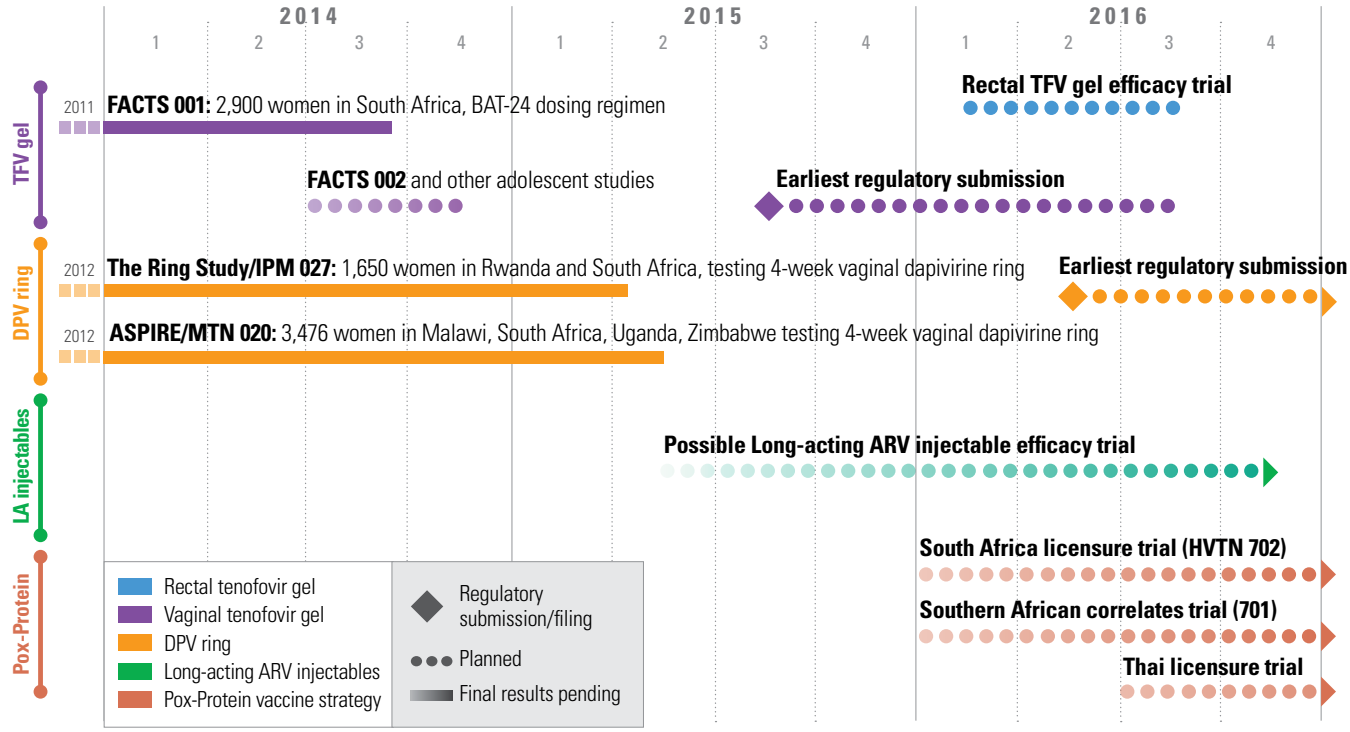
In the best-case scenario, the microbicide field will have one or more options on a licensure track in the next two years. These topical ARV-based prevention strategies will follow in the footsteps of daily oral tenofovir-based PrEP. The first microbicides will be different from daily oral PrEP for many 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".

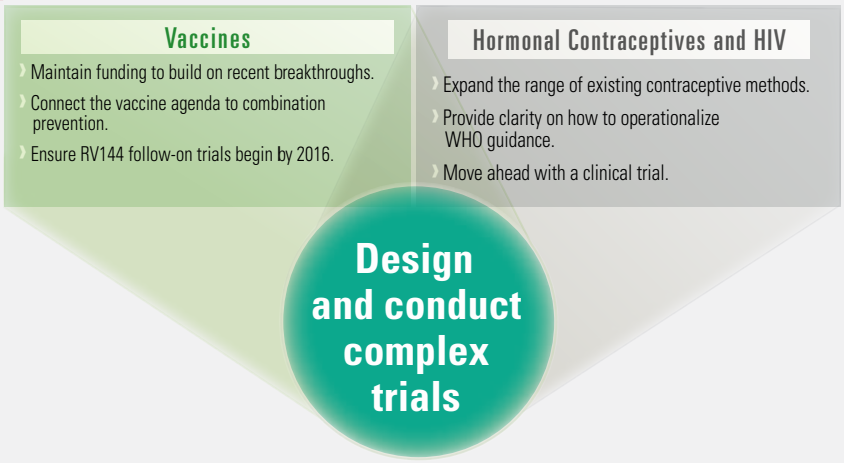
This needs to change. Informed civil society demand is going to be essential to catalyzing action that gets products across the gap between positive trial results and eventual introduction—and this demand can't just be cultivated once there is a positive result. Advocates, funders and trial teams need 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.

Research Reality Checks

Much of HIV prevention research is organized by intervention. There are separate leadership structures, funding streams and scientific agendas for PrEP, microbicides, vaccines and so on. In the real world, the borders blur. The same issues arise in different fields, although joint discussion and problem solving is unusual. It's essential to merge some of these dialogues and dismantle the siloes that separate different realms, like family planning and HIV prevention. These distinctions hinder progress. To address this, we have identified four priority actions focused on overlapping areas.



The AIDS vaccine field and the arena of hormonal contraception and HIV risk are both grappling with questions about how to proceed when there is uncertainty about whether a product may have caused harm. Even with—or because of— these questions, it is important to move forward with carefully designed research. This requires funding, clear messaging and smart trial designs.

AIDS vaccines: Proceed—with deliberate speed

There is a lot happening in the AIDS vaccine field—in many different areas. The past year has brought increased clarity about the design and sequence of trials to build on the result of the RV144 trial, which enrolled over 16,000 volunteers in Thailand and found evidence of modest protection in 2009. There also continue to be exciting breakthroughs in antibody-based research with progress in understanding how potent, broadly neutralizing antibodies (BNAbs) mature in the body, and an increasingly clear picture of virus-antibody binding sites. Efforts to evaluate passive

RV144 Follow-on Trials: Lagging timelines

The next scheduled efficacy trials in the AIDS vaccine field are meant to build on the results of the Thai RV144 trial that showed modest efficacy in 2009. As one next step, a consortium known as the Pox-Protein Public-Private Partnership (P5) was formed to move an RV144-like vaccine strategy into additional trials in Southern Africa and Thailand.

While there is now clarity, particularly about the regimens that will be evaluated in Southern Africa, the timelines for trial launch continue to be pushed back. It has taken longer than expected to select and manufacture the protein boost that will be used in the trials. Novartis, the P5 partner developing the boost, has finally begun manufacture of the clade C boost for the South African licensure trial, which is scheduled to begin in 2016.

A proposed Southern African "correlates" clinical study will gather information on other RV144-like vaccines, but is not designed to lead to licensure. There are still questions about when the Thai trial might begin, since the clade B/E boost that would be used in that trial hasn't been finalized. As the Thai trial timeline slips, there is discussion about whether an additional industry partner should step in to work on a different protein boost.

Regarding these delays, some stakeholders say that the science of developing and manufacturing a new candidate can't be rushed; others argue that industry hasn't treated the project with sufficient urgency. The truth almost certainly lies somewhere in between.

AVAC thinks it is useful to look at the current coordinating structures and make sure that they are still adding efficiency. Is there a different approach to coordination that could allow the Southern African and Thai trials to proceed more quickly? We also look for the current timelines to hold. RV144 provided the proof of concept that an HIV vaccine is, in fact, possible. However, the continued delays in launching trials designed to build on this result make it harder to maintain the optimism.

immunization strategies that infuse BNAbs directly—rather than teaching the body to make them via a vaccine—are also moving ahead.

But if the RV144 follow-on trials (see box, left) are the next—albeit delayed—big thing, and broadly neutralizing antibodies are touted as the hope on the long-term horizon, what happens in between?

As the graphic on page 23 shows, the candidates that could move into clinical trials in the midterm (e.g., the next five to seven years) use various vectors including adenoviruses found only in chimpanzees, "alternative" human adenoviruses, such as Ad26 and Ad35 and, possibly, replicating vectors that use attenuated, non-disease causing versions of viruses to stimulate the immune system.

Decisions about moving these vectors forward will need to weigh scientific promise against the imperative to protect trial participants. All prevention research weighs these concerns. But they will be intensified for AIDS vaccines given the data from a meta-analysis of the Step and Phambili studies, which shows that recipients of a particular Ad5-vectored vaccine strategy may have been at increased risk of acquiring HIV compared to placebo recipients (see box, page 24 for a full description of the meta-analysis.) There will also be safety concerns with replicating vectors, whose potency derives in part from the fact that the disabled virus still retains some of its functions—and so stimulates the immune system on an ongoing basis. Introducing a disabled version of any virus in a vaccine is a risk that has to be balanced against the potential protective benefits of the strategy.

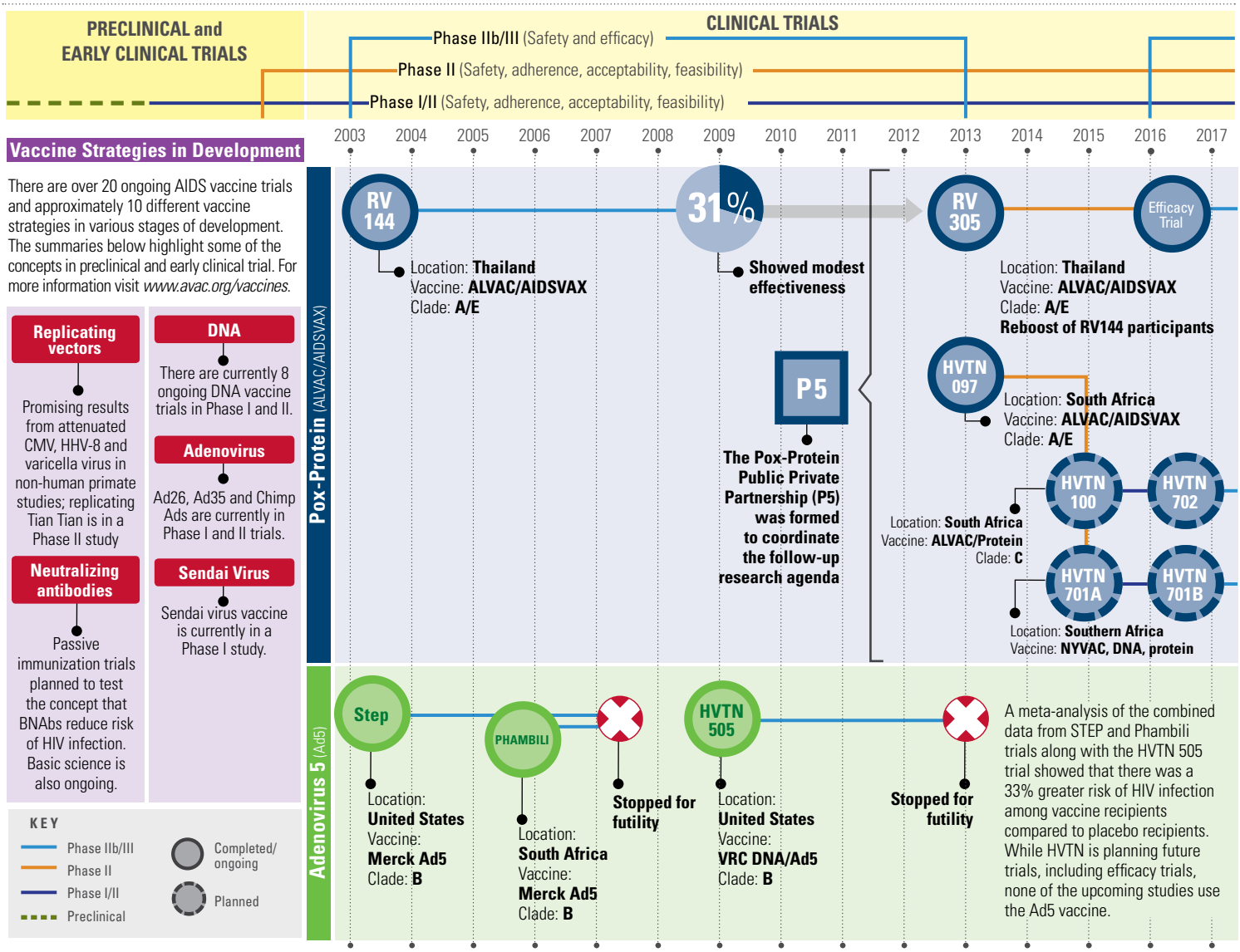
The guiding principle for the field is always to err on the side of caution. The question now is how much caution—and how should the field proceed.

Looking at the questions related to adenoviruses, there is consensus that "Ad5 is dead" for AIDS vaccines. While Ad5 is still being used as a vector in TB vaccine research, there won't be any more AIDS vaccine clinical trials based on that vector. But what about alternative Ads—and about other vectored candidates? It is hard to say without knowing what caused the apparent enhancement of risk.

One possible explanation is that the vaccine-induced immune cells that migrated to the sites of HIV infection—e.g., the vaginal or rectal mucosa—which is what these vaccine strategies were designed to do. But if the cellular immunity wasn't part of a potent response that blocked or controlled the virus then the immune cells would have become targets HIV. A vaccine that results in more target cells at the site of exposure could theoretically increase a person's risk of acquiring HIV.

AIDS Vaccine Research: An overview (December 2013)

This graphic shows the big picture of AIDS vaccine concepts and clinical trials in process and on the horizon. It is an intentionally simplified representation of a complex field. Some approaches are not listed, or described in full detail—and related arenas like therapeutic vaccines and cure research are omitted.



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

At an Ad5 "mini-summit" convened by the US National Institutes of Health in September 2013, Tony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID), laid out the four key questions facing the field:

- Is there a problem with some or all adenovirus 5 vectors?
- Is this a problem with Ad5 only or all adenovirus vectors?
- Is it a problem with any vaccine that causes activated cells to migrate to muscosal surfaces [as was perhaps the case with the Step study]?
- Is this a universal problem that is only seen when the vaccine is not efficacious in preventing acquisition of infection?

Up Close: The meta-analysis of Ad5 candidates

In 2013 the vaccine field grappled with the results of a meta-analysis of data from trials evaluating vaccine strategies that included a vector based on adenovirus serotype 5 (Ad5). In scientific terms, a meta-analysis pools together data from multiple clinical trials of the same treatment or intervention—or of multiple similar treatments or interventions. This approach is used to systematically and quantitatively review the data on a given topic. By combining data, meta-analyses may sometimes allow for a more definitive conclusion about a topic, since larger data sets can allow for more precision, as well as exploration across sub-groups.

The analysis, conducted by Peter Gilbert and colleagues at the HIV Vaccine Trials Network, looked at infections in the vaccine and placebo arms of the Step, Phambili and HVTN 505 trials. Pooling data from these trials, there were 200 infections among participants who received at least one injection of the vaccine; there were 147 infections in the comparable placebo group. Overall, this translated into a 33 percent elevated risk in vaccine recipients compared with placebo recipients. No trend to higher risk of HIV infection was seen in HVTN 505. When the data from this trial were excluded, the vaccine-associated risk in Step and Phambili rose to 41percent.

The Ad5 strategy tested in HVTN 505 contained synthetic fragments of HIV envelope (the outer coating of the virus). The vaccines in Step and Phambili did not. It is possible that immune responses targeting *env* elicited by the HVTN 505 vaccine may have mitigated the risk seen in the other two Ad5 trials. There is discussion now about whether *env* should be consistently used as a vaccine insert based on these data.

Like all meta-analyses, this one has limitations. By definition it was conducted post-hoc (it wasn't planned before the trials were launched), and it isn't as statistically conclusive as it might be if there were larger data sets. Step and Phambili data are not directly comparable. Step participants were in the trial for much longer than Phambili participants—and much of the data from Phambili was collected after participants learned whether they had received the vaccine or the placebo. Overall, 80 percent of infections were in men—primarily men who were uncircumcised and had pre-existing antibodies to Ad5. The available data suggest that there was more enhancement in men than women— and one proposal for mitigating risk is to move other Ad candidates forward in women first. But the numbers are small. Even with these limitations, the meta-analysis is being taken seriously as an indication that the Ad5 candidate in Step and Phambili affected risk of HIV infection. This development is an absolute worst-case scenario for the field. Upcoming vaccine trials, like the RV144 follow-on trials, will vigilantly monitor for both harm and efficacy.

A complementary perspective on the issue came at the AIDS Vaccine 2013 conference in Barcelona from Glenda Gray, Director of the Office of AIDS Research at the South African Medical Research Council and of the University of the Witwatersrand in South Africa. In a succinct summary of the state of the field, she said:

- It is possible to develop a vaccine regimen that will prevent acquisition of HIV.
- It is possible to develop a vaccine regimen that may increase the risk of HIV acquisition.
- It is possible that many HIV vaccine regimens will need to "balance" these factors associated with increased acquisition (e.g., a strong but only partially effective mucosal T-cell response) with the factors associated with protection from acquisition (a partially effective antibody response).

There are no definitive answers to Fauci's questions—and there's a world of complexity in Gray's bullet points. Proceeding with caution is difficult, since it isn't clear how to predict, measure or mitigate risk. There aren't obvious correlates of risk linked to the Ad5-vectored candidates, and there is debate about what types of markers might be predictive. There isn't likely to be agreement in this area anytime soon, and there may never be a filter for screening out candidates that induce cell-mediated immunity and are more likely to increase risk of infection. (Candidates that induce broadly neutralizing antibodies wouldn't be expected to have this problem since BNAbs aren't cells and can't be infected.)

Could trials be designed to manage risk? Yes—but there are uncertainties here, too. One proposal at the mini-summit was to offer participants PrEP, a monoclonal antibody or a microbicide for a finite period to provide additional protection. But the fact that the apparent enhancement emerged early in the Step trial and late in the Phambili trial complicates even this reasonable suggestion.

So where does this leave the field? One option is to hold off on alternative Ad candidates and focus on broadly neutralizing antibodies and the RV144 follow-on trials since there is no evidence of enhancement from that strategy. This would be an extremely risk-averse approach—and in AVAC's view, it is an excess of caution for a field that needs to evaluate a diversity of approaches.

Replicating vectors also raise complex questions about balancing risks and benefits. Some of the most promising animal data seen to date has come from these vaccines, but it may be difficult to move them into humans. At Oregon Health Sciences University, Louis Picker and colleagues are working with an attenuated cytomegalovirus vector. In one study, half of the animals vaccinated and subsequently infected with SIV were able to clear infection. In animal studies, promising results have also been seen with vaccines using attenuated versions of varicella-zoster virus (VZV) and HHV-8 (a herpes virus tied to the AIDS-related cancer Kaposi's sarcoma). For all of the excitement about these data, it's still not clear if and how replicating vectors based on these viruses can be evaluated in humans, given safety concerns. The promise is there—and should be pursued. But as with the Ad-vectored candidates, the next steps must balance urgency and caution. Specifically, the field should:

- **Develop clear and actionable recommendations based on discussions at the Ad5 mini-summit.** Work is already underway to do this. Given that there were strong, sometimes conflicting opinions, it may be a challenge to put forward recommendations that steer the field in one direction or another. But this is what's needed, not just a summary of the issues. These need not be set in stone; they can build in opportunities for course correction, too.

- **Map the pathway for clinical trials of replicating vectors.** The Ad5 mini-summit was a frank, productive discussion and an excellent model for generating an agenda for action. The Global HIV Vaccine Enterprise has established itself as a key convener on "timely topics". This approach should be turned to replicating vectors, engaging civil society throughout. One key issue is the possibility that regulatory authorities might view these candidates differently depending on the severity of the epidemic. Discussion is needed as to whether it would be acceptable to move ahead outside of the US, if the US FDA advised against a replicating vector.

- **Apply rigorous standards for immunogenicity.** Alternative Ads and replicating vectors that move into clinical trials should be held to a rigorous standard in terms of the immune responses that they induce, the immunogenicity. It's not known what types of immune responses will be protective, but the field can use the best available information to choose stringent criteria for immunogenicity.

- **Be prepared to discard candidates.** A candidate shouldn't move into larger trials just because it is the next in line. The field has to be selective in its investments, looking at factors like inserts and adjuvants as well as immunogenicity to select candidates that are qualitatively or quantitatively different from what has been tested before.

- **Maintain investment in community engagement.** Clinical trials are invaluable to advancing the search for an AIDS vaccine. And clinical trials of the complexity anticipated in the future cannot happen without robust, well-funded stakeholder engagement. Yet various aspects of stakeholder engagement are being scaled back. The US NIAID has cut funding for its engagement on prevention research with US community-based organizations—a decision that is penny-wise (no new trials are planned in the US) but pound foolish (stakeholder engagement cannot be switched on and off—it depends on sustained investment).

Hormonal contraceptives and HIV risk: Invest in a complex trial

Over the past year, AVAC has intensified its work in the area of hormonal contraception and HIV risk. We see this issue as fundamental to effective HIV prevention for women. It is one where action must be taken, even in the midst of uncertainty. As the figure on page 29 shows, there are mixed data concerning the relationship between injectable progestogen-only hormonal contraceptives like Depo-Provera and HIV risk. Some studies suggest that this method increases women's risk of acquiring HIV, others do not.

The two main issues in this arena are: how to proceed in the context of uncertainty and whether to attempt to conduct a randomized controlled trial that might eliminate some of this uncertainty. In terms of what to do next, there are immediate steps, such as moving to increase method mix—the range of family planning options that women can choose from. At present, roughly 60 percent of women in sub-Saharan Africa use injectable contraceptives. This option is discrete and long-acting. It is selected and, given available options, preferred by many women. Many family planning programs in sub-Saharan Africa offer women few other choices—perhaps the contraceptive pill, which requires daily use, and condoms. In the context of limited choices, it is hard to know which options women actually prefer.

Another next step must be providing practical information to policy makers and service providers about how to operationalize the 2012 WHO technical guidance note on hormonal contraceptives,[2] which included new language on progestogen-only contraceptives specifying that women who are at high risk of HIV should be strongly urged to use condoms when using this method. Nearly two years after the guidance note was issued, there has been less-than-satisfying progress in this area. WHO had initially committed to developing a communications strategy; the work is being finalized in partnership with Johns Hopkins University, and a strategy is expected in 2014. Unfortunately, there has been scant involvement of civil society in this latest process even though many women's groups involved in a 2012 consultation on the topic had clear recommendations and expertise that should have been incorporated.

These steps won't address the underlying question about whether specific hormonal contraceptives increase HIV risk. Here, the major question is whether to attempt a randomized controlled trial that would seek to answer the question of how various methods, including Depo-Provera, impact HIV risk. WHO, FHI 360, Wits

[2] World Health Organization. "Hormonal Contraception and HIV: Technical Statement." *http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.08_eng.pdf.* Accessed November 27, 2013.

Reproductive Health & HIV institute (WRHI), University of Washington (UW), Statistical Center for HIV/AIDS Research & Prevention (SCHARP), Eastern Cape Department of Health/University of Witwatersrand/University of Fort Hare, International Centre for Reproductive Health/University of Nairobi, Kenya Medical Research Institute (KEMRI), and University of Zimbabwe are collaborating on the trial. The Bill & Melinda Gates Foundation (BMGF) has committed US$30 million—about half of what the trial, as it is currently designed, is expected to cost. Unless full funds are committed, the trial design may be scaled back or it may not happen at all.

The proposed trial, known as Evidence for Contraceptive Options and HIV Outcomes, or ECHO, would randomize women to receive one of four effective long-acting contraceptives: Depo-Provera (a long-acting progestogen-only injectable), NET-EN (another injectable), Jadelle (an implant), or a copper intrauterine device (IUD). HIV incidence will be compared across all four arms. This design would gather information on each strategy. The oral contraceptive pill, which also contains synthetic hormones, isn't being evaluated; it is not long-acting and is less feasible for many women. The copper IUD is the only method among the four that does not contain any synthetic hormones. (Hormones alter women's genital tracts—regulating the menstrual cycle and the immune environment and altering the thickness and other aspects of the vaginal wall and cervix. If a link exists between any of the hormonal contraceptive options and HIV risk, it is likely related one of these interactions, which don't occur with non-hormonal methods like the copper IUD, the diaphragm or condoms.)

ECHO could provide answers as to whether use of any of these methods increase women's risk for HIV. This is important. The absence of data on other hormonal contraceptive methods does not mean that they have no impact on HIV risk. Technologies like NET-EN and Jadelle have not been widely used, so there's been less opportunity to collect the kind of observational data that exists for Depo-Provera. Without a trial like ECHO, there will continue to be open questions about these methods, too.

There are pros and cons to moving ahead with ECHO. On the one hand, the trial is the best hope of getting a clear answer about how different methods impact HIV risk. Without the trial, there will always be an open question about Depo-Provera—and about the hormonal methods that might become more widely used.

On the other hand, there is the argument that resources required to fund the trial would be better spent on expanding method mix. South Africa has already taken steps to move away from Depo and increase the use of other methods with a revised contraception policy that emphasizes an increase in other methods such as implants and the IUD.[3]

However, South Africa is one of only a handful of countries in sub-Saharan Africa that has the resources to implement an expanded method mix independent of donor policy, and it is not clear that funders or national policy makers will shift away from Depo in the absence of more concrete data. Nor is there information about how many of these methods affect HIV risk.

[3] Department of Health, Republic of South Africa. National Contraception and Fertility Planning Policy and Service Delivery Guidelines. *http://www.doh.gov.za/docs/policy/2013/contraception_fertility_planning.pdf, 2012.* (Accessed November 27, 2013).

Valid questions exist about the trial, many of which have been raised by African civil society advocates closely tracking the issue. Would women accept being randomized? Would they remain on the method for the full 12-month duration that trial planners say would be needed to get a clear answer? Would some or all of the methods be available to women once the trial was concluded, even if they had not previously been part of the country's contraceptive package?

Advocates have also raised questions about acting on the outcomes. Widespread introduction of the copper IUD, for example, would entail implementation challenges similar to those seen with voluntary medical male circumcision; both involve staff training, a simple medical procedure and a range of supplies that are not routinely on hand in most resource-poor settings.

The reality is that, unless additional resources are forthcoming, these questions are moot. The trial will not proceed, or it might be scaled back to a two-arm design comparing Depo to a copper IUD. In AVAC's view, the trial design should not be decided by finances. A four-arm trial will provide valuable information; a two-arm trial won't provide necessary information about other hormonal methods. Seeking multiple donors is ideal, but having other stakeholders demonstrate support for a research concept by chipping in shouldn't be a prerequisite for every trial, and probably shouldn't be for this one. If the trial budget isn't met by outside sources, the BMGF should strongly consider paying for it in its entirety. The design should incorporate clear stopping rules—so that if women participants discontinue or switch methods at rates that make the trial unfeasible, it can be stopped without delay.

At AVAC, we think this four-arm trial should move forward. The information that it stands to provide could shape global family planning programs in ways that expand women's options, addressing both family planning and HIV prevention needs. It is important to try to gather information that can be used to ensure that women have access to the best and safest family planning methods. If Depo-Provera does not increase risk, it should remain an option for those who like it, and if Depo-Provera does increase risk a move to other methods could reduce women's HIV risk in high-incidence settings in sub-Saharan Africa.

It may turn out that it is not feasible because women choose not to enroll and/or to remain on the options to which they are randomized. But the trial can be designed so that this becomes apparent sooner rather than later. We also recognize that there isn't consensus among civil society on the issue—and that more women's groups need to weigh in. For this reason, it is also essential that there be extensive, meaningful stakeholder engagement about this trial and the broader constellation of issues related to hormonal contraception and HIV. The ECHO trial, method mix expansion, and a clear communications strategy on the WHO technical guidance need to be discussed in a single conversation, and addressed in a single agenda.

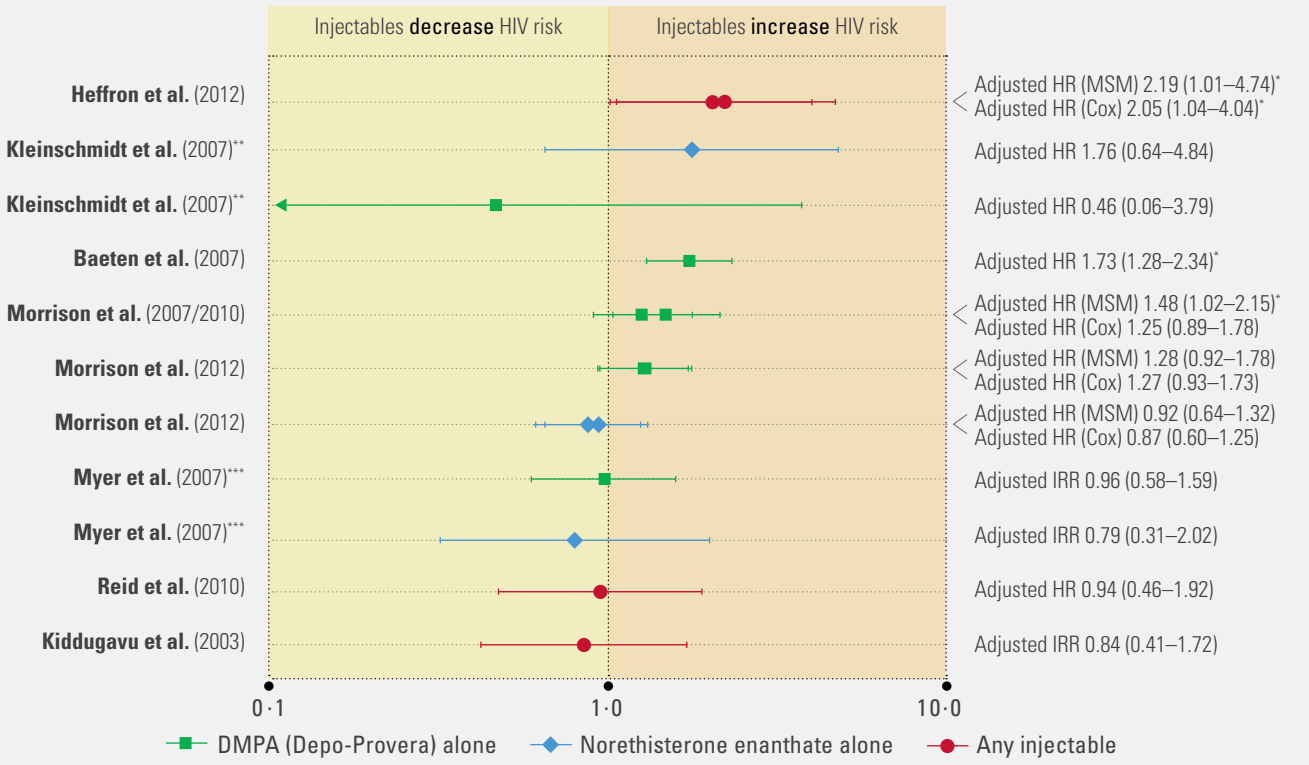
ECHO will have much in common—sites, countries, communities—with research on female-initiated methods. If the trial moves forward, it will be essential to conduct and mine the research described in first section of the Report. This includes exploring women's views of research, trust or lack thereof with respect to specific trials and research in general, and expectations and concerns about preserving fertility versus accessing state-of-the-art gynecological care.

Key next steps include the following:

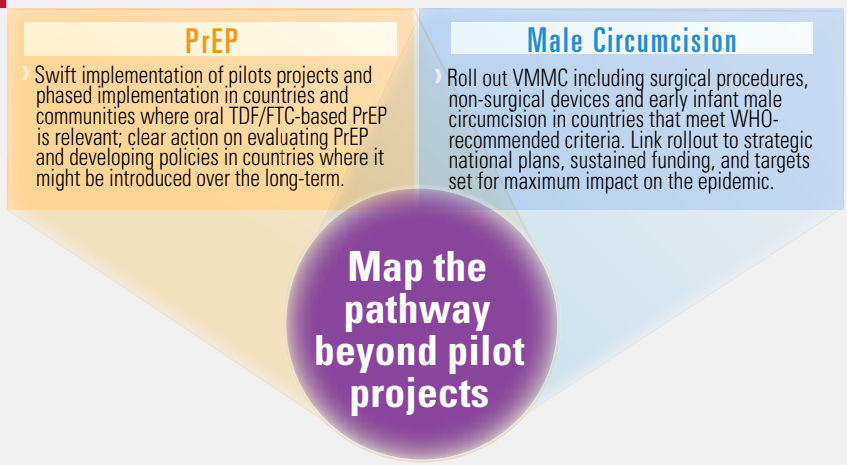
- **New or existing donors should commit resources for the four-arm trial.**
- **The ECHO team should develop a formal relationship with a women's civil society steering committee** or task force that is pan-African and independent of site-specific community advisory mechanisms.
- **The ECHO team should use Good Participatory Practice (GPP) guidelines to structure stakeholder engagement** designed to determine whether the trial should happen and what its should design should be. GPP should be implemented throughout the trial if it moves forward.
- **Funders, researchers and advocates need to "connect the dots" among the ECHO trial, the uncertainty about hormonal contraceptives and HIV risk, and Family Planning 2020 (FP2020) initiative.** FP2020 is a multiyear, multimillion dollar initiative to expand access to family planning worldwide. FP2020 is focused on expansion of long-acting methods like Depo-Provera that are discrete and sought out by many women. FP2020 hasn't explicitly addressed the issue of hormonal contraceptives and HIV risk. Harmonized messaging on how FP2020, HIV prevention, the ECHO and uncertainty about Depo-Provera and other methods fit together is essential.

Use of Injectable Contraceptives and HIV acquisition: The data to date

This graphic summarizes the results of studies that gathered information on the relationship between injectable hormonal contraceptives and HIV risk. Different studies have drawn different conclusions. This is the reason for current uncertainty. None of these studies was designed to specifically evaluate this interaction. Discussions about a trial that would directly address the question are underway.



Source: CB Polis and KM Curtis. "Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence." The Lancet (2013) *http://dx.doi.org/10.1016/S1473-3099(13)70155-5*



Pilot projects work if they are part of a strategic plan—if some thought has been given to what will happen once results emerge. This has been done, to a large extent, with projects involving non-surgical devices for VMMC; there is less clarity and planning for demonstration projects of daily oral PrEP.

PrEP: A piecemeal search for a niche

In last year's *AVAC Report,* we called for a core set of PrEP demonstration projects. While there has been some progress toward that end, there is no over-arching strategy. The majority of planned and ongoing projects are taking place in the United States, and many of the international projects are open-label or follow-on demonstration projects being conducted by the research sites and teams that conducted the PrEP efficacy trials that found benefit (for a lexicon of post-trial evaluations, see page 39).

Research teams have a critical role to play in moving a strategy like PrEP forward. But government AIDS control programs are also key in moving towards roll out. Now is the time to forge these linkages. Without them, open-label extension studies may be seen more as an extension of the research than part of a national effort to evaluate a new strategy. (As one case in point, consider Uganda, where the Partners Demonstration Project is ongoing, but the AIDS Control Program head has already declared that PrEP isn't going to be added to the country's prevention programming.)

The current array of demonstration projects will provide useful information, as will other open-label studies and an array of projects in the United States. But, overall, this is still a piecemeal search for a niche for this potentially powerful product. There is no overarching strategy for ensuring that demonstration projects answer key questions pertaining to PrEP in sex workers, men who have sex with men (MSM), or serodiscordant couples. This doesn't mean that PrEP won't end up being used by or offered to these groups. But the current demonstration projects will leave gaps in the knowledge that could be used to build effective programs.

This suite of demonstration projects may be all that happens. Accepting this reality, there are still next steps that can be taken to maintain momentum. Specifically:

- **Normative agencies and funders and other partners working on demonstration projects should provide a cohesive analysis of the kinds of information that the current suite of projects will and will not provide**—explaining what will be known, and when.

- **Normative agencies, research funders and early-adopter countries should articulate what guidance will be expected or needed in three to five years:** what comes after the current guidance on demonstration projects, and the mention of PrEP in the WHO's comprehensive ARV guidelines?
- A **multi-stakeholder group that includes funders, researchers, policy makers and advocates from countries where PrEP might be introduced should collaborate on forward-looking strategy to fill specific gaps**—such as whether and how to introduce PrEP to African MSM, the gender dynamics of PrEP and treatment as prevention in serodiscordant couples; the acceptability of PrEP to sex workers—who are the focus of several demonstration projects.

Planned PrEP Demonstration Projects in Resource-Poor Settings as of December 2013

There are a range of planned or ongoing demonstration projects or open-label extension studies happening in the United States and Europe. This table includes those few projects in resource-poor settings that are not linked to one of the efficacy trials. A complete list is available at *www.avac.org/prep*.

Trial/project	Sponsor/funder	Location	Population	Status
Partners Demonstration Project	Led by a team of scientists from Kenya, Uganda and the US; funded by NIMH/NIH, USAID and BMGF	Kenya, Uganda	Serodiscordant couples	All four sites open and enrolling as of August 2013; results expected in 2016.
LVCT and SWOP	Implemented by national partners in collaboration with WHO, UNAIDS, O'Neill Institute of Georgetown University, London School of Hygiene and Tropical Medicine, Imperial College London; funded by Bill & Melinda Gates Foundation	Kenya	Young women, female sex workers and MSM	Formative research in planning phase.
Nigerian National Agency for the Control of AIDS		Nigeria	Serodiscordant couples	Formative discussions underway.
Wits Reproductive Health and HIV Institute		South Africa	Female sex workers	Expected start date of February 2014, with expected completion September 2016.
Durbar (DMSC) and Ashodaya Samithi		India	Female and transgender sex workers	Feasibility study underway.
Implementation of PrEP	Oswaldo Cruz Foundation	Brazil	MSM and transgender women	Starting January 2014.

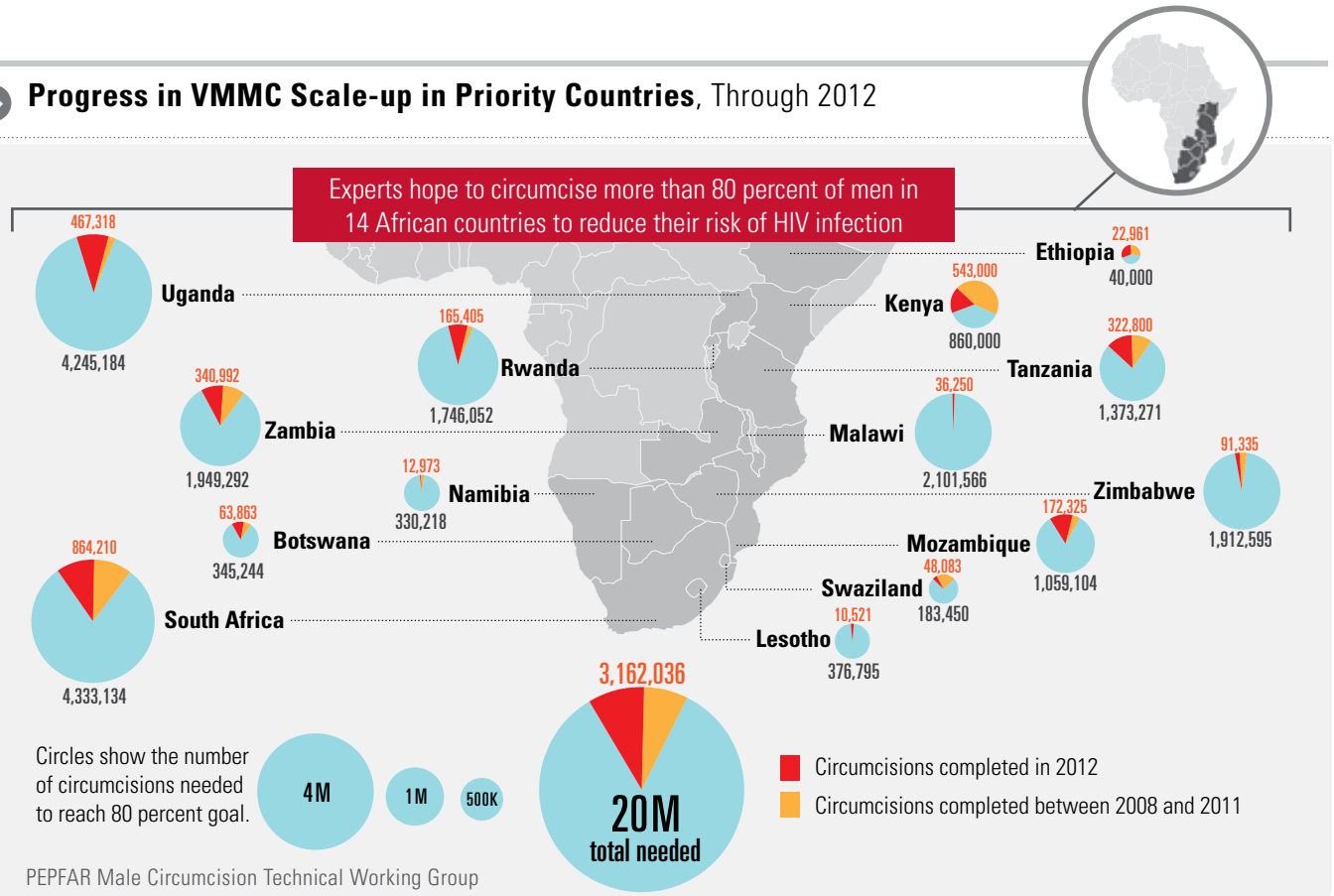
Voluntary medical male circumcision: Non-surgical devices poised on the brink—with questions on price, positioning and more

In April, the World Health Organization prequalified PrePex, a nonsurgical device which allows adult male circumcision without the use of sutures.[4] Other devices are in development. A guidance note for integrating these devices into VMMC programs is forthcoming. Studies have launched to evaluate the safety, feasibility, and ideal service delivery models for device-based circumcision.

Information from the evaluation studies will clarify the anecdotes and assumptions that currently characterize talk about the device—with positive comments like "it will be quicker, easier, cheaper" countered by stories of odor, discomfort or early displacement of the device, which must be worn for seven days. PEPFAR, which has funded the bulk of surgical male circumcision procedures worldwide, is also conducting many of these device evaluation studies. There is close coordination among the studies in different countries. Since PEPFAR is also an implementing partner for existing surgical VMMC programs, there is a clear

[4] WHO. "Information on the PrePex device for adult male circumcision for HIV prevention." *http://www.who.int/hiv/topics/malecircumcision/prepex_device_update/en/ 2013* (accessed December 1, 2013).

Progress in VMMC Scale-up in Priority Countries, Through 2012



PEPFAR Male Circumcision Technical Working Group

Counting Cuts: Getting better at monitoring VMMC

Circumcision should be one of the easiest things to monitor—yet the numbers are out of date. As *AVAC Report 2013* was going to press, total figures for 2012 had just been released. The good news is that the updated figures showed even greater progress than has already been documented. Scale up is moving in the right direction. The problem is that without regularly updated figures, country- and global-level planning efforts are hampered. It is hard to identify gaps in funding by donors or country governments—and to identify countries that are doing exemplary work that can provide insights for their neighbors. To stay on track to begin to end the epidemic, it is critical to track progress in real time. Monitoring and reporting needs to improve—VMMC is one area to watch.

route for moving from the results of these studies to broader introduction in public health programs.

This year AVAC will be looking for these evaluation studies to provide clear, concise information about men's and women's experiences with and perceptions of devices, provider attitudes, resource needs and the cost-effectiveness of these devices compared with standard surgical procedures.[5] This information should guide decisions about where to introduce non-surgical devices—and where they should not be scaled up.

For non-surgical devices to be introduced, they must be affordable. As *AVAC Report* went to press, such a price still hadn't been determined for PrePex, the one device that has been prequalified by WHO to date. The manufacturer, Circ MedTech is in negotiations with the Global Fund to Fight AIDS, Tuberculosis and Malaria and PEPFAR on possible bulk procurement, which could lead to a drop in the currently quoted price of US$20 per device plus an estimated US$6 for the accompanying supply kit. At this price, non-surgical circumcision using PrePex isn't cost-effective compared to surgical procedures. The device should be affordable—equivalent to and/or cheaper than surgical procedures—to move forward. Additional research

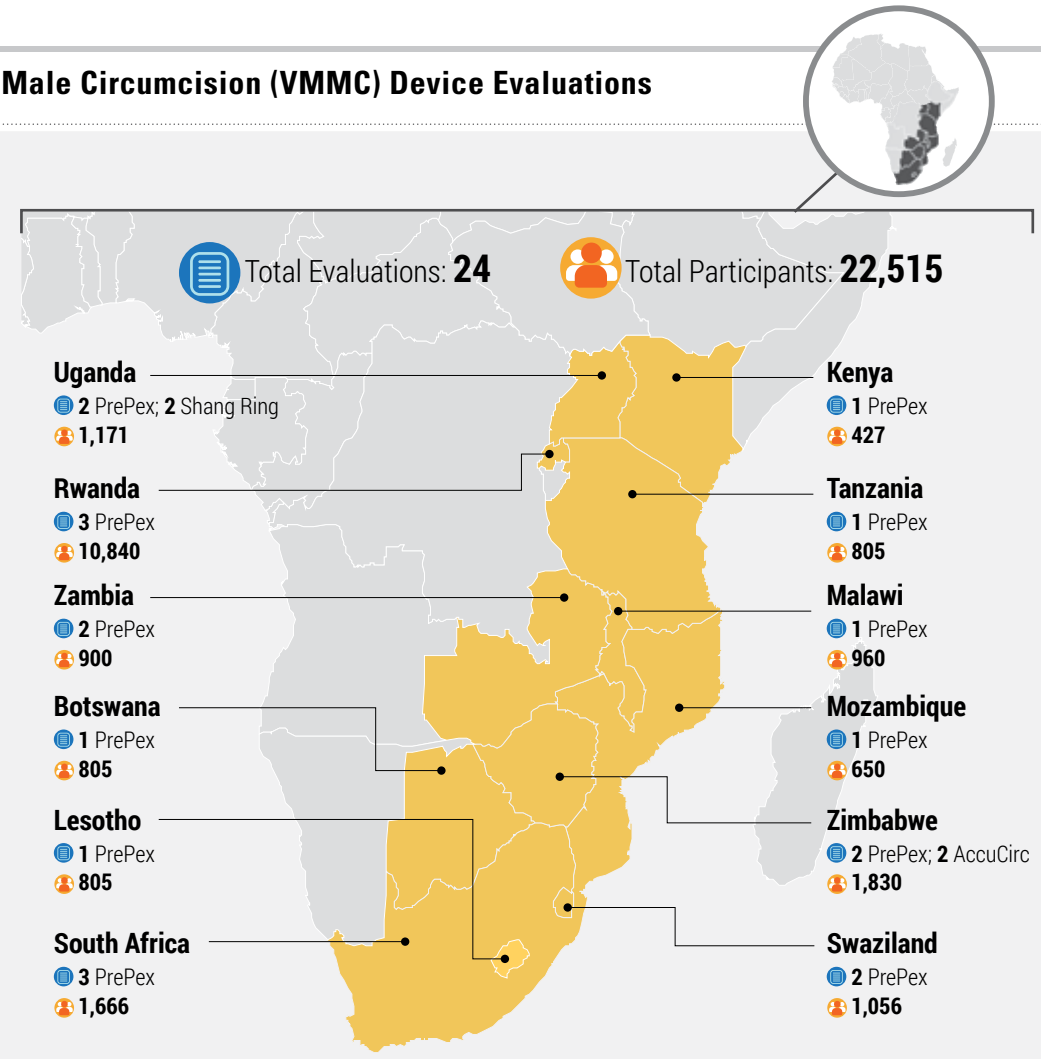
[5] Njeuhmeli, E. "Voluntary medical male circumcision: Summary of Devices Costing and Modeling Studies." PEPFAR (2013) *http://www.malecircumcision.org/resources/documents/6-ENjeuhmeli-Summary%20Device%20Costing%20Studies.pdf* (Accessed December 1, 2013).

is needed to understand whether introduction of devices would affect overall demand for male circumcision; what the incremental costs of adding devices to existing surgical programs would be; and where cost-savings for surgical and non-surgical programs could be found. To keep non-surgical device introduction on track, it is key to:

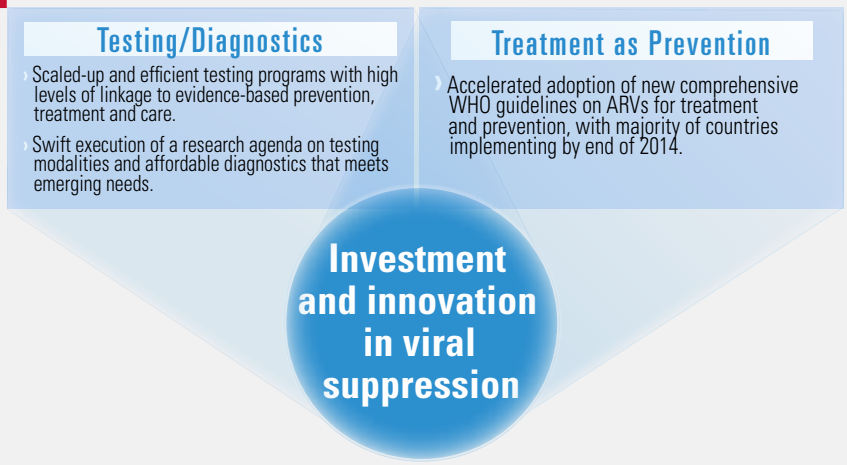
- **Manage expectations**: these devices aren't automatically simpler, cheaper or preferable to surgery.
- **Use evaluation studies to flesh out cost-effectiveness models** comparing surgical versus non-surgical procedures.
- **Set a fair, affordable price for the device.**
- PEPFAR and other device evaluation teams should help **ensure that ministries of health and other decision makers receive balanced information on the devices** from a range of sources—including advocates, modelers and implementers, as well as the companies marketing the products.

Voluntary Medical Male Circumcision (VMMC) Device Evaluations

There is a range of evaluation studies underway to learn more about how non-surgical devices can be used for adult male circumcision. These evaluations, also called implementation pilots, address questions about safety, efficacy, etc. The World Health Organization has already determined that one device, known as PrePex, meets required standards of quality, safety and efficacy for international use. Evaluations of PrePex and other devices will provide information on how to use these strategies in the real world. Most evaluations are enrolling, ongoing or recently completed. Results can be expected within a year.



For up-to-date information on voluntary medical male circumcision visit *malecircumcision.org* and *avac.org/malecircumcision.*



ART doesn't preserve health and reduce transmission risk—virologic suppression does. It's an essential distinction that prevention advocates need to help amplify. We need to pay at least as much attention to what is happening after people start ART, as we do to how many people start at all. Virologic suppression—having a viral load that is at or close to undetectable—is key.

This year WHO released eagerly anticipated comprehensive antiretroviral treatment (ART) guidelines addressing how to optimize ART for both treatment and prevention.[6] The guidance recommends raising the CD4 threshold for treatment initiation to 500 CD4 cells or below—with priority given to people who are symptomatic or have CD4 cell counts at or below 350. As the graphic on page 37 illustrates, this shift in guidelines will increase the gap between the number of people eligible for ART worldwide and those currently receiving it. According to analyses included in the new guidelines, implementation of the new criteria for ART initiation stands to reduce annual incidence and mortality more than 33 percent by 2026.

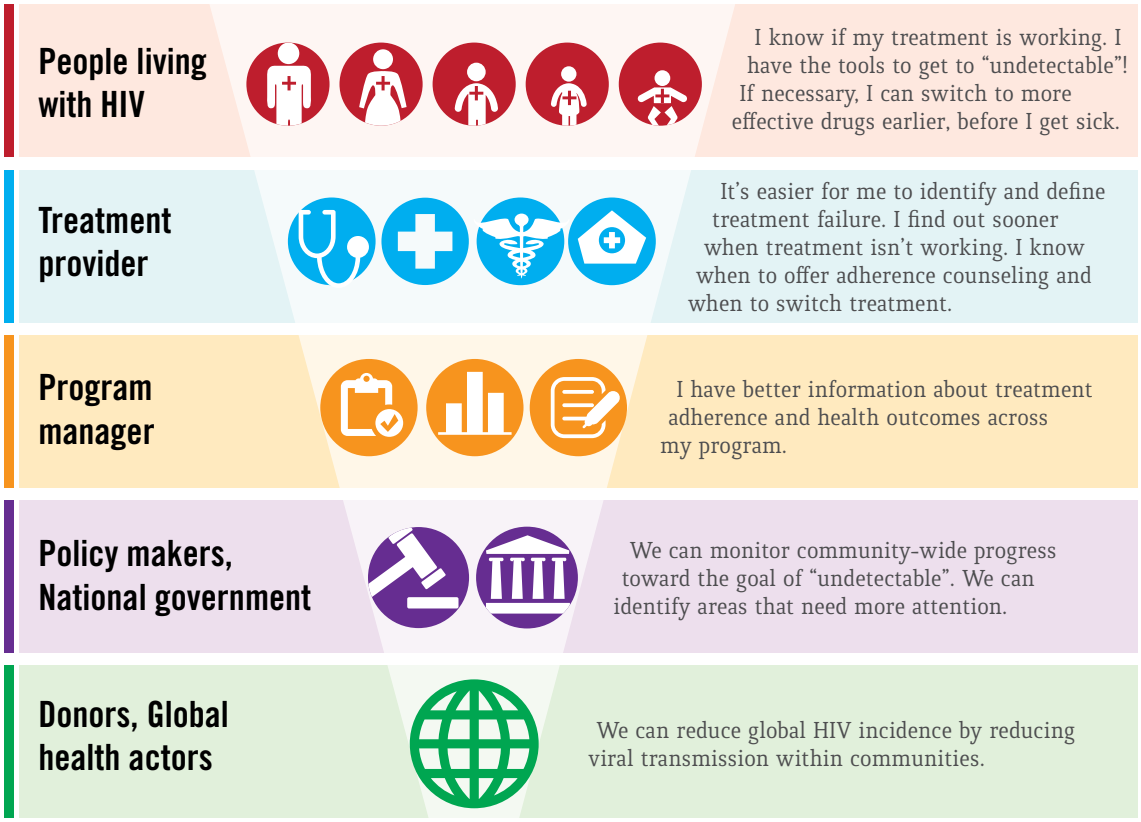
There has been considerable discussion about the feasibility of implementing these guidelines and the need to address the gaps in the "treatment cascade"—the steps that move an HIV-positive individual from an initial HIV-positive test result to care to ART initiation to sustained, effective ART treatment.

The reality that sometimes gets lost in this discussion is that ART doesn't preserve health and reduce transmission risk—virologic suppression does. Virologic suppression—having a viral load that is at or close to undetectable—is key to reducing the risk of transmission. (Right now, virologic suppression can only be achieved through effective ART and management of HIV-related infections—though investigations into therapeutic vaccines and a cure could lead to other options in the long run.)

To make progess toward virologic suppression, it has to be measured. One key step to take in the coming year is to expand access to viral load testing. The new WHO guidelines recommend viral load monitoring as the "preferred approach compared with immunological and clinical monitoring." This is a shift away from previous guidelines that recommended monitoring CD4 count and clinical outcomes to gauge the response to ART. The Guidelines recommend routine testing defined as every six to 12 months—or "at least every 12 months".

[6] WHO. "Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection." (2013) *http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf* (Accessed December 1, 2013).

Viral Load Testing Delivers Systemic Benefits from the Individual to the Institution

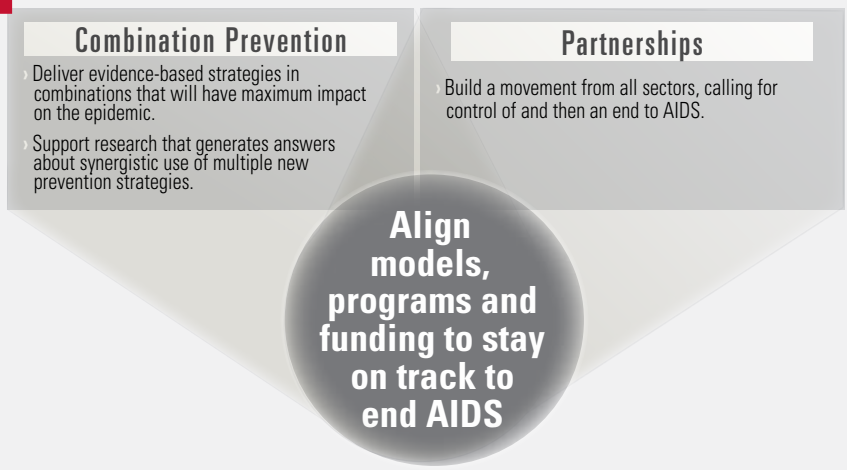


Médecins Sans Frontières/Doctors without Borders (2012). Undetectable: How Viral Load Monitoring Can Improve HIV Treatment in Developing Countries. *http://www.msfaccess.org/content/undetectable-how-viral-load-monitoring-can-improve-hiv-treatment-developing-countries* (Accessed November 7, 2013).

Implementing routine viral load testing would be a major shift for many of the countries with high HIV burdens. There is limited access to viral load testing in sub-Saharan Africa. Having a viral load test should never be a prerequisite for accessing care. However, if the world is serious about using treatment as prevention as part of comprehensive combination prevention, then expanding access to this monitoring test should be a priority.

There are many benefits to making viral load testing more routine: Knowledge that viral load is undetectable can be a profound motivation for people to adhere to treatment regimens, and detectable viral load can be an early warning sign that adherence counseling needs to be intensified. In the best-case scenario, this intensified counseling helps a person do better on his or her current ART combination, avoiding the need to change to a second- or third-line regimen.

Virologic suppression is achieved when people take their drugs correctly and consistently. For many people, this level of adherence requires support from ART programs, peer educators, family and friends. It also requires that drugs be in stock at clinics that are accessible to people wherever they live. Scale up of viral load testing needs to be accompanied by innovative ART service delivery. Approaches to adherence support should be evaluated through analysis of retention records at clinics as well as viral load samples (a rough picture of adherence levels at a clinic can be obtained by measuring viral load in pooled samples from several patients.)



To achieve ambitious targets for high-impact prevention and treatment, models and programs need to be connected in a feedback loop. This must be supported by full funding and visionary leadership at national and international levels.

In last year's *AVAC Report,* one priority recommendation was to end the confusion about "combination prevention"—a term that runs the risk of becoming a catch-all, rather than connoting a specific set of strategic interventions. This year there are some noteworthy examples of countries that are clarifying the combination prevention for specific contexts. Kenya and the United States, countries with distinctly different characteristics, have taken similar approaches to defining and implementing high-impact prevention. If similar approaches can work for countries on opposite ends of the development spectrum, then many other countries should be able to follow suit.

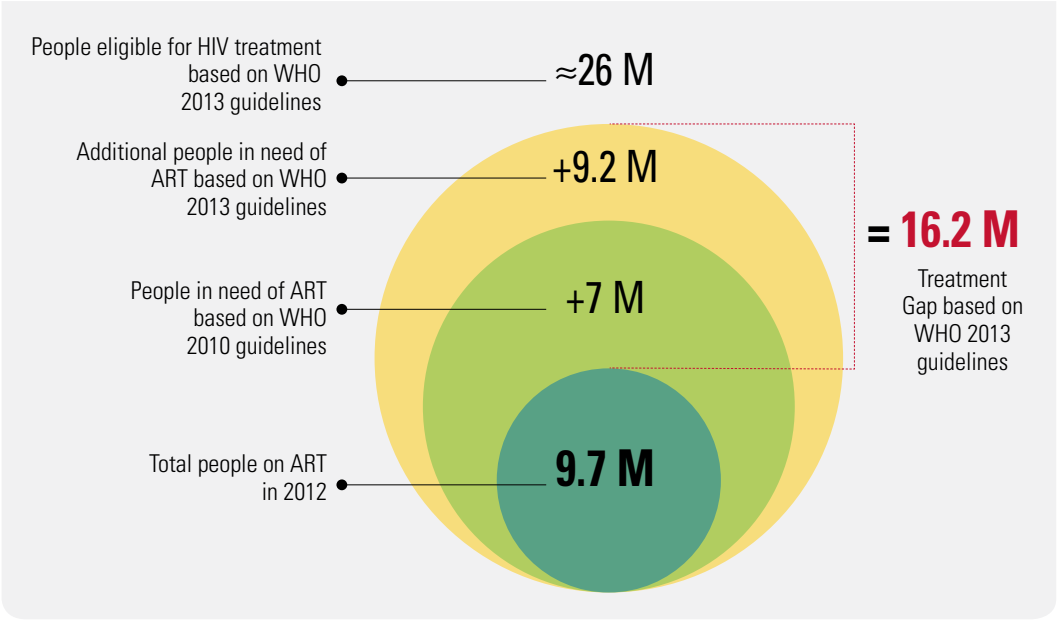
In both countries the approach is defined by geographic prioritization, strategic use of modeling to guide planning, targets and resource allocation and a focus on a limited set of evidence-based approaches.

In the United States, the Centers for Disease Control and Prevention's *High Impact HIV Prevention*[7] (HIP) document lays out the core principles of this approach. Funding opportunities launched since HIP was put forward have been closely aligned with these principles. In Kenya, the framing document is the *Prevention Revolution Roadmap.* As *AVAC Report* went to press, the document was still being finalized and prepared for a national launch. The draft version groups Kenya's counties into clusters of high-, medium- and low-incidence and prevalence and specifies the core set of strategies to be rolled out in each type of setting.

It is encouraging to see such clarity. Rigorous monitoring and impact evaluation will reveal what it looks like in reality as plans unfold. The priority in these and other countries must be to establish a continuous feedback loop between the models that are guiding country decision making and the information gleaned from "combination" or "high-impact" programs. Do the changes in approach result in hoped-for decreases in HIV incidence and prevalence? Is it possible to achieve ambitious targets for treatment and testing? Models and programs will both need to

[7] CDC. High-Impact HIV Prevention: CDC's Approach to Reducing HIV Infections in the United States. (2011) *http://www.cdc.gov/hiv/strategy/hihp/.* (Accessed December 1, 2013).

The Global HIV Treatment Gap : Existing people on ART versus people eligible under past and current WHO guidelines



be refined—and for this to happen there must be full funding and visionary leadership at national and international levels.

2014 will provide multiple tests of the alignment of global leadership with the goals of combination prevention. It will be the first full year that the new funding model at the Global Fund to Fight AIDS Tuberculosis and Malaria is in effect. The model is supposed to be steering countries toward implementing high-impact interventions. More than 100 country concept notes are expected to be submitted by April 2014—and it will be critical for advocates to both influence and track country requests, as well as look at what is returned for revision by the Technical Review Panel.

This is also a pivotal time for United States AIDS program PEPFAR. Ambassador Eric Goosby's tenure as head of the program ended in late October 2013. It is essential that the next head of PEPFAR demonstrate clear, visionary commitment to achieving the goals laid out in the *PEPFAR Blueprint: Creating an AIDS-free Generation*[8] released a year ago.

Right now, the objectives in that document are not fully aligned with actions on the ground. Of chief concern are reports from several countries that the transition to "country ownership" of PEPFAR-funded programs is happening too rapidly to ensure continuity of high-quality, high-impact combination prevention that includes VMMC, ART programs with effective adherence support and retention programs, HIV testing that links to prevention and care as needed—and more. Country ownership is essential to the long-term effort to end the AIDS epidemic. And it is necessary and appropriate

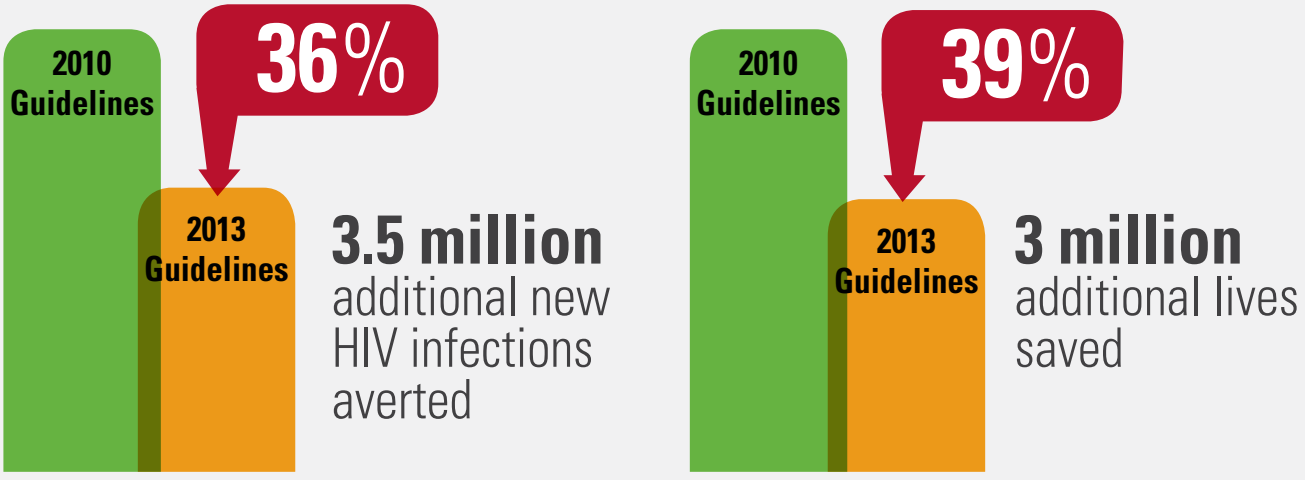
[8] PEPFAR. "PEPFAR Blueprint: Creating an AIDS-Free Generation." 2012. *http://www.pepfar.gov/documents/organization/201386.pdf* (Accessed December 1, 2013).

to explore the ways that countries can both spend more on and provide more of their HIV prevention and care services. But this is only an appropriate goal if countries are ready and able to assume these responsibilities.

In an assessment of PEPFAR released earlier this year, the Institute of Medicine warned that transition away from direct support for service delivery could compromise quality of and access to services for some period of time.[9] The warnings come at the precise moment when this program should be doubling down on its effort to begin to end the AIDS epidemic. This, after all, is the goal laid out in the *Blueprint.* Country operating plans for PEPFAR in 2014 must embody the goals of the *Blueprint.* The new leader of PEPFAR should ensure that each country completes the type of transition plan described in a recent commentary by amfAR's Chris Collins and Chris Beyrer, of Johns Hopkins University and president-elect of the International AIDS Society. Collins and Beyrer call for plans that include metrics to gauge progress towards milestones of transition readiness—as well as "external commitment and careful monitoring to ensure external donors fill gaps to maintain scale-up of strategic services."[10] If the new PEPFAR head treats this as a top priority, he or she will demonstrate the sort of leadership that is urgently needed today.

2013 WHO ARV guidelines can decrease new infections and deaths

WHO 2013 guidelines recommend initiating ART in HIV positive people with CD4 cell counts of 500 or below. Implementing these guidelines will reduce infections and save lives.



Source: WHO/UNAIDS/UNICEF (2013). "Global Update on HIV Treatment 2013: Results, Impact and Opportunities." *http://www.who.int/hiv/data/global_treatment_report_presentation_2013.pdf* (Accessed November 7, 2013).

[9] Institute of Medicine of the National Academies. "Evaluation of PEPFAR." (2013) *http://www.iom.edu/Reports/2013/Evaluation-of-PEPFAR.aspx* (Accessed December 1, 2013).

[10] Chris Collins and Chris Beyrer. "Country ownership and the turning point for HV/AIDS." The Lancet Global Health (2013). doi:10.1016/S2214-109X(13)70092-5.

From Research to Rollout: Evaluations that move a product to the "real world"

Post-trial access

- Intervention provided to trial participants and, sometimes, their communities, after the trial is over and before a product is available for widespread use.

Open label extensions

- Intervention made available, often for a specific time frame, in the context of a follow-on study protocol in which participants from the previous randomized controlled trial (RCT) know that they are receiving the active intervention.
- Gather information about how a product works in people who are now aware of the potential benefit.

Open label / implementation studies

- Research protocols similar to above but enrolling new participants—e.g., those who were not previously enrolled in the RCTs and who might be in open label extensions (OLEs).

Demonstration projects

- "Road test" use of new option in real-world settings—not in trial site.
- Can address both infrastructure needs to deliver intervention and ways individuals integrate it into daily activities and decision making.
- Can help answer core questions about which populations will gain greatest benefit from new interventions, how best to provide those tools and ensure that people use them as directed, and how to integrate new tools with existing methods and health systems.

Product introduction

- Complex process of formally making new options widely available. Can include:
  - Meeting complex regulatory requirements, prequalification by WHO, and various country-specific requirements.
  - Overcoming logistical challenges, such as production scale-up, supply and logistics issues that come with manufacturing and introducing a new product.
  - Building awareness of and demand for new prevention methods in relevant communities through education, marketing, promotion and other activities.
  - Working with health ministries, funding agencies and implementing partners to ensure that new interventions are integrated with other proven strategies and health systems.

Scale-up

- Process of ramping up access to new options for all who need them. Scale-up requires mobilization of sufficient resources for procurement, distribution, delivery, worker training and other costs associated with rollout; quick identification and resolution of potential bottlenecks; and engagement with at-risk communities to ensure a sense of ownership over the scale-up.

No Turning Back

Beyond the Tipping Point

We close this year's *AVAC Report* with a look at progress toward reaching an epidemic "tipping point" in countries around the world. The tipping point is an interim milestone towards the ultimate goal of beginning to end the AIDS epidemic.

In a given country, AIDS epidemic reaches its "tipping point" when the number of annual new HIV infections falls below the annual increase in patients starting ART. Coverage matters.

Countries first have to achieve approximately 66 percent ART coverage before a valid tipping point calculation can be made. The quality of ART care matters too; as we discuss in the preceding pages, it's not just starting on ART but staying on it and achieving virologic suppression that matters for both individual and public health.

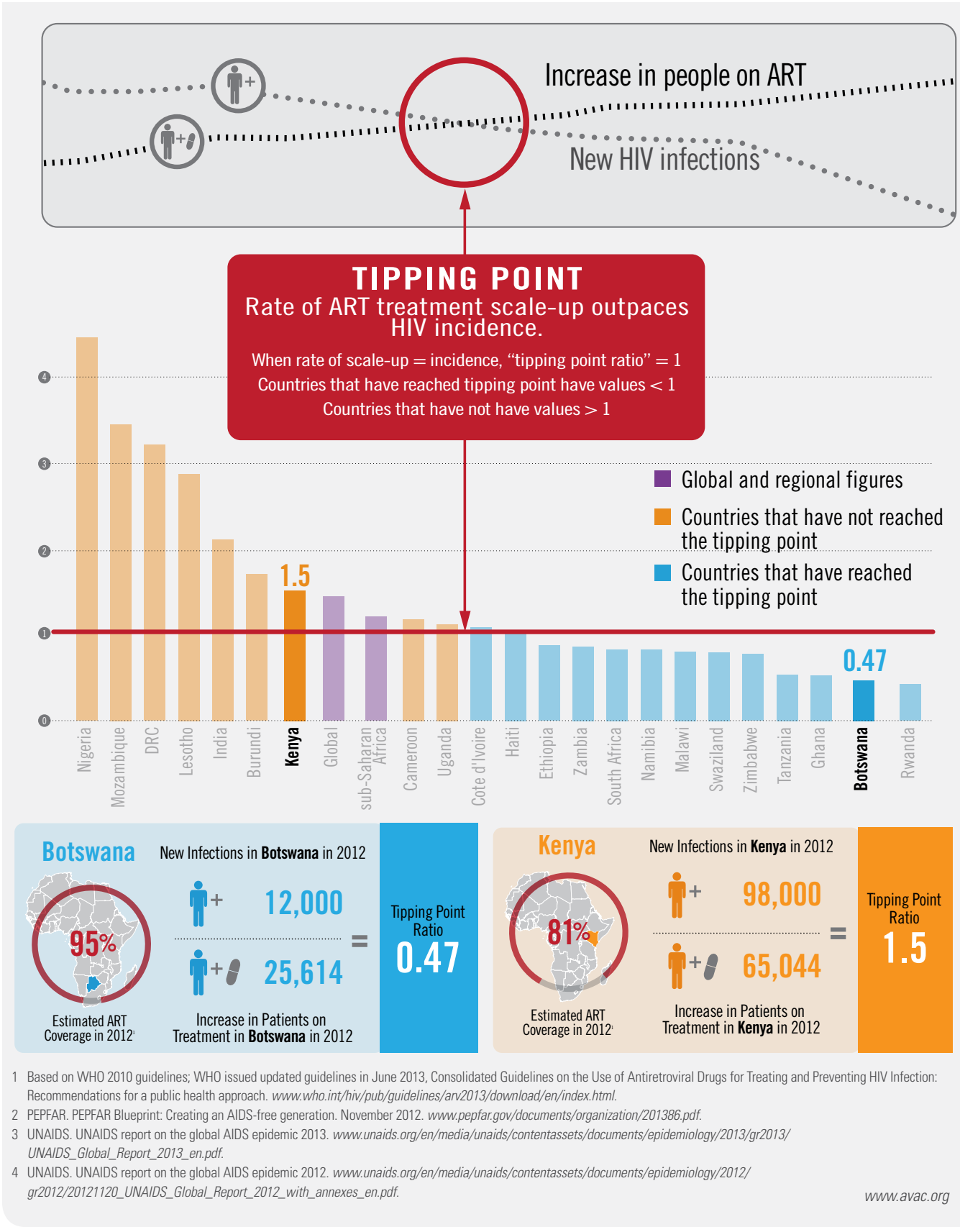
As the graphic opposite shows, many countries have reached the tipping point. This is exciting. However, a country can reach the tipping point and then tip back—returning to a situation where incidence outstrips the rate of ART initiation.

To reach the tipping point, the rate at which people are started on treatment should accelerate immediately. To stay on course, countries and donors need to increase financial and human resource commitments to strategic combination prevention.

Achieving the tipping point is an interim goal. ART coverage alone will not get incidence down to zero. Expanded, high-impact prevention is needed to bring the epidemic to a conclusive end. This involves strategies we have—voluntary medical male circumcision, male and female condoms and harm reduction.

At the same time, as we've argued in these pages, it's critical to continue conducting research that guides delivery of emerging strategies, like oral PrEP, and eventually leads to identification of a microbicide, vaccine and a cure. It will not always be easy. But it is essential work that will ultimately lead to a truly better world.

The Tipping Point: Understanding a crucial milestone in the AIDS response



1 Based on WHO 2010 guidelines; WHO issued updated guidelines in June 2013, Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a public health approach. *www.who.int/hiv/pub/guidelines/arv2013/download/en/index.html.*

2 PEPFAR. PEPFAR Blueprint: Creating an AIDS-free generation. November 2012. *www.pepfar.gov/documents/organization/201386.pdf.*

3 UNAIDS. UNAIDS report on the global AIDS epidemic 2013. *www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf.*

4 UNAIDS. UNAIDS report on the global AIDS epidemic 2012. *www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_with_annexes_en.pdf.*

www.avac.org

About AVAC

Founded in 1995, AVAC is an international non-profit organization that uses education, policy analysis, advocacy and community mobilization to accelerate the ethical development and global delivery of biomedical HIV prevention options as part of a comprehensive response to the pandemic. AVAC is dedicated to:

- Translating complex scientific ideas to communities and translating community needs and perceptions to the scientific community.
- Managing expectations about the process of product research and development, testing and delivery.
- Holding agencies accountable for accelerating ethical research, development and delivery of HIV prevention options.
- Expanding international partnerships to ensure local relevance and a global movement.
- Ensuring that policy and advocacy are based on evidence.
- Convening coalitions, partnerships, working groups and think tanks for specific issues.
- Developing and widely disseminating high-quality user-friendly materials.

AVAC focuses in four priority areas:

- Develop and advocate for policy options to facilitate the implementation of available biomedical HIV prevention options as well as the expeditious and ethical development and evaluation of new ones.
- Ensure that rights and interests of trial participants, eventual users and communities are fully represented and respected in the scientific, product development, clinical trial and access processes.
- Monitor HIV prevention research and development and mobilize political, financial and community support for sustained research as part of a comprehensive response.
- Build an informed, action-oriented global coalition of civil society and community-based organizations that exchange information and experiences.

For more information on AVAC's work and how to support it, please visit *www.avac.org*.

Good Participatory Practice Initiative

In November 2007, UNAIDS and AVAC published *Good Participatory Practice (GPP) Guidelines for Biomedical HIV Prevention Trials,* which set global standards for stakeholder engagement in HIV prevention research. The updated 2011 version provides the first systematic framework for trial funders, sponsors and implementers to effectively engage a broad range of stakeholders throughout the research process—from trial design and planning, through conduct, results dissemination and post-trial access. Since 2008, AVAC has supported research and stakeholder groups in Africa, the Americas, Asia and Europe in various GPP efforts, such as: critical review and feedback on the first edition, trial site rollout and evaluation of practices, implementation in trials and implementation through ethics and regulatory bodies at national levels. AVAC has also developed a growing set of supplementary tools, including a participatory training manual, a trial site self-assessment toolkit and planning templates. The guidelines, including translated versions, and all tools are available at *www.avac.org/gpp*.

HIV Prevention Research Advocacy Fellowship Program

The HIV Prevention Research Advocacy Fellowship Program provides support to emerging and mid-career advocates to implement projects related to biomedical HIV prevention research activities in their countries and communities. The program is designed to expand the capacity of civil society advocates and their host organizations to monitor, support and help shape biomedical HIV prevention research worldwide. The Advocacy Fellowship is guided by the belief that effective, sustainable advocacy grows out of work that reflects organizational and individual interests and priorities.

National Stakeholder Engagement

National stakeholder engagement is different from the types of activities undertaken to prepare for and conduct a study in specific locations—although some groups may be involved in both trial-specific outreach and broader stakeholder engagement. One of the main differences is that, in this process, stakeholders are asked to provide input and guidance on steps that can happen in the short, medium and long term to prepare for the results from an ongoing study and/or to take action on implementing new research findings or prevention strategies, such as combination prevention.

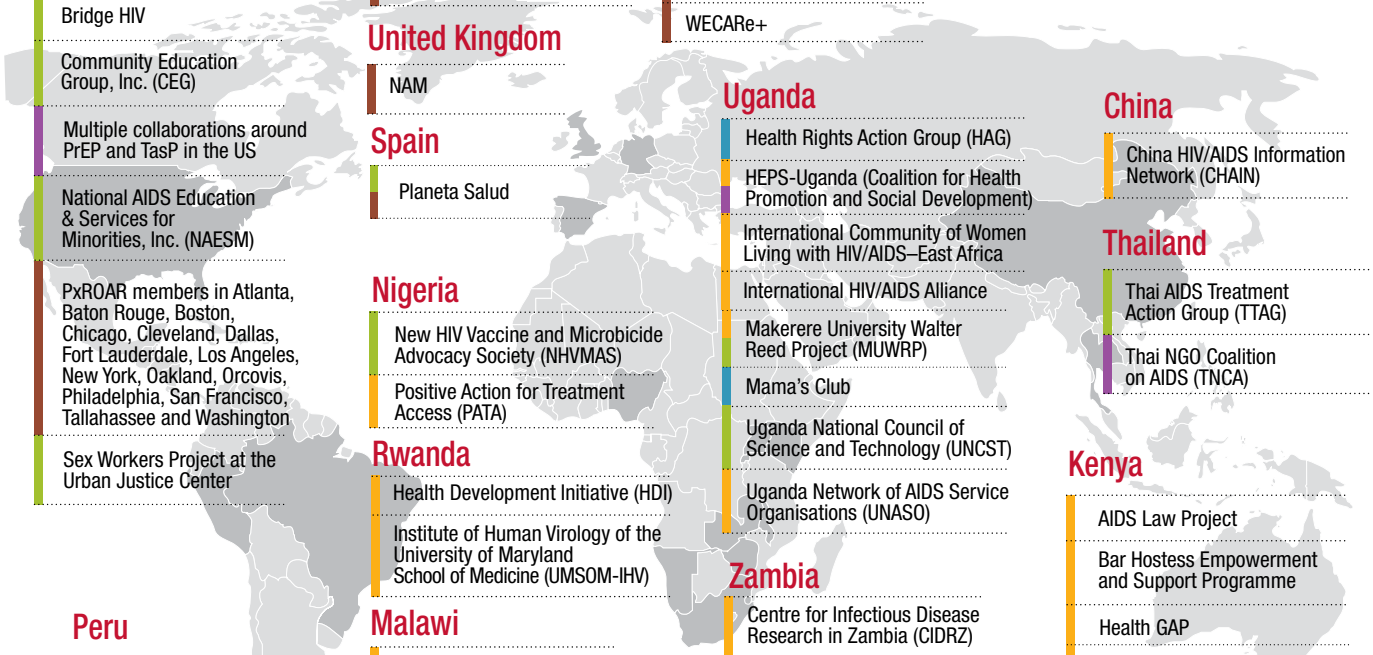
Prevention Research, Outreach, Advocacy and Representation (PxROAR)

The PxROAR program has two goals: to educate its members in HIV prevention research science, implementation and advocacy; and to provide a platform for specific prevention research advocacy campaigns. There are two cadres of PxROAR advocates: one based in the US and one based in Europe. Both groups represent the range of HIV-affected communities.

Women's HIV Prevention Tracking Project (WHiPT)

WHiPT was launched in 2008 to support women's community-based efforts to monitor, evaluate and develop or expand advocacy around new and emerging HIV prevention strategies. The pilot phase, a collaboration with the ATHENA Network, focused on monitoring women's views of and concerns about implementation of voluntary medical male circumcision in five African countries. New WHiPT initiatives focus on tracking issues around hormonal contraceptives and HIV risk, oral PrEP using TDF/FTC for women, and efficacy trials of woman-controlled HIV prevention methods.

Global Prevention Research Advocacy Partnerships



United States
- Be the Generation (BTG)
- Bridge HIV
- Community Education Group, Inc. (CEG)
- Multiple collaborations around PrEP and TasP in the US
- National AIDS Education & Services for Minorities, Inc. (NAESM)
- PxROAR members in Atlanta, Baton Rouge, Boston, Chicago, Cleveland, Dallas, Fort Lauderdale, Los Angeles, New York, Oakland, Orcovis, Philadelphia, San Francisco, Tallahassee and Washington
- Sex Workers Project at the Urban Justice Center

Germany
- German Sexuality and Health Foundation (GSSG)

United Kingdom
- NAM

Spain
- Planeta Salud

Europe
- Migrant African MSM Sexual Health Group in Europe
- WECARe+

Uganda
- Health Rights Action Group (HAG)
- HEPS-Uganda (Coalition for Health Promotion and Social Development)
- International Community of Women Living with HIV/AIDS–East Africa
- International HIV/AIDS Alliance
- Makerere University Walter Reed Project (MUWRP)
- Mama's Club
- Uganda National Council of Science and Technology (UNCST)
- Uganda Network of AIDS Service Organisations (UNASO)

China
- China HIV/AIDS Information Network (CHAIN)

Thailand
- Thai AIDS Treatment Action Group (TTAG)
- Thai NGO Coalition on AIDS (TNCA)

Nigeria
- New HIV Vaccine and Microbicide Advocacy Society (NHVMAS)
- Positive Action for Treatment Access (PATA)

Rwanda
- Health Development Initiative (HDI)
- Institute of Human Virology of the University of Maryland School of Medicine (UMSOM-IHV)

Zambia
- Centre for Infectious Disease Research in Zambia (CIDRZ)
- Treatment Advocacy and Literacy Campaign (TALC)

Kenya
- AIDS Law Project
- Bar Hostess Empowerment and Support Programme
- Health GAP
- Kenya AIDS NGOs Consortium (KANCO)
- Kenya AIDS Vaccine Initiative (KAVI)
- Kenya Medical Research Institute (KEMRI)
- National Empowerment Network of People Living with HIV/AIDS in Kenya (NEPHAK)
- Nyanza Reproductive Health Society (NRHS)
- Partners' PrEP – Thika Site
- University of Nairobi Centre for HIV Prevention & Research (UoN-CHIVPR)
- Women Fighting AIDS in Kenya (WOFAK)

Peru
- Asociación Civil Selva Amazónica
- Epicentro

Malawi
- Centre for the Development of People (CEDEP)

Namibia
- Namibia Women's Health Network (NWHN)

Swaziland
- Swaziland for Positive Living (SWAPOL)

Brazil
- Grupo de Incentivo à Vida (GIV)
- Unidade de Pesquisa de Vacina Anti-HIV (UPSP)

South Africa
- AIDS Legal Network (ALN)
- Centre for the AIDS Programme of Research in South Africa (CAPRISA)
- Desmond Tutu HIV Foundation (DTHF)
- Global Network of People living with HIV/AIDS (GNP+)
- Networking HIV/AIDS Community of South Africa (NACOSA)
- Perinatal HIV Research Unit (PHRU)
- Sonke Gender Justice Forum
- South African National AIDS Council (SANAC)
- Southern African AIDS Trust (SAT)
- Treatment Action Campaign (TAC)
- Wits Reproductive Health and HIV Institute (WRHI)
- World AIDS Campaign

Zimbabwe
- Centre for Sexual Health and HIV AIDS Research – Zimbabwe (CeSHHAR Zimbabwe)
- University of Zimbabwe–University of California San Francisco Collaboration (UZ-UCSF)
- Zimbabwe AIDS Prevention Project–University of Zimbabwe (ZAPP-UZ)
- Zimbabwe Women Against HIV/AIDS, Poverty and Violence (ZWAAPV)

KEY

- Good Participatory Practice Initiative
- HIV Prevention Research Advocacy Fellowship Program
- National Stakeholder Engagement
- HIV PPrevention Research, Outreach, Advocacy and Representation (PxROAR)
- HIV PWomen's HIV Prevention Tracking Project (WHiPT)

International Partners

AVAC has long-standing relationships with a number of international and national groups, product-development partnerships and research networks including:

- AMAG
- amfAR
- ATHENA Network
- BTG Bridge
- Center for Health and Gender Equity (CHANGE)
- CONRAD
- EATG
- Forum for Collaborative HIV Research
- FHI 360
- Georgetown
- GHTC
- Global HIV Vaccine Enterprise
- GNP+
- Health Global Access Project (Health GAP)
- HPTN
- HVTN
- IAVI
- ICW
- Imperial College
- International AIDS Society (IAS)
- IPM
- IRMA
- ITPC
- LSHTM
- MSMGF
- MTN
- PATH
- SAT
- TAG
- UNAIDS
- WHO

AVAC Resources

WEBSITE
www.avac.org

For the latest updates in HIV prevention, visit the **AVAC website**. It includes our publications as well as comprehensive coverage of the full range of biomedical HIV prevention interventions in an easy-to-use format that is searchable by intervention and by topic.

PUBLICATIONS
www.avac.org/publications

AVAC publications aim to translate the complex issues of biomedical HIV prevention research for a range of audiences. We have materials that explain current scientific issues in simple language and other documents that explore the issues of trial participants and affected communities.

DATABASES
www.avac.org/pxrd *and* www.avac.org/researchliteracy

The AVAC website hosts **two searchable databases**: one on biomedical HIV prevention research clinical trials, products and sites, and one that includes research literacy resources for understanding HIV prevention research.

MAILING LISTS
www.avac.org/mailinglists

The **Advocates' Network** is an electronic network for anyone interested in receiving timely updates about developments in the biomedical HIV prevention field.

P-Values is AVAC's monthly bulletin highlighting advocacy work by our partners and stakeholders around the world.

The **Weekly NewsDigest** is a compilation of media coverage, published research, policy news and materials on HIV prevention options.

SOCIAL MEDIA

www.facebook.com/hivpxresearch

www.twitter.com/hivpxresearch

www.youtube.com/hivpxresearch

AVAC
Global Advocacy for HIV Prevention

423 West 127th Street
4th floor
New York, NY 10027
USA

T +1 212 796 6423
F +1 646 365 3452
E avac@avac.org
W www.avac.org

SOCIAL MEDIA
www.facebook.com/hivpxresearch
www.twitter.com/hivpxresearch
www.youtube.com/hivpxresearch

December 2013

423 West 127th Street
4th floor
New York, NY 10027 USA
www.avac.org