

MAKING MESSAGES

and how to untangle them



ANNUAL REPORT 2017

Acknowledgements

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In Memoriam: Mark Wainberg (1946–2017) and Prudence Mabele (1971–2017)

This year's *AVAC Report* is dedicated to Mark Wainberg and Prudence Mabele, both powerful forces in the global fight, who wore many "hats", defied categories and left us too soon. Wainberg was a microbiologist, an AIDS activist and a researcher who was passionate about finding the best treatment regimens for HIV and ensuring access for all in need. Mabele was a sangoma (traditional healer), a health and human rights activist and one of the first Black South African women to publicly state that she was living with HIV—a step that took enormous bravery and was just one of many ways that Pru changed and saved so many lives.

Both Mark and Prudence are remembered for their generosity of spirit, as mentors, friends and makers of common cause with issues intertwined with HIV. As President of the

International AIDS Society from 1998 to 2000, Wainberg made the historic decision to hold the first International AIDS Conference in sub-Saharan Africa. Durban 2000 helped shift the global consensus on whether people with HIV in resource-poor settings should have access to antiretrovirals, and it provided a show of global unity regarding AIDS denialism. Prudence, with her booming laugh and radiant smile, took on HIV and its intersectionalities: TB, youth, poverty, women's status in society and the right to health. She was the first to the microphone to speak truth; the first to belt out just the right song at the right moment; and she was never afraid to call out injustice wherever she saw it.

We carry them with us always. Rest in peace and power, Mark and Pru.

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LETTER FROM THE EXECUTIVE DIRECTOR

Start Making Sense!

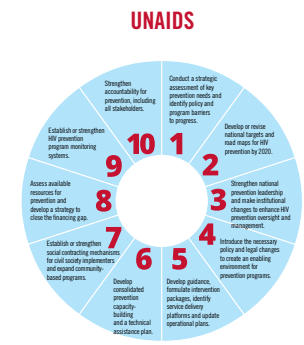
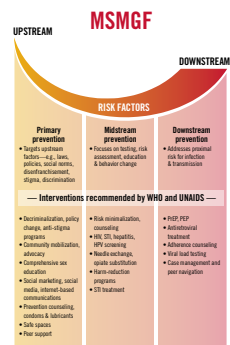
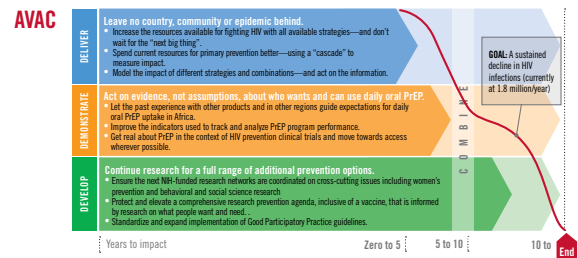
In this year’s AVAC Report—*Mixed Messages and How to Untangle Them*—we have set ourselves the task of clarifying the profoundly complex field of biomedical HIV prevention and research. This is never an easy task, but it is made all the more complicated—and exciting—in the current environment.

One definition of “mixed message” is “a showing of thoughts or feelings that are very different from one another.” Based on this, the term “biomedical prevention” is itself a mixed message, since it suggests that there are prevention strategies that can be extricated from the messy reality of human behavior, social relations and structural arrangements that preserve and exacerbate inequalities. As the Global Forum on MSM & HIV points out (see Figure 2, p. 5), all biomedical options are fundamentally social in that they involve relationships with our bodies, partners, clinics, communities and countries.

So, yes, we muddy the waters by even using the term “biomedical prevention”. And yet, we do—as we have for the past 22 years. Preventing new HIV diagnoses depends on wresting clarity from complexity, and not side-stepping difficult issues. We need biomedical choices that work for all bodies, at all times. What makes them “work” is social, behavioral and structural context. It involves funding, collaboration, legal protection and a healthy dose of patience as new things like daily oral PrEP become familiar and the “next big ideas” that generate so much excitement—e.g., injectables, implants and vaccines—wind their way through the complex product development process.

Three Ways of Making Sense of HIV Prevention

The next few pages show full-scale images of different conceptualizations of prevention, as developed by AVAC, the Global Forum on MSM & HIV (MSMGF) and UNAIDS. Each has strengths and, undoubtedly, omissions. AVAC’s “3D” graphic emphasizes the need to develop new tools while demonstrating the effectiveness of emerging options and delivering, at scale, what is available today. UNAIDS omits elements of this “research-to-rollout” continuum, and leaves the definition of prevention out—focusing on the “how” rather than the “what”. MSMGF’s view is a clear picture of the various levels at which prevention operates in the context of today’s tools, but it doesn’t tackle the funding gap. Taken together, they—and other visualizations not shown here—make up a whole that may be more than the sum of its parts, but only if we work together to ensure that there is consistency in the messages and actions, no matter what’s put in or left out of the picture.





RECOMMENDATIONS

Make These Your Messages

1

Systemic prevention (such as long-acting injectable antiretrovirals or a vaccine) is a prevention priority—but not a standalone solution.

Stop saying: *Long-acting injectable options are what's needed because people can't or won't use other options.*

Funders and decision-makers involved in prevention research need to develop products that people will want and use. This means asking people—via well-designed, human-centered research—and acting on the answers. Who's accountable? Many groups—including the US NIH's Division of AIDS, which is reevaluating its trials network structure and scientific priorities. (See page 7 for more.)

2

Daily oral PrEP as a prevention tool is struggling in some contexts and soaring in others.

Stop saying: *Lots of people don't want to take oral PrEP, so it's failing.*

People using PrEP are the ones whose “non-adherence” is counted, but there are other defaulters to pay attention to, including governments and funders who are advancing disjointed programs without involving civil society, including the people most in need, such as young women and key populations. When these programs falter, it's not the user's fault.

When the people who need it feel ownership of the product and the program, any strategy—including PrEP—can work. Oral PrEP definitely isn't for everyone, but many people who might want it still need a chance to try. (See page 21 for more.)

3

We're on track to epidemic control if and only if the funding gap is closed, rights infringements and violations are addressed, civil society is involved and comprehensive prevention and research are prioritized in a way that has never been seen before.

Stop saying: *A country or community's progress to date is the same as its future path.*

Today there are only a few countries that are even possibly on track to achieve epidemic control. This good news leaves raging epidemics elsewhere, particularly in places where human rights are in shambles and HIV is concentrated in key populations. This isn't the kind of partial progress we can settle for. (See page 31 for more.)

Figure 1 The UNAIDS 10-Point Plan for Making Progress on Prevention



Source: UNAIDS. 2017. *HIV Prevention 2020 Roadmap*. <http://www.unaids.org/en/resources/documents/2017/hiv-prevention-2020-road-map>.

In the pages that follow, we delve deep into a vast, disparate range of topics. The commitment to clarity starts at home, so here's how we see it all fitting together:

First: It is a dynamic time for HIV prevention. There are more trials of new concepts, more programs for daily oral PrEP and more attention to HIV prevention in country plans than a year ago (or ever before). This is fertile ground for progress. Our Report focuses on challenges and proposed fixes, but the overall message is that science continues to deliver and needs to be sustained.

Second: Issues and themes recur across institutions, so sometimes the best way to see the big picture is

with a tight focus. In Section 1, we offer a deep dive into the decisions that the National Institutes of Health's Division of AIDS (DAIDS) will make about the future of its HIV clinical trials networks. While these decisions are happening in real time and affect many countries, communities and clinical trials, the DAIDS networks aren't even the sum total of US-funded research, let alone global research endeavors. However, the key recommendation we make is for all research stakeholders: don't make the mistake of thinking there are shortcuts in HIV prevention. No single shot (or series of shots) or implant will solve adherence issues and therefore make pills, gels and rings obsolete.

Third: The inconvenient truth about HIV funding and progress towards "Fast Track" targets is the most important truth today. There isn't enough money; the progress isn't sufficient or consistent, even though there are places where the context is promising. We must not confuse progress, however real, with a guarantee of success.

Since our last *AVAC Report*, we have seen an expansion of global efforts focused on prevention for HIV-negative individuals. This broad category of efforts to prevent HIV acquisition encompasses everything from daily oral PrEP to harm reduction to male and female condoms, and it has the public health moniker of "primary prevention". This sets it apart from ART for people living with HIV, a "secondary" prevention strategy with proven benefits for individual health.

The list of efforts is long and overlapping: a Global Prevention Coalition launched in October 2017 by UNAIDS and UNFPA; a new HIV Prevention 2020

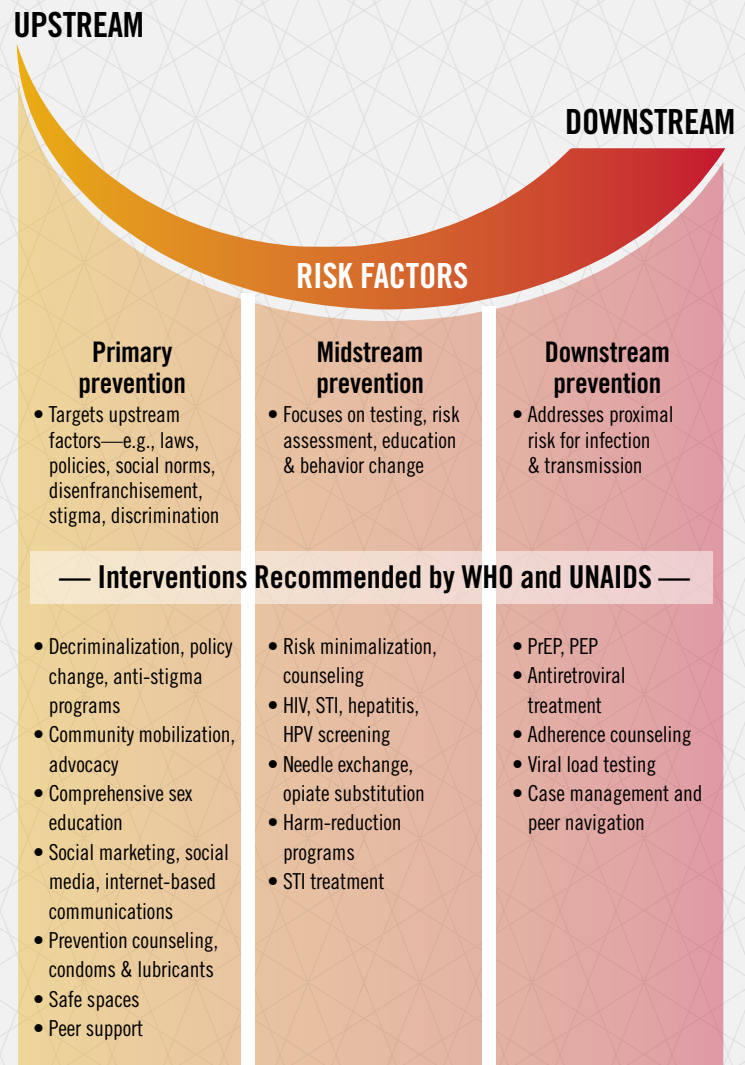
Road Map; a Global PrEP Working Group launched by WHO; and so on. Targets for primary HIV prevention are now understood to be as important as UNAIDS' "90-90-90" targets focused on HIV testing, linkage to ART and virologic suppression that have been the main focus for so many years. It's terrific that the binary seems to belong to bygone days.

But where, aside from shuffling through position papers and roadmaps, does that leave us? Quite simply, with a mixed message in which the policies say one thing and the situation for people living with and at risk of HIV says something else entirely. Primary and secondary prevention are essential and "epidemic control" is possible, but the funding is missing, and the commitment to comprehensive programming—including continued research for new strategies—is uneven.

These mixed messages are perhaps most pronounced in the context of prevention for women and girls, and all those who are collectively known as "key populations". The draft UNAIDS/UNFPA "scorecard" for its Prevention Road Map¹ advances clear metrics for tracking VMMC and PrEP as part of general prevention, but when it comes to the urgent needs of key populations, it veers away from specifics. In a world where homosexuality and sex work are explicit or implicit grounds for surveillance, violence, imprisonment and intimidation, providing a condom and an HIV test is not effective prevention. Yet this is often what counting "prevention interventions offered" amounts to. It makes no sense. The real answer lies in highlighting the targets for structural change that UNAIDS set out in 2016—and then taking bold activist steps to achieve them.

The main thing that cuts across all of these issues is resources. The total estimated investment in global

Figure 2 **MSMGF's Model for Conceptualizing Prevention**



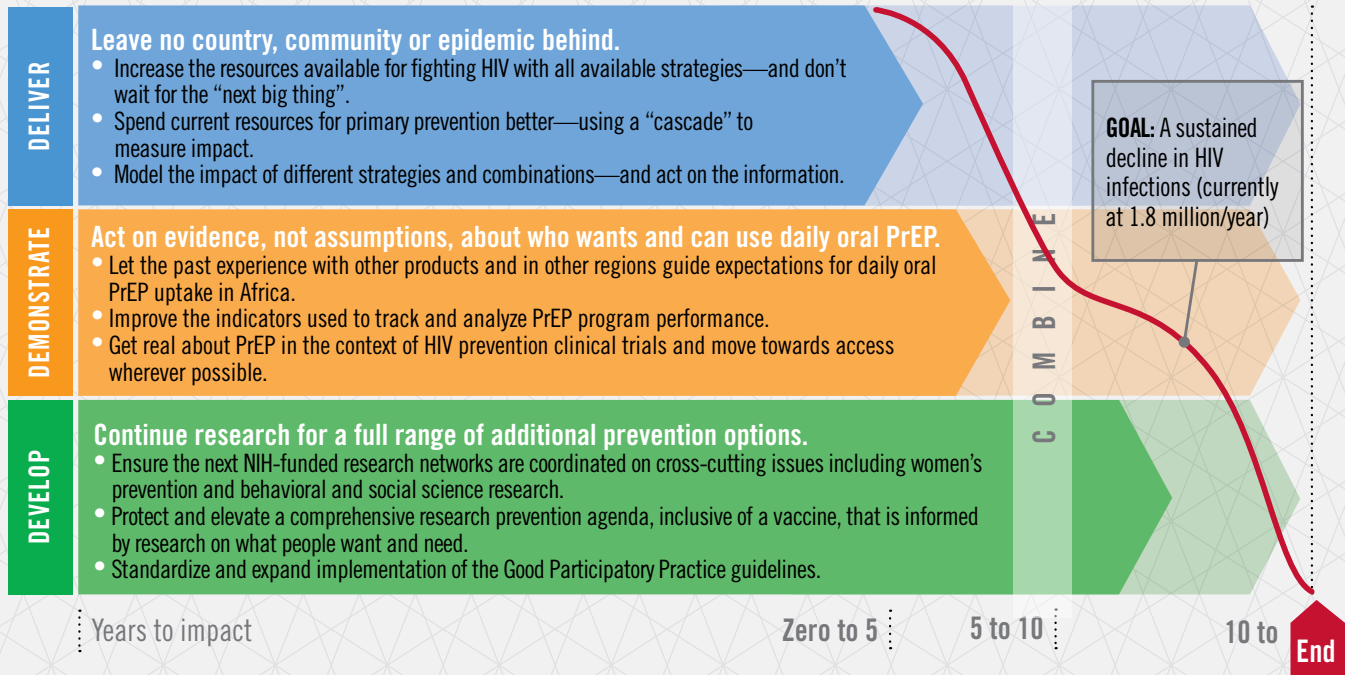
Source: Global Forum on MSM & HIV. 2017. *Reconsidering Primary HIV Prevention*.

AIDS must increase to US\$26.1 billion by 2020 if the Fast Track targets are to be met. The world was seven billion dollars short of this in 2016, and annual funding is already declining year-on-year. The rhetoric is that "flat is the new normal" and that efficiencies must be found to save money, which can then be reinvested. PEPFAR's updated strategic plan signals another shift in funder/implementer strategy.² The program says that it will now focus resources

¹ UNAIDS. 2017. *Towards a Global HIV Prevention Coalition and Road Map*. http://www.unaids.org/sites/default/files/media_asset/towards-global-HIV-prevention-coalition-and-road-map_en.pdf.

² PEPFAR. 2017. *Strategy for Accelerating Epidemic Control*. <https://www.pepfar.gov/documents/organization/274400.pdf>.

Figure 3 **AVAC's "3D" View of the World: 2017 and beyond**



and attention in 13 countries that are on track to achieve epidemic control. Meanwhile, non-focus countries—among others—will receive less attention and money, even as their epidemics grow. Russia, for example, has the highest number of HIV cases in Europe, with incidence and AIDS deaths rising year-on-year. None of the interventions with known efficacy for HIV prevention, including harm reduction programs, ART on demand, PrEP or tailored interventions for drug users, sex workers and MSM are available to scale. Russia is not an exception, but a caution and a call to action for all.

At the country level, no amount of prioritization or boosting of political will can ever improve prevention if the resource envelope is consumed almost entirely by commodities (e.g., antiretroviral medications, HIV test kits etc.) and meeting the needs of a high-quality, rights-based ART program.

A final word on why this year's focus is on saying what you mean—and acting on it.

To work on the frontlines of HIV/AIDS is to defend freedom of speech to its fullest extent and to deplore all forms of violence—physical, psychological, structural—that are incited or permitted as a result of that speech. We know that often-silenced voices must guide the conversation—see page 36 for some of the ways that AVAC and our partners are working to speak truth to power. We may not always agree, but we're here, we're listening and we're ready to add our voices to those of our allies until this hard and necessary work is done.

Mitchell Warren
Executive Director, AVAC

No Shortcuts

RECOMMENDATION

1

Make this your message: ***Systemic prevention (long-acting injectable antiretrovirals or a vaccine) is a prevention priority—but not a standalone solution.***

Stop saying: *Long-acting injectable options are what's needed because people can't or won't use other options.*

Funders and decision-makers involved in prevention research need to develop products that people will want and use. This means asking people—via well-designed, human-centered research—and acting on the answers. Who's accountable? Many groups—including the US NIH's Division of AIDS, which is reevaluating its trials network structure and scientific priorities.

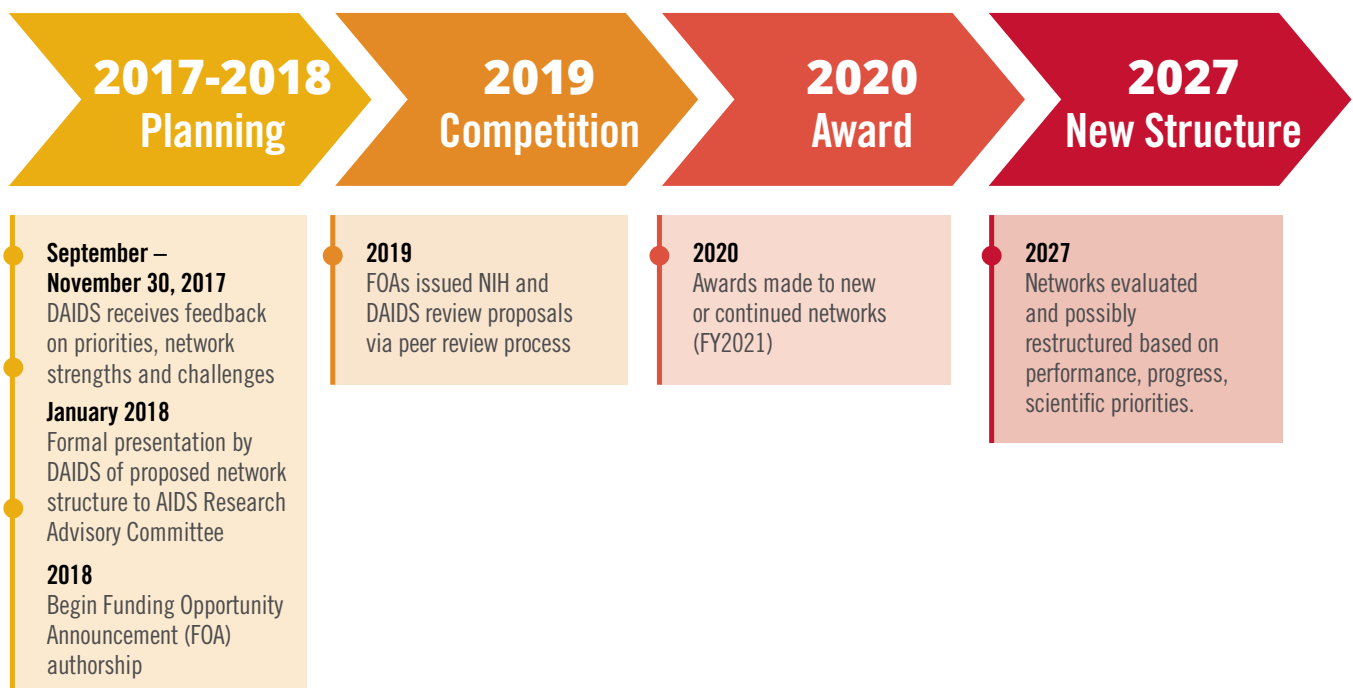
On November 30, 2017 the US National Institutes of Health (NIH)'s Division of AIDS (DAIDS) closed the public comment period for input into the future of its clinical trial networks. The US government funds about three-quarters of the global budget for HIV prevention research. The agencies that receive these funds (see page 15) do not break down budgets by research entity, but with a budget of US\$1.4 billion in FY18, the US National Institute of Allergy and Infectious Diseases receives about 46 percent of the total NIH investment in HIV research. Money from this budget line flows to the DAIDS-supported clinical trials networks, including the HIV Vaccine Trials Network, the Microbicide Trials Network and the HIV Prevention Trials Networks. With so much heft in its own budget and as part of the US research investment, DAIDS and its decisions matter for the overall direction of the field. In the pages that follow, we dive deep into what DAIDS' networks have done to date and what we need and expect them to do in the future. But the recommendations we foreground apply to the whole research enterprise: governmental, philanthropic and private funders alike. Chiefly: now is not the time to settle for a single approach to HIV prevention. A robust research agenda must align with the needs and preferences of the people most at risk of HIV. This means long-acting reversible methods, vaccines and user-controlled methods, as well. As the contraceptive field has taught us, choice isn't a luxury, it's a necessity for programmatic health. This is a message for the whole range of stakeholders engaged in HIV prevention research.

So what does this mean for DAIDS and its networks? The current structure (see pages 10-11) will be in place through 2019, and the new network structure will be in place from 2020 to 2027. Decisions today must intentionally and explicitly consider future needs. Much of the debate today is about what those needs actually are, how we know and who decides. AVAC and our civil society allies know that people most at risk of and living with HIV must lead these discussions, and so we begin this section with the core premises developed by a civil society collaborative focused on DAIDS-related advocacy.

Civil society's core premises for prevention³

- ▶ Cisgender and transgender men and women, along with children and adolescents, deserve safe and effective HIV prevention options that provide easy, efficient protection, enabling all to lead vital, healthy lives.
- ▶ Those same individuals have numerous and diverse sexual health needs, beyond protection from HIV, including protection from other sexually transmitted infections and—for many women—managing fertility decisions.
- ▶ Individuals have varying needs across their lifespans; effective HIV prevention packages will include an array of options to meet those needs.
- ▶ Desire and sexual satisfaction are important considerations in the development of any new technology intended for prevention of HIV and other sexually transmitted infections, since these factors inevitably affect product adoption and continued use.
- ▶ Those most in need of new HIV prevention strategies should be substantively involved in research prioritization and conduct, both via stakeholder engagement and in senior scientific leadership that is representative of the most affected populations.

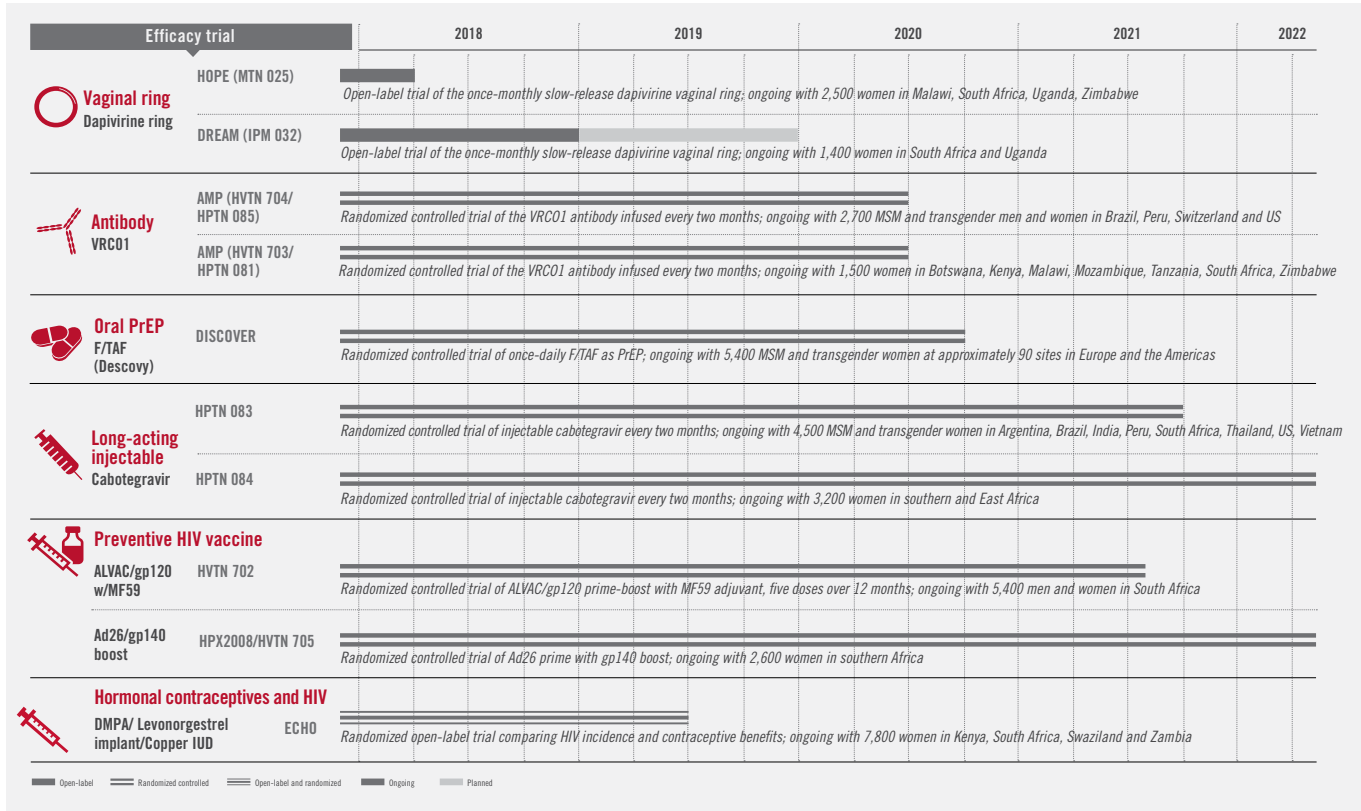
Figure 4 **Timeline for DAIDS HIV Trials Network Recompetition**



Adapted from Dr. Carl Dieffenbach, Director, Division of AIDS.

³ Developed by an *ad hoc* group of advocates based primarily in the US, in coalition with non-US partners, that mobilized in early 2017 to develop core premises on which to build a DAIDS-focused advocacy agenda.

Figure 5 The Years Ahead in Biomedical HIV Prevention Research



Using these core premises as a foundation, we recommend the following:

Set up structures to address cross-cutting and user-focused questions

As shown on pages 10-11, the DAIDS-funded networks have merged and split into different focal areas over the years. The current proposal would merge the networks focused on prevention (HPTN) and microbicides (MTN), and leave others intact. Whatever the final structure, the networks must be better coordinated and more consistent than they have been in the past. Specifically, the new structure must explicitly incorporate mechanisms including dedicated budget lines, cross-cutting research agendas and cross-network coordinating mechanisms that focus on:

- Bonafide behavioral and social science research (BSSR). This starts with making clear distinctions between the methodologies and purposes of these related but distinct disciplines, includes ensuring consistency in approaches to prioritizing



Recommendations for Network Structure and Cross-Cutting Issues

- ▶ A comprehensive, cross-network behavioral and social science research agenda that supports consistency in approaches and focus across networks. It should be reviewed on an annual basis and updated as needed.
- ▶ Establishment of either a network core or cross-cutting mechanism that guides thinking and investment related to product introduction from the earliest stages of product development.
- ▶ Institutionalized and consistent research engagement across networks via a funded community and stakeholder engagement division within the core of each network and/or via a cross-network mechanism. This will ensure consistent implementation of the Good Participatory Practice (GPP) Guidelines for stakeholder engagement at site level and, importantly, beyond trial communities.

Figure 6 **NIH-Funded HIV Trial Networks: A family tree**

1991
-
1998

The beginning. The Pediatric AIDS Clinical Trials Group (PACTG) and the AIDS Clinical Trial Group (ACTG) were the primary US-funded networks funding research on treatments to block viral replication and treat opportunistic infections in adults and children living with HIV. ACTG 016 was the first trial of the antiretroviral AZT. The drug, which is still used today as part of combination therapy, was tested on its own as “monotherapy”. HIV Network for Prevention Trials (HIVNET) was focused on HIV prevention trials, including vaccine and non-vaccine studies such as HIVNET 016, a landmark trial that found two doses of nevirapine (one to mother and one to newborn) slashed rates of vertical transmission. The AIDS Vaccine Evaluation Group (AVEG) focused on early-phase vaccine research. Established in 1989 and funded through 1997, the Community Programs for Clinical Research on AIDS (CPCRA) was an NIH-funded research enterprise that focused on community-driven and -based treatment research.

1999
-
2005

An era of expansion. Under the network structure launched in 1999, the HIV Vaccine Trials Network (HVTN) was distinct from the HIV Prevention Trials Network (HPTN). In this period, the HPTN launched the pilot phase of HPTN 052, the landmark study that showed that initiating antiretroviral treatment in people living with HIV at CD4 cell counts of 500 or above improved the clinical health of individuals and reduced the risk of onward transmission to primary sexual partners. The same period also saw the launch of the Step and Phambili vaccine trials by the HVTN.

2006
-
2012

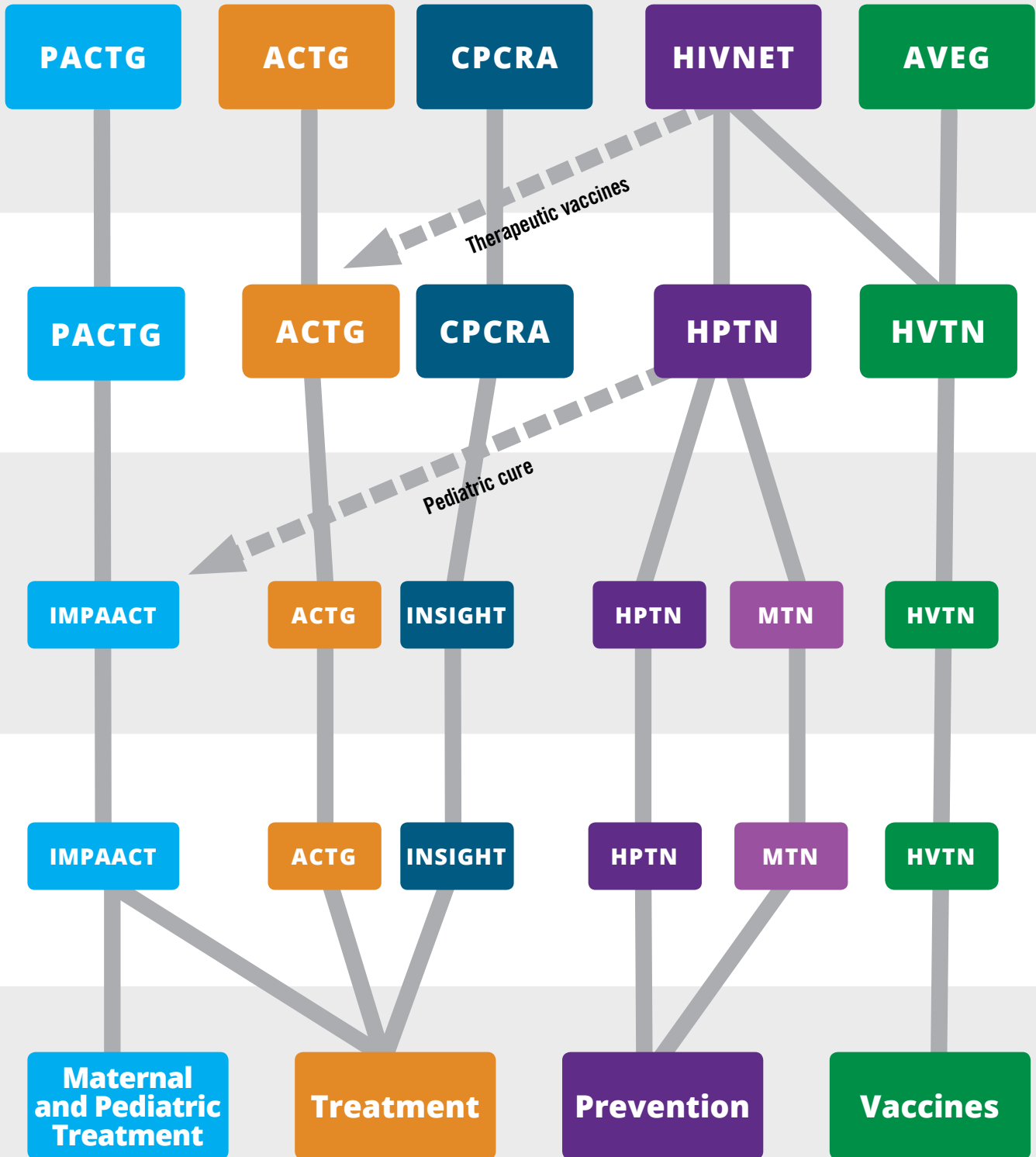
The “women’s prevention” moment. The Microbicide Trials Network (MTN) received funding in 2006 for trials focused on vaginal and rectal topical products (e.g., gels, rings, suppositories etc). In this period, the network launched VOICE—a study of oral PrEP and topical vaginal tenofovir gel—as well as trials of rectal microbicides. The INSIGHT network was created as a merger of two previous treatment-focused groups, and it launched ESPRIT, SMART and START, all trials of treatment in people living with HIV. They were designed to understand when to start ART, whether treatment interruptions were possible and how best to deliver lifelong ART. IMPAACT was launched as a merger of the PACTG and the perinatal science working group of the HPTN. During this time, initial results from HPTN 052 were released, showing benefits of treatment initiation at CD4 count above 500. Additional data were released from non-network PrEP and microbicide trials.

2013
-
2020

The era of evidence. By 2013, non-network trials of a vaccine and a microbicide had shown efficacy. Daily oral PrEP was approved by multiple regulators, and in 2015 it was recommended by the WHO. Nearly nine million voluntary medical male circumcision procedures had been conducted worldwide, following clinical trial evidence released in 2006. The MTN moved ahead with rectal microbicide research and one of the two efficacy trials of the dapivirine ring, which showed modest efficacy. The HVTN and the HPTN jointly launched two large-scale antibody-mediated prevention (AMP) trials. HPTN also launched two long-acting injectable efficacy trials, and the HVTN began two large-scale vaccine trials.

2021
-
2027

The future? NIH-funded prevention research networks will need to be able to identify and evaluate prevention options that people most at risk of HIV can use safely and consistently—in the context of an array of first-generation strategies like daily oral PrEP, dapivirine ring and possibly even long-acting injectable PrEP. The trials will be more complex to explain and recruit for and the science more sophisticated. Coordination around approaches to product selection, planning for product introduction and research that incorporates the needs and preferences of those most at risk of HIV will be as important as they have ever been.





The Enterprise Evolves

The Global HIV Vaccine Enterprise, an alliance of independent organizations dedicated to HIV vaccine research, formed an official partnership with the International AIDS Society in 2017, marking an end to its status as a free-standing entity and the beginning of a new chapter in its work. The Enterprise began as a conceptual collaborative framework for uniting the field. It was articulated in a *Science* article in 2003, and in the ensuing years, it has convened a range of virtual and in-person consultations and served as the secretariat for the “big tent” that houses the diverse stakeholders engaged in the search for an HIV vaccine. It also oversaw the launch of the HIV Research for Prevention (HIVR4P) conference, the only gathering devoted exclusively to biomedical prevention.

Since his appointment in 2012, the Enterprise was led by AVAC founder and former board member Bill Snow, who retired in late 2016. The same period has seen advances in vaccine and passive immunization clinical trials, basic science work on antibodies and immunogens, and much more. In its new iteration, the Enterprise programs will be housed at the International AIDS Society, which will convene the vaccine field on key issues and be responsible for HIVR4P. As the pages of this Report detail, there are major challenges and opportunities for the HIV vaccine field and the broader prevention enterprise today and in the years to come. AVAC looks forward to working with the IAS in the forthright and transparent engagement on these issues.

questions, acting on answers and a thorough, funded approach to incorporating BSSR into clinical trials and to funding standalone work.

- Market research with potential users early in the research life cycle to understand potential product preferences, barriers and facilitators of future uptake etc.
- Research that addresses different routes of transmission and is funded and prioritized based on global burden/need.
- Product introduction and implementation science that provides a framework for identifying and advancing products people will use and for products that work in clinical trials, a mechanism for handing them off to groups with experience in product introduction and implementation science.
- Research with women in all their diversities.
- Research with infants, children and young people.
- Community and stakeholder engagement via implementation of the Good Participatory Practice guidelines beyond individual trials and trial sites.

We do not think that the current networks consistently value this work. The existing structure does not have a way to correct for this heterogeneity, which includes different policies with respect to trial conduct and standard of prevention, community and stakeholder engagement at the site and above site level, and incorporation of behavioral and social science research into trials. The MTN and IMPAACT are the two networks with an explicit focus on the prevention and treatment needs of cisgender women and adolescent girls. HVTN and HPTN both have significant investments in efficacy trials in women, particularly in sub-Saharan Africa, but they have not advanced these trials under an overarching women’s prevention research agenda or been guided by a set of core principles about how to talk about, implement and act on the findings of trials of products that women can use. If explicit steps are not taken to incorporate the strengths of the existing networks into the new structure, they could be lost or diminished, to the detriment of all. Strengths to maintain include:

- An explicit focus on the needs of cisgender girls and women and of all people who engage in anal sex, as articulated by the Microbicide Trials Network (MTN) and IMPAACT, which also focus on children and infants.
- Engagement of stakeholders, including civil society and other key decision-makers above the site and trial community level, to ensure that new trials and interventions are understood and adjusted based on real-life national contexts and community concerns. Each network has undertaken engagements at this level that have worked, and some have forged more durable partnerships. HPTN is the only network with a distinct ethics review process (distinct from regulation) that includes the Ethics Working Group and inclusion of someone with a particular ethical expertise in protocols. The MTN has shown a robust commitment to GPP at and beyond site and trial level. These relationships and best practices can be captured through the review and solicitation of civil society input—and must not be lost in the new network structure.

No shortcuts via long-acting products and no shortsighted plans that leave out implementation science

Dr. Carl Dieffenbach, the head of DAIDS, is a long-time friend and colleague of many new and veteran prevention advocates. He doesn't mince words, and in the straight-talking tour conducted in the run-up to the recompetition, he's been clear that the priority for the next generation of prevention is developing a product that's long-acting and systemic: a shot of antiretrovirals, a vaccine, an infusion of antibodies. The rationale? Many people have multiple vulnerabilities or sites of exposure. People have vaginal and anal sex. They have penetrative sex, and not all use the terms "vagina" and "anus" but prefer "front hole" and "back hole" or other non-gendered anatomical names. People have all types of sex and use drugs. So a prevention tool that protects all bodies and body parts, and one that works in the

Table 1 Prevention Paradigm, 2017–beyond

Different strokes for different folks		
Methods	Contraception	HIV prevention
Behavior	✓	✓
Barrier methods	✓	✓
Gels	✓	✗ <i>Proof of concept, but no product likely in near future</i>
Rings	✓	✓ <i>Under regulatory review</i>
Oral pill	✓	✓
Injectables	✓	? <i>1 LAI, 1 bnAb, 2 vaccines in Phase III; others in preclinical</i>
Implants	✓	? <i>Multiple in preclinical</i>
Surgical procedures	✓	✓
Treatment	N/A	✓

blood too—and lasts for a long time—has a lot going for it. And that's what Dr. Dieffenbach has argued: "We must develop prevention modalities that are safe, desired and highly effective. These tools should provide systemic protection irrespective of route of exposure." That's something that topical products can't do.

As AVAC and many other stakeholders have said, the fact that women in some trials of gels, rings and pills didn't use the product consistently says as much—or more—about research and how it is run as it does about what women want. Clinical trials may offer health services, counseling or other benefits that are highly desirable. Low adherence in the context of a trial does not mean that products won't be used in real life. And yet, four years later, people (including DAIDS leadership and, sometimes, other advocates)



Recommendations for Scientific Agenda and Decision-Making

- ▶ Investment in a product portfolio supported by scientific and behavioral/social scientific evidence about clinical efficacy and needs, preferences and priorities of prevention users, providers and payers.
- ▶ A cross-network strategic collaboration mechanism with budgetary and decision-making authority that guides the overall agenda with transparency and accountability.
- ▶ A fast-track, “hands-off” approach to implementation research on interventions, with an emphasis on efficiency, engagement with national governments and integration into combination prevention packages.

are confusing what is known—many women in trials did not use the products—with what is believed: women do not want and will not use the same products once efficacy is known. Some people can and will take daily oral PrEP. Some can and would use a microbicide. It is inaccurate and potentially dangerous to say otherwise.

Dr. Dieffenbach has also served as the spokesperson for the NIAID position that trials to date show that women don’t want to use adherence-dependent methods. In a blog on the issue, he wrote, “The candidate microbicides currently in the research pipeline have limited proven efficacy, and it has not been demonstrated that the most vulnerable users would choose or adhere to these products. Coitally dependent products, including condoms, require use with each sex act, creating a major adherence challenge.” In an interview with AVAC he said, more succinctly, “Women have run away from gels.” This statement isn’t true. In trials, women didn’t use the gel consistently; but that could be because of the research context, not the product.

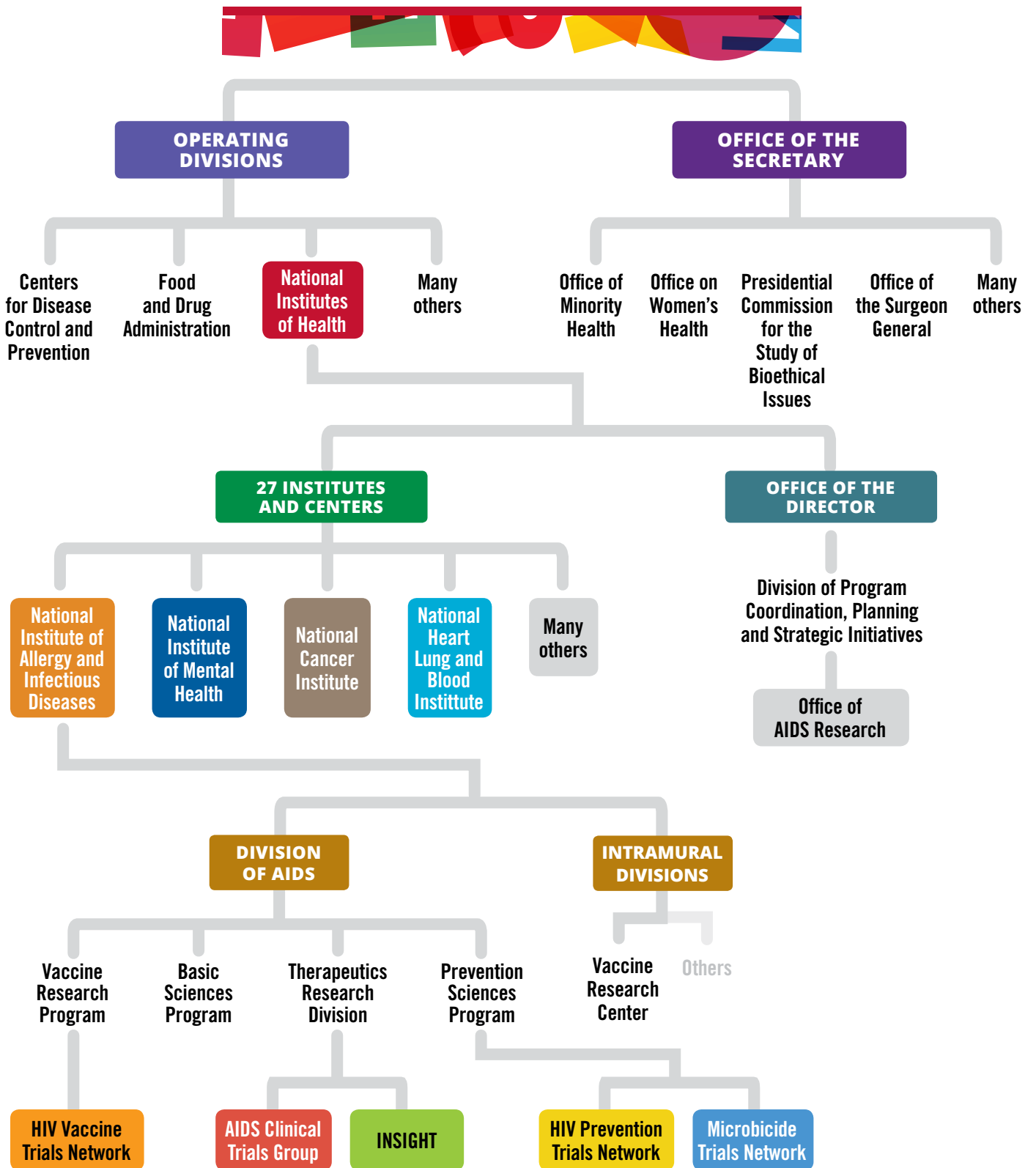
In response, advocates for specific products like topical microbicides have acted up and fought back, and AVAC has been proud to be part of this organizing. We have also been part of efforts to accelerate and support the introduction of oral PrEP, working alongside advocates and, in a newer role, providing technical support at the country and policy-maker level. And we remain steadfast in the pursuit of longer-acting methods and a vaccine. Women at risk of HIV need access to a range of options for simultaneously controlling fertility outcomes and reducing the risk of HIV. Research on these multipurpose technologies should be a priority for the next generation of trials.

All of this work—and much more—supports two conclusions that we feel must guide both DAIDS and all other research funders:

- ▶ There is no rationale either in public health or in HIV prevention for an exclusive focus on long-acting systemic products.
- ▶ Products are only as good as their programs, and today’s clinical trials must anticipate introduction like never before. An emphasis on injectables without a solid plan for product introduction research will lead to an innovation pileup—lots of products but no working programs and no benefit to people.

For DAIDS and others, acting on these points means seeking out and integrating different types of information on preference, feasibility and more, and then being guided by those decisions, which cannot be confined to product siloes. The vaccine agenda cannot advance in parallel with the long-acting injectable agenda, and so on. In the DAIDS network context, there is no cross-network coordination mechanism within the mandate. The Office of HIV/AIDS Network Coordination (HANC), which works across the networks, has portions of this mandate in its mission statement, but it is not driving product portfolio decisions or comprehensive agendas of the type described in this section. The Office of AIDS Research (OAR) measures research against goals set

Figure 7 US HIV Research: A family tree



Deprioritizing Women's Lives in 2017

Playing with the Fine Print: Hormonal contraception and HIV risk

In early 2017, the World Health Organization (WHO) announced that it had reclassified progestogen-only contraceptives (such as DMPA, also known as Depo-Provera) in its Medical Eligibility Criteria (MEC) system, that is designed to support global consistency. This change shifted DMPA, the bi-monthly injectable NET-EN and a subcutaneous form of DMPA (marketed as Sayana Press (SP)) from a classification of “MEC 1” to “MEC 2.” A product with an MEC 1 classification can be used without restrictions; a product with a MEC 2 is one for which the “benefits outweigh the theoretical or proven risks” of the product.

WHO emphasized that this shift was motivated by a review of the available evidence and a commitment to women's rights to full information about the products they use in their bodies. This was a welcome validation of principles that women working on this issue have articulated for years.

But the celebration—such as it was—has been short lived. In the months following the MEC shift, not a single country has shifted its messaging to provide HIV-negative women with clear information that DMPA, NET-EN and SP all have clear benefits *and* could possibly and theoretically increase women's risk of HIV. Instead, the majority of programs that have engaged the MEC at all have seized on fine print from the MEC guidance stating that no woman should be denied DMPA or other methods because she is at high risk for HIV. This is absolutely true, and women working on this issue have made the informed choice of methods a clarion call. However, limiting the message to the fact that women deserve to choose their own method—without the counter-

balancing information that MEC 2 choices may, theoretically, affect a woman's HIV risk—is inadequate and selective at best. SP is the focus of a dynamic push involving FP2020, PATH, African countries, the Bill & Melinda Gates Foundation and many other funders. It's an easy-to-use method that could expand access to contraceptives in the many parts of the world where women struggle to gain access to comprehensive services. We're completely supportive of this and believe that the strengths of this method, and of the women who might use it, are such that full information about theoretical risks could be conveyed without jeopardizing introduction.

2018 will likely bring the results of the ECHO trial, a randomized study evaluating how DMPA, the Jadelle implant and the copper IUD affect women's HIV risk. Even this trial, as important as it is, won't settle the question, since NET-EN and SP (not included in ECHO) have different traits than DMPA. If ECHO does find that DMPA increases women's risk of HIV, there will be no fine print to hide behind. Both NET-EN and SP will be impacted unless or until further research is done to see if they also heighten HIV risk. WHO, along with countries with high HIV prevalence and high DMPA use (largely East and Southern Africa) must start developing messages and programs that provide broader contraceptive choice, information and comprehensive HIV prevention, including daily oral PrEP where available. This way, the many women who do want to continue using DMPA or other methods will be able to do so whatever the findings. Those for whom a theoretical risk is of concern will be able to choose an alternative. This is a win-win situation that must be pursued. There is no time to lose.

The Global Gag Rule: An active front in the war on women

It's a dangerous time to be a woman on planet Earth. The past year has brought an assault on the programs, services and funding for comprehensive, evidence-based sexual and reproductive health services that all humans deserve, both in the US and worldwide. In the US, this year has seen a reckoning with the pervasiveness of sexual violence in women's lives—though the cases making headlines are largely focused on white men and women, leaving issues of race and class still under-discussed. There are many fronts in this fight—and in every instance, strong, resilient women and their allies are banding together as peaceful warriors, focused on their rights and those of their daughters and sisters, comrades and friends.

All of this work is negatively impacted and sometimes endangered by the expansion of the Global Gag Rule (GGR), as implemented by the Trump Administration in 2017. The GGR has historically barred foreign NGOs receiving US family planning funding from counseling about, referring to or advocating for the legalization of abortion as a family planning method. The expanded GGR applies this restriction to all US global health spending—approximately US\$8 billion in aid. It also bars countries from using funds from any source (including non-US funds) for abortion-related activities, as a condition for receiving US funding.

The damage is already underway. In an October 2017 report, Human Rights Watch found that in Kenya and Uganda, GGR-related changes “have resulted in a loss of training and equipment from nongovernmental groups for government health clinics, and widespread confusion about implementation.” In many contexts, confusion is leading NGOs to scale back services or messages that they may not even be required to shift.

A six-month review of the policy was underway at the end of 2017. It is imperative that the State Department

act on these early warning signs and do the following:

- Take steps to strengthen and expand comprehensive sexual and reproductive health programming for women, including post-abortion care, contraceptive access and HIV prevention. The purpose of the GGR is not to gut women's health services or to demolish the progress made in integrating HIV and SRHR to date. The State Department should protect its investments in the lives and health of women and children.
- Communicate clearly and frequently about what GGR compliance is and is not, to forestall any over-interpretation, chilling effect or unnecessary cessation of activities and services.
- Conduct ongoing and annually reported reviews of the impact of the GGR, including data on deaths from unsafe abortions, and report these findings to Congress.
- Grant case-by-case exemptions to mitigate the policy's harm.

AVAC itself has been impacted by the GGR, as some of our work on prevention research advocacy is funded by USAID, and includes onward granting to foreign NGOs working on HIV prevention, women's health and rights and other intersecting issues. As a failure to sign the GGR would have cut off significant funding for civil society work in this space, we undertook, starting in January 2017, intensive consultations with the groups that would be impacted to determine the course of action for ourselves and our partners. The decision was taken to accede to GGR compliance in AVAC's grant agreement with USAID. We accompanied this compliance, however, with the explicit statement that we opposed the policy and would work to mitigate its harm at every turn. Our partners continue to receive funding and to work without restriction on their core issues. It is a draconian and anti-health choice, and one that no coalition should have to face. We are grateful to our allies who have guided us through and now live with the consequences of our decision.

by a consultative process but has little to no recourse if NIAID disagrees with its priorities. NIAID itself must practice true transparency and coordination for these networks, perhaps via its existing Strategic Working Group, or using some version of HANC and OAR structures as models for a cross-network coordinating structure. Such structure could even inform the field about how to better set a truly comprehensive prevention agenda.

For DAIDS and for all stakeholders, user preferences must be part of the decision-making process in reality—and not just in rhetoric. DAIDS has been clear that understanding the user is essential, but it often rounds out these two truths with an inaccurate statement—that the young people, particularly girls and women, who are most at risk of HIV in sub-Saharan Africa can't and won't use adherence-dependent methods like daily oral PrEP. (To be fair, some microbicide activists also say the same thing.) As discussed in Section Two (p. 21), it is premature to use this logic. It's also dangerous to the delivery effort. The question shouldn't be settled by artful debate but through thoughtful rollout and monitoring. Even so, daily oral PrEP may not work in some contexts or communities.

Finally, DAIDS must foreground the importance of implementation science—in its own work and for the field. Research to find out how best to deliver proven products or packages of services isn't easy, and it isn't DAIDS' forte. All stakeholders, including DAIDS, must take concrete steps to avert the “innovation pileup” that might emerge if some of the products, antibodies or vaccines under consideration today show benefit. There needs to be a plan for funding countries and partners with proven

implementation science skills to support the introduction of newly proven products. High efficacy won't mean high impact unless there are programs that work. In the next iteration of networks, DAIDS should play to its strengths and build in mechanisms such as RFAs or protocol requirements that lay the groundwork for a handoff to partners that can do implementation science efficiently and well. As a first step, product introduction plans should be incorporated into the protocols for all products in clinical trials—an approach already used by the Wellcome Trust.

Recognize that HIV is global—and the research agenda must be, too

As the graphics on page 20 show, the US government funds the lion's share of HIV prevention research conducted worldwide. That's why this section is so focused on upcoming decisions about how this funding will be allocated, and how agendas will be set. But the decisions and funding cannot come from the US alone. In the context of the current application of the Global Gag Rule (see box, p. 17), it is particularly important that additional funders continue to add resources to the search for effective, safe and acceptable ways for women and adolescents to control their fertility and their HIV risk. And in every context, it is essential to diversify funding resources. This year's *HIV Resource Tracking Report* documents how funding is increasingly consolidated into large commitments from a handful of sources. It's a trend that can and should be reversed by expanded investments from Europe and from lower-middle and middle-income countries where research is happening—and where it is not, as South-South investment and collaboration is a core component of a robust research future.

Watch Your Language: What we'd like to see DAIDS and others say and do about the prevention pipeline

Advocates who have been working on DAIDS-related issues in recent months will be watching closely to see whether our feedback has been reflected in the “Funding Opportunity Announcement” (FOA) that DAIDS is expected to issue in early 2018. The FOAs set the tone, priorities and parameters for applications that research networks must submit. If a topic or issue isn't included in a FOA, it doesn't mean

it can't be added later, but it won't be what the proposals emphasize. In the table below, we capture what DAIDS has said so far about the MTN and HPTN—the two prevention trials networks that could change the most starting in 2020—and we share what we think the priorities should be in the FOAs—and for all research networks.

	What DAIDS has said in 2017	What AVAC thinks the priorities should be
Microbicide Trials Network	<ul style="list-style-type: none"> • While microbicides offer promise, and we are pleased to see the ring progress to regulatory review, the remaining microbicide research field faces substantial barriers to developing successful products. • The candidate microbicides currently in the research pipeline have limited proven efficacy, and it has not been demonstrated that the most vulnerable users would choose or adhere to these products. Coitally dependent products, including condoms, require use with each sex act, creating a major adherence challenge. For women, microbicide products designed for vaginal use do not protect during anal sex. Further, topical agents deliver a concentrated level of protection to a targeted tissue, but if that tissue tears, or the virus moves through the layer of protection, HIV infection can occur. • It is essential that the microbicide field complete ongoing studies to assess the feasibility of success for these modalities and continue to innovate new delivery methods that clear these obstacles. Despite the challenges that microbicides must overcome, we remain interested in and supportive of a preclinical agenda for concept discovery that focuses on improving desirability, adherence and efficacy. 	<ul style="list-style-type: none"> • Evaluate the HIV prevention product needs and preferences of vulnerable populations, including adolescent girls and young women, gay men and other men who have sex with men, trans women and US minorities utilizing user-centered design approaches. • Bring to licensure the systemic and topical candidates for vaginal and rectal use that show the most promise. • Evaluate and optimize strategies for HIV prevention, integrating behavioral and social science and biomedical strategies. • Evaluate the most promising candidates for multi-purpose prevention. • Evaluate and optimize the most promising next-generation PrEP products.
HIV Prevention Trials Network	<ul style="list-style-type: none"> • Develop tools that are: <ul style="list-style-type: none"> – Safe – Acceptable – Desired – Highly effective – Protective system-wide – Next generation, where appropriate • Define the needs of vulnerable populations and tailor-fit prevention strategies to them. • Interventions will include populations most at risk, including adolescents, young adults and US minorities. 	

US Funding for HIV Prevention R&D: A case for accountability, transparency and action

As the figures below show, the US government finances the lion's share of HIV prevention research and development, with European and host country governments, private sector and philanthropic

contributions rounding out the rest of the resources. A full breakdown of contributions by sector, as well as a look at how different donors invest in different interventions, can be found at hivresourcetracking.org.

Figure 8 US Public Sector Investment in HIV Prevention R&D, Compared to All Other Funding, 2012-2016 (US\$ billions)

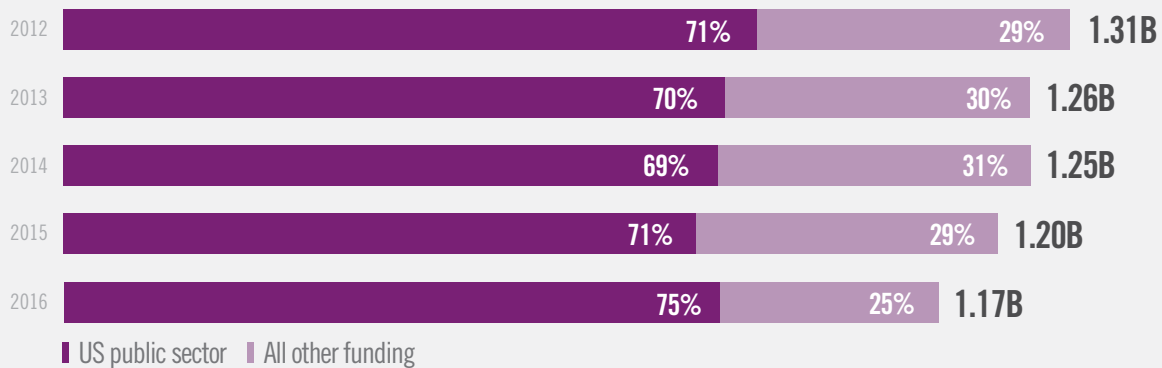
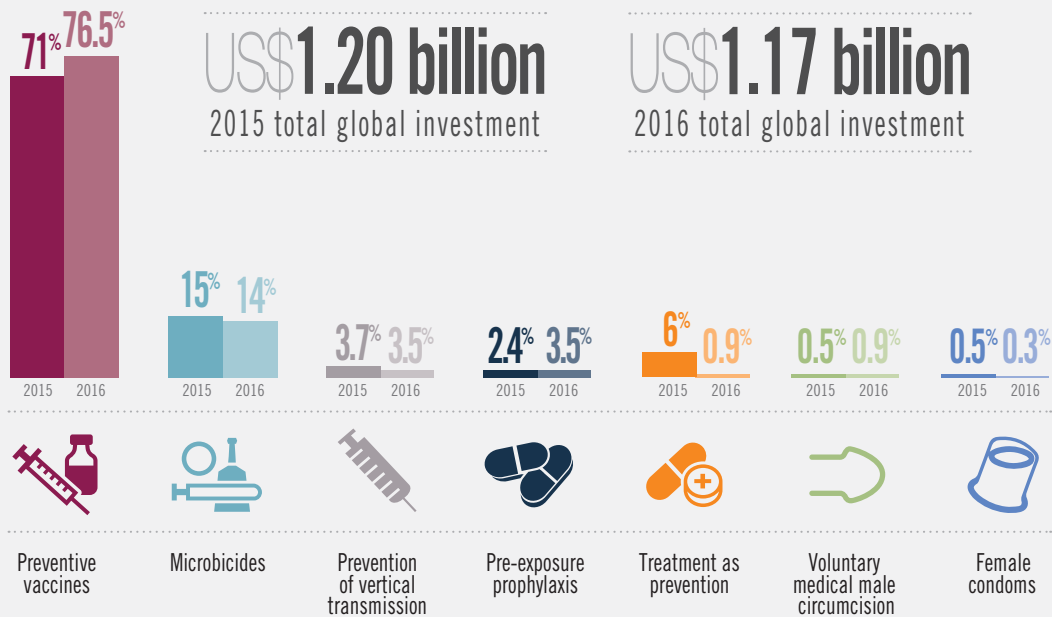


Figure 9 Total Global HIV Prevention R&D Investment by Prevention Option, 2015-2016



Resource Tracking for HIV Prevention Research & Development. *HIV Prevention Research & Development Investments, 2000-2016: Investment priorities in a challenging global health landscape to fund innovation.* www.hivresourcetracking.org.

Let's Get Real

RECOMMENDATION

2

Make this your message: *Daily oral PrEP as a prevention tool is struggling in some contexts and soaring in others.*

Stop saying: *Lots of people don't want to take oral PrEP, so it's failing.*

People using PrEP are the ones whose “non-adherence” is counted, but there are other defaulters to pay attention to, including governments and funders who are advancing disjointed programs without involving civil society, including the people most in need, such as young women and key populations. When these programs falter, it's not the user's fault.

When the people who need it feel ownership of the product and the program, any strategy—including PrEP—can work. Oral PrEP definitely isn't for everyone, but many people who might want it still need a chance to try.

Get real about PrEP in the “real world”

Daily oral PrEP programs are in more places and reaching more people than ever before. In sub-Saharan Africa alone, over 10 countries have daily oral PrEP in their national HIV guidelines or strategic plans (see Figure 14, p. 28), and new developments occur in the region and globally almost every day. The scale and scope of PrEP programs vary widely, from relatively small, discrete demonstration projects and implementation science activities in several countries to national programs in Kenya and South Africa.

And yet even in these early days, judgments about the feasibility of daily oral PrEP in sub-Saharan Africa are already being rendered. Often the conclusion is: the people being offered PrEP, such as sex workers, adolescents or men who have sex with men don't want it or don't stay on it during periods of risk. It's a simple story—and it's likely wrong.

The data used to support these statements come from places like South Africa, which started its PrEP program in female sex workers in June 2016 and expanded to men who have sex with men in April 2017 and to university campus clinics in late 2017, and so has the most information to report. The overall picture of uptake in South Africa (see Figure 13, p. 26) would seem to align with the conclusion that the people being offered PrEP don't want to stay on it. Twelve months after rollout began, just seven percent of HIV-negative sex workers in South Africa chose to start PrEP when offered, according to a mid-2017 presentation by Dr. Yogan Pillay, Deputy Director-General in South Africa's National Department of Health. Uptake was far higher in a South African demonstration project among women sex workers

Table 2 Prevention Research & Oral PrEP Rollout: The evolving context for HIV prevention research

As the table below shows, many of the current or planned prevention trials are taking place in countries where daily oral PrEP is, or will soon be, available. This has implications for many aspects of trial design.

	PrEP STATUS						TRIALS							
	Approved	Regulatory application filed	Guidelines issued	Demonstration projects (**planned)	Large-scale implementation initiatives	National health system delivery (**planned)	Antibody		Preventive vaccine		Long-acting injectable		Microbicide/oral PrEP	HC-HIV
							HVTN 703/HPTN 081	HVTN 704/HPTN 085	HVTN 702	HPX2008/HVTN 705	HPTN 083	HPTN 084	REACH/MTN034/MPM 045	ECHO
Argentina														
Botswana		●	●				●					●		
Brazil		●		●	●			●			●			
Kenya	●		●	●	●	●	●					●	●	●
Malawi	●			**			●		●			●		
Mozambique		●		●			●		●					
Peru	●			●				●			●			
South Africa	●		●	●	●		●		●	●	●	●	●	●
Swaziland	●			●								●		●
Switzerland								●						
Tanzania	●			●			●							
Thailand	●			●	●						●			
Uganda		●	●	●								●	●	
United States	●		●	●	●	●		●			●			
Vietnam				●							●			
Zambia	●		●	●						●				●
Zimbabwe	●		●	●			●			●		●		

in Johannesburg, where more than 98 percent of those eligible for PrEP chose to start, but just 22 percent of those who started returned for their 12-month visit.⁴

Already, these and similar reports and anecdotes about low uptake and high rates of discontinuation among those initially offered PrEP in Africa are being used as a reason to look beyond daily oral PrEP for the next solution. A major impetus for the research agenda discussed in the previous section is the belief that adherence-dependent methods won't work and that long-acting systemic methods such as an injectable antiretroviral are essential. But it isn't just the leadership of the US Division of AIDS that holds this view. Some proponents of adherence-dependent

topical prevention—rectal and vaginal microbicides—also point out that daily pill-taking isn't for everyone, and that prevention used at the time of sex is also important.

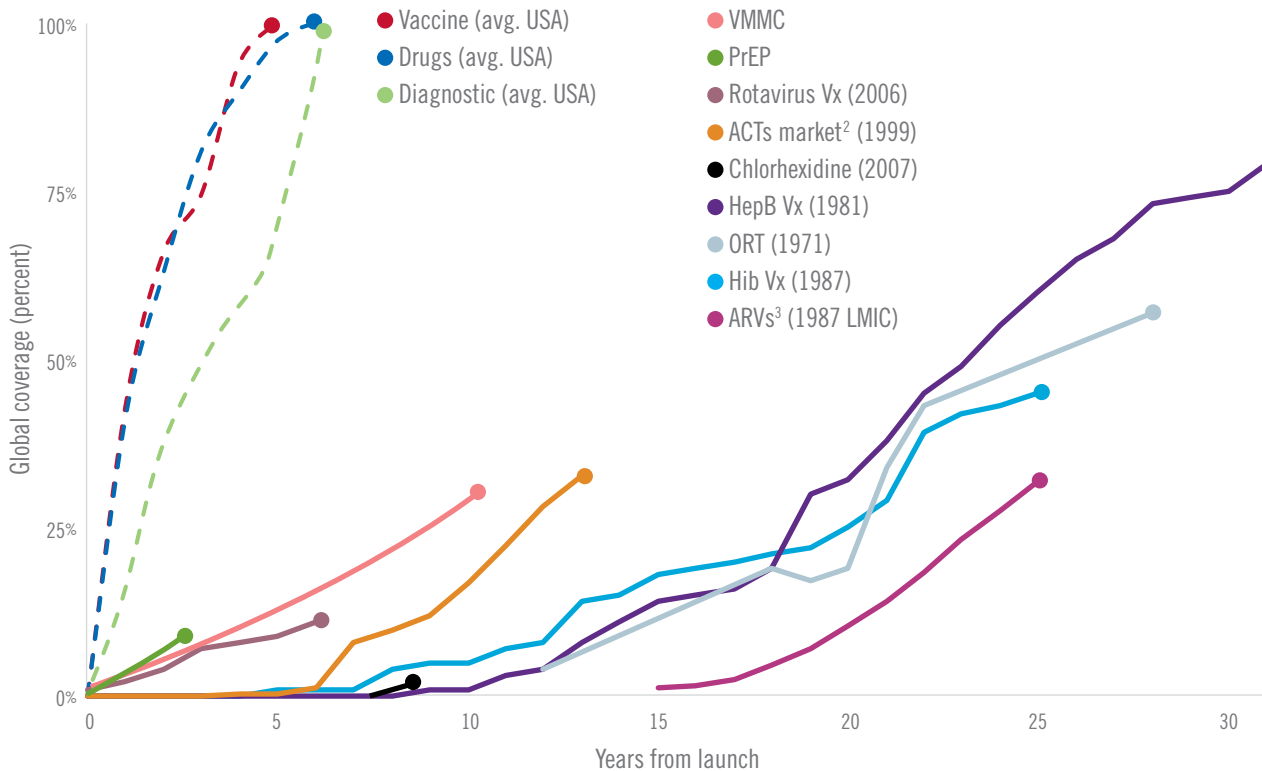
Everyone's right, of course. All different kinds of methods are needed. But the conclusion that daily oral PrEP doesn't have a role in sub-Saharan Africa based on the information collected to date is wrong and must be corrected.

It is too soon to tell what the role of daily oral PrEP could or should be in the lives of people of all genders living in sub-Saharan Africa. The trajectories of product uptake for other strategies (see Figure 10, right) show just how long it takes for a new

⁴ Eakle R, Gomez GB, Naicker N, Bothma R, Mbogua J, Cabrera Escobar MA et al. 2017. HIV Pre-Exposure Prophylaxis and Early Antiretroviral Treatment Among Female Sex Workers in South Africa: Results from a prospective observational demonstration project. *PLoS Med*.14(11): e1002444. <https://doi.org/10.1371/journal.pmed.1002444>.

Figure 10 The Delivery Challenge

This figure shows the time from introduction to achievement of public health coverage targets both globally and (in dashed lines) in the US. The message: it takes time and, based on history, today's prevention tools are not off track.



Product launch year is shown in parentheses. LMIC = Lower- and middle-income countries

intervention to catch on. The story of PrEP in the US (see Figure 11, p. 24) shows that it took real time for people to embrace the strategy. So does the story of VMMC introduction in sub-Saharan Africa. Early accounts of uptake do not predict the future.

The last time that there existed such a pivotal moment for prevention advocates to help clarify early information on a product and work to ensure its success was probably in the earliest days of the female condom. That was the last time that HIV-negative women and girls were offered a strategy that they could use in their bodies to reduce the risk of HIV. The bottom-line lesson from the past 25 years of experience delivering the female condom and so many other public health interventions is that the program matters as much, if not more, than the product.

So what kinds of counter-arguments can we make as we understand that, yes, small numbers of people are

using PrEP in some settings for now, and many of those people are choosing to stop PrEP months after starting it? Here are a few to consider:

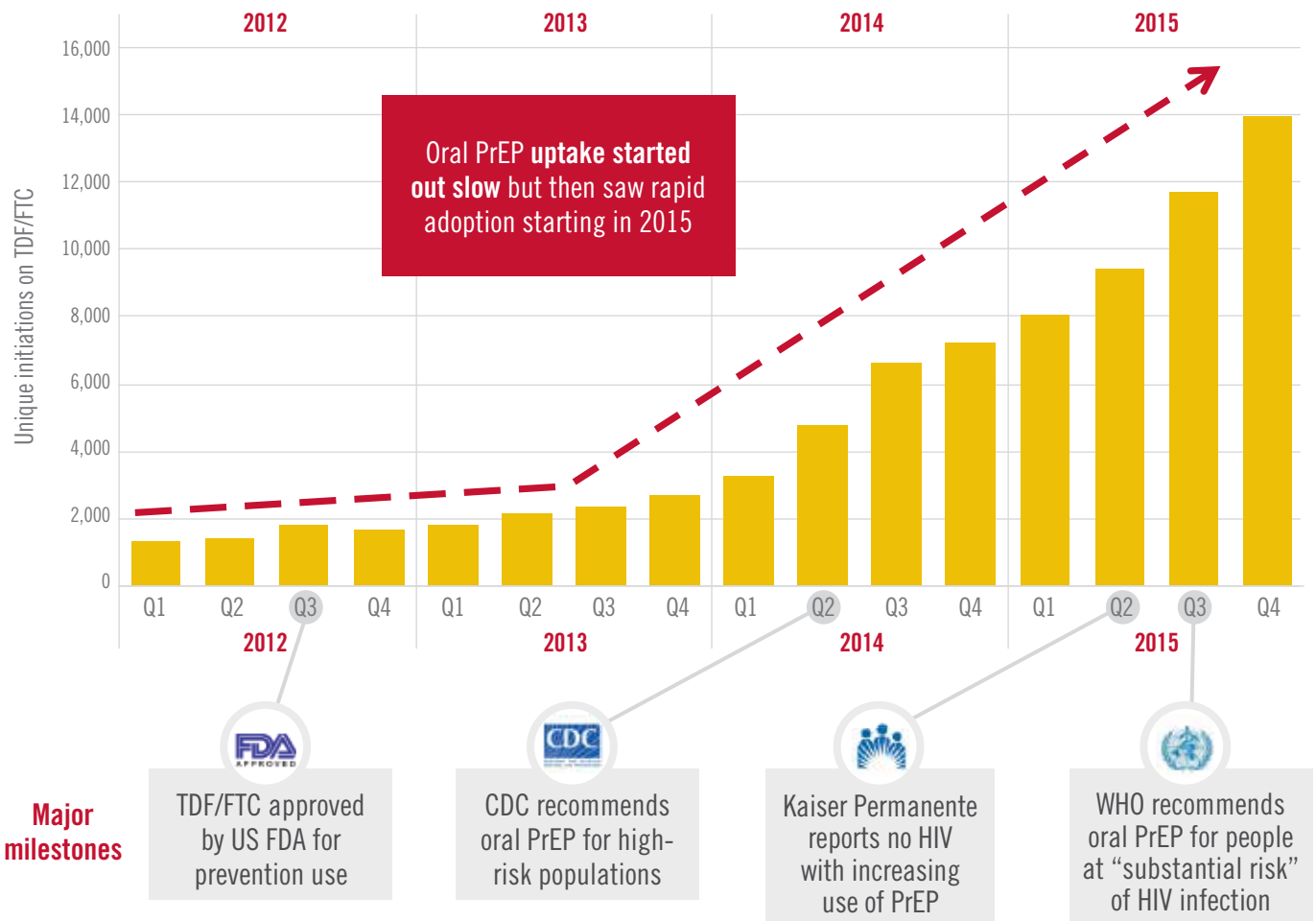
- Introduction takes time, and PrEP is following familiar patterns.** In the US and the UK, there is powerful evidence that PrEP use is slashing rates of new HIV diagnoses among gay men and other men who have sex with men. But it was just a few years ago that PrEP was being described as too slow and even a failure in the US; now uptake is surging among gay men and other men who have sex with men (see Figure 11, p. 24), discontinuation rates are dropping compared to 2012-13 and real-world data suggest that it's working as HIV prevention in dramatic ways.
- Uptake can look artificially low if the denominator is wrong.** In Dr. Pillay's July 2017 presentation, uptake was calculated by dividing the number of female sex workers who initiated PrEP (the

numerator) by *all* HIV-negative sex workers who were offered it (the denominator). Some of these women were older, more experienced sex workers who may have had a high rate of condom use with partners; others might have had life circumstances such as an impending move to a different part of the country or an unstable home situation that made it impossible to initiate PrEP when offered. South Africa is now moving to a new approach of calculating uptake that assesses individual risk and need of PrEP—a sign that early figures can be misleading and that measurement needs time to evolve. Different sex workers have different levels of risk—and there are a range of tools and approaches being used to “segment” this and other populations. Using a denominator of “high-risk sex workers with low condom use” might give a

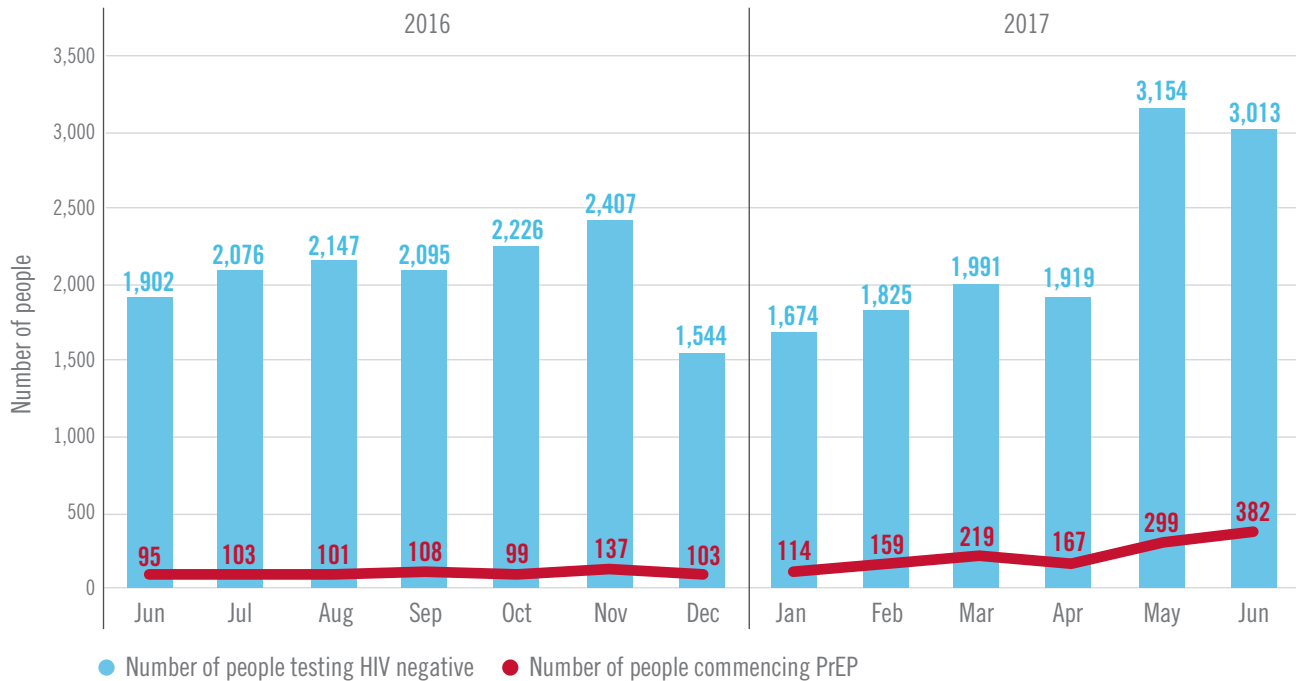
higher uptake number using the same calculation—or it might not. But if uptake is calculated using broad categories, then the percent uptake will almost certainly look artificially low.

- **Policy makers and programs can also be “non-compliant” or “lost to follow-up”.** If a person on PrEP isn’t taking pills, she may be called non-compliant. But if that PrEP is coming from a clinic where staff appear judgemental about PrEP use, or in a context of community suspicion of the new strategy, then the person taking PrEP isn’t non-compliant, the program is. Advocates need access to information about and partnerships with the sites of PrEP delivery and the organizers of national-level communications campaigns in order to be partners in successful programs.

Figure 11 Oral PrEP Uptake in the United States



Source: Mera et al. IAS. <http://programme.ias2017.org/Abstract/Abstract/1614>

Figure 12 The South Africa PrEP Story: What “starting out” looks like

Source: Yogan Pillay. 2017. Presented at Pre-Exposure Prophylaxis (PrEP): Moving from Demonstration Projects to Wider Implementation. IAS 2017. <http://programme.ias2017.org/Programme/Session/176>.

- **Today’s data on people’s continued use of PrEP do not predict the future.** Daily oral PrEP asks people to change their behaviors in ways that may be unfamiliar and even uncomfortable. It is highly possible that some people will start and stop PrEP a few times before settling into regular use, while others will use PrEP, discontinue and perhaps intensify condom use. It’s misleading and misguided to use initial uptake figures as the basis for long-term predictions about how people will use PrEP. Instead, the early information needs to be used—as it is in many places—to devise innovative support strategies for people taking and providing PrEP, to help people who do want to use the strategy to start and stay on it when the time is right.

Get real about PrEP in the context of clinical trials

The conversation about the place of daily oral PrEP in the context of biomedical prevention trials of other strategies is interesting, vexing, sometimes troubling—and not going away. As Table 2 (p. 22)

shows, many of the sub-Saharan African trials of vaccines, antibody-mediated prevention and injectable PrEP are being conducted in countries where daily oral PrEP is or will be introduced. The approach to providing PrEP in the context of these studies varies widely. In trials like HPTN 084, which is testing long-acting injectable PrEP, daily oral PrEP is part of the study design. In vaccine trials and other studies that aren’t testing PrEP strategies directly, the most common approach is to counsel about and offer referrals to PrEP. Few trials offer PrEP on-site.

Today’s discourse reminds AVAC of the debate 15 years ago about the provision of ART for participants in the context of prevention trials at a time when ART was not at all a standard of care for eligible citizens in the host country, when programs were spotty at best and when there was no clear path to funding or programs that might deliver ART to participants after the completion of a trial. At that time, there were research sponsors that argued that it was best to wait for the country to introduce ART, rather than to provide it solely to seroconverters in

the trial context. Such an approach, they reasoned, would create further inequalities between communities with access to the clinics, health providers and other services associated with research. The US Military HIV Research Program, under the leadership of Dr. Debbi Birx—now the US Global AIDS Ambassador—decided to offer ART to all the people in the community where a given trial was taking place, thereby avoiding local inequities. In this approach, the provision of antiretroviral treatment to people living with HIV in Africa was inevitable, a human rights issue and something to be accelerated.

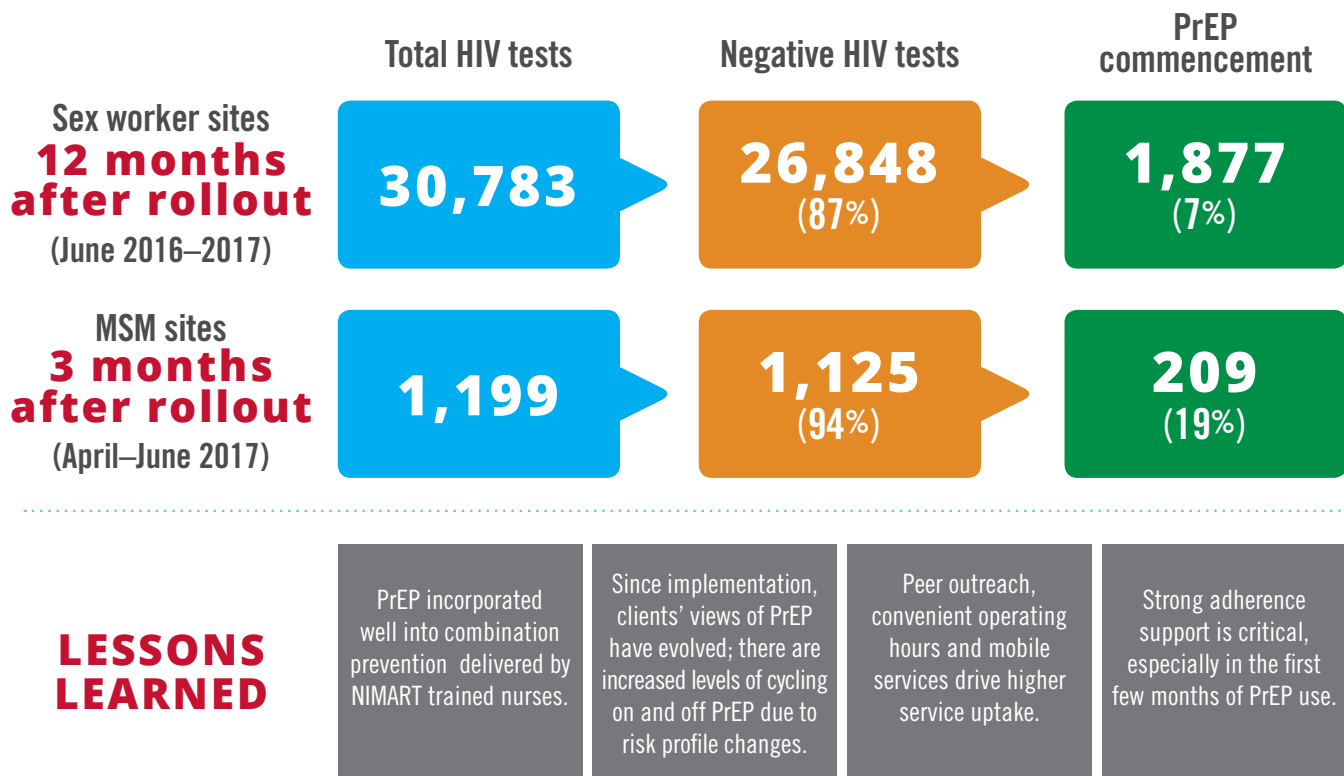
When it comes to oral PrEP, variations on these positions exist today, and that’s to be expected. What’s more surprising is that an additional thread of today’s debate is calling into question the efficacy of PrEP with direct and elliptical statements suggesting that the available data raise questions

about whether daily oral tenofovir-based regimens “work in women,” or whether there might be a biologically plausible mechanism for why they do not.

When addressing the complex issue of PrEP access by trial participants, we cannot afford to go down a path of “PrEP denialism” that questions the science of the regimen. There are several things that are known. These include:

- Daily oral PrEP works in men and women who take it correctly and consistently, including in men and women who have anal and vaginal sex.
- It takes longer for a cisgender woman taking a daily oral PrEP regimen to achieve protective drug levels in the blood and vaginal tissue mucosa than it does for a cisgender man to achieve protective concentrations in the rectum. Less is known about the drug in transgender bodies.

Figure 13 Oral PrEP Uptake in South Africa: A snapshot from mid-2017



Note: HIV testing numbers reflect new tests, not routine testing for current PrEP users.

Source: Yogan Pillay. 2017. Presented at *Pre-Exposure Prophylaxis (PrEP): Moving from demonstration projects to wider implementation*. IAS 2017. <http://programme.ias2017.org/Programme/Session/176>.

- Daily oral PrEP is also “less forgiving” in people whose primary risk is via vaginal exposure, meaning that adherence has to be high for it to protect in the context of vaginal sex.
- There are no data suggesting that bacteria that are part of the vaginal microbiome impact levels of PrEP or PrEP protection in the context of oral PrEP, even while evidence exists to suggest that vaginal bacteria might reduce the efficacy of tenofovir-based PrEP when it is delivered topically in a gel.
- TDF and FTC, the two drugs in the approved daily oral PrEP regimen, were approved for use as HIV treatment by the US FDA in 2001 and 2003, respectively. Since then, they have been used by millions of people living with HIV in every part of the world. These drugs have been used to effectively treat HIV of all different subtypes or clades. There is no evidence whatsoever that there are differences in TDF/FTC safety or efficacy based on the gender, geography or circulating subtype. Undermining the regulatory process with scientific conjecture could undermine all future efforts to develop prevention products.
- The World Health Organization has recommended PrEP for all people, men and women, at substantial risk of HIV, and the substance of these recommendations constitutes global guidance and expert assessment of available evidence.

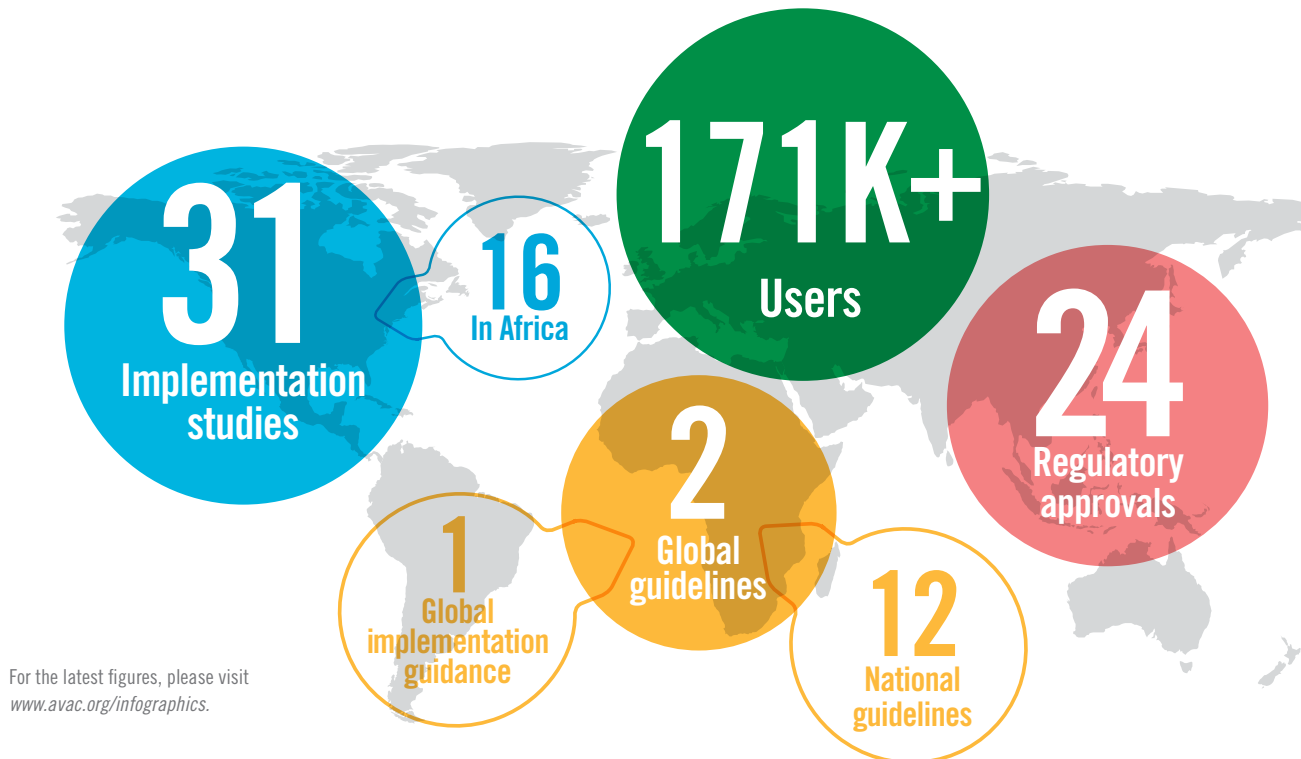
To be clear, there are many questions about oral PrEP using TDF/FTC that need to be answered, particularly about how to deliver it in programs that meet people’s needs and support them in choosing to start and stay on PrEP safely. Biology *does* impact HIV treatment and prevention. For example, far more needs to be done to understand how HIV risk is impacted by the hormonal milieu of cisgender women who are pregnant, menstruating, pubescent or menopausal, as well as those who are taking hormonal contraceptives. Also, far too little is known about how daily oral PrEP works in transgender men and women taking hormones. There should be neither stifling of inquiry nor sowing of doubt.

All conversations about PrEP in the context of trials should happen in the context of the basic information on this page. To play with the facts—suggesting that there is any evidence that women with protective levels of oral TDF/FTC in their blood are less protected than men, for example—is to play with fire. The suggestion that PrEP doesn’t work runs counter to both WHO guidance and, in many places, national policy. We need new tools too much to jeopardize the research endeavor. In some trial sites in Southern Africa, HIV vaccine strategy and long-acting injectable PrEP trials are happening side by side. Participants must be told the same thing regardless of what trial they happen to enroll in. It may undermine comprehension and trust to tell members of the same community that oral PrEP is “proven” in injectable PrEP trials and “may not work in women” in vaccine trials. A dedicated forum on this matter was convened by the South African Medical Research Council (SA MRC) in November 2017. As concrete outcomes, the SA MRC and the NIH-funded Fred Hutchinson Cancer Research Center (FHCR) will establish a fund to cover the cost of oral PrEP and HIV testing for HIV prevention trial participants for the duration of the trial. Trial sites and their communities will decide how to provide PrEP at their site, and this will likely look different at different sites. Sites will be encouraged to work with implementing partners to optimize PrEP access and to support adherence, and researchers will work with the South African National Department of Health’s (NDOH) PrEP technical working group to support establishment of demonstration projects closer to trial sites. AVAC looks forward to seeing these commitments in action.

AVAC’s position on oral PrEP access in trials draws on what HVTN Principal Investigator Larry Corey and his colleagues wrote in the *Lancet* in 2003. We adapt and assert that:

One research organization, product developer or funder cannot reverse global inequities in HIV prevention or care, but researchers from wealthy countries who work with resource-poor countries have an obligation to try to narrow the equity gap.

Figure 14 **A Global Look at PrEP Introduction (December 2017)**



HIV vaccine and prevention researchers can work with communities to develop, implement and assess high-quality prevention and treatment models for participants in research programs, and can encourage the development of sustainable community access to good quality, comprehensive HIV prevention. Epidemic context and the likely trajectory of introduction is also critical—just as it was in the context of ART. Given the extraordinarily high rates of HIV in young women and key populations, the expanding array of oral PrEP programs and the multi-year timeframe for additional options, it is forward-thinking and public-health minded to seriously explore PrEP provision as part of the standard of care.

Get real about primary prevention

As the letter from the Executive Director discusses, there are more visions than ever before of what

“primary prevention”—that is, prevention focused on HIV-negative individuals—is and should be. In this context, the case for daily oral PrEP is part of the case for a holistic approach that understands that different groups need different strategies, and that injectable systemic prevention will be a lifesaver for some and unacceptable for others. We make this case with an urgency fueled in large part by the changing population dynamics in sub-Saharan Africa. The so-called “youth bulge” has doubled the number of young people in some countries, compared to the start of the epidemic (see Figure 16, p. 30). In this context, even with dropping incidence and prevalence, there are still more young people living with and at risk for HIV than ever before. The world cannot afford to discard any tool that might help these young people live long, healthy lives—whether with HIV or HIV-free.

Divide and Conquer: An advocate's guide to PrEP indicators

An “indicator” is a measurable parameter that helps people who pay for, design and provide services to track whether they are doing what they set out to do. It could be the number of HIV tests provided or the number of people living with HIV who are on

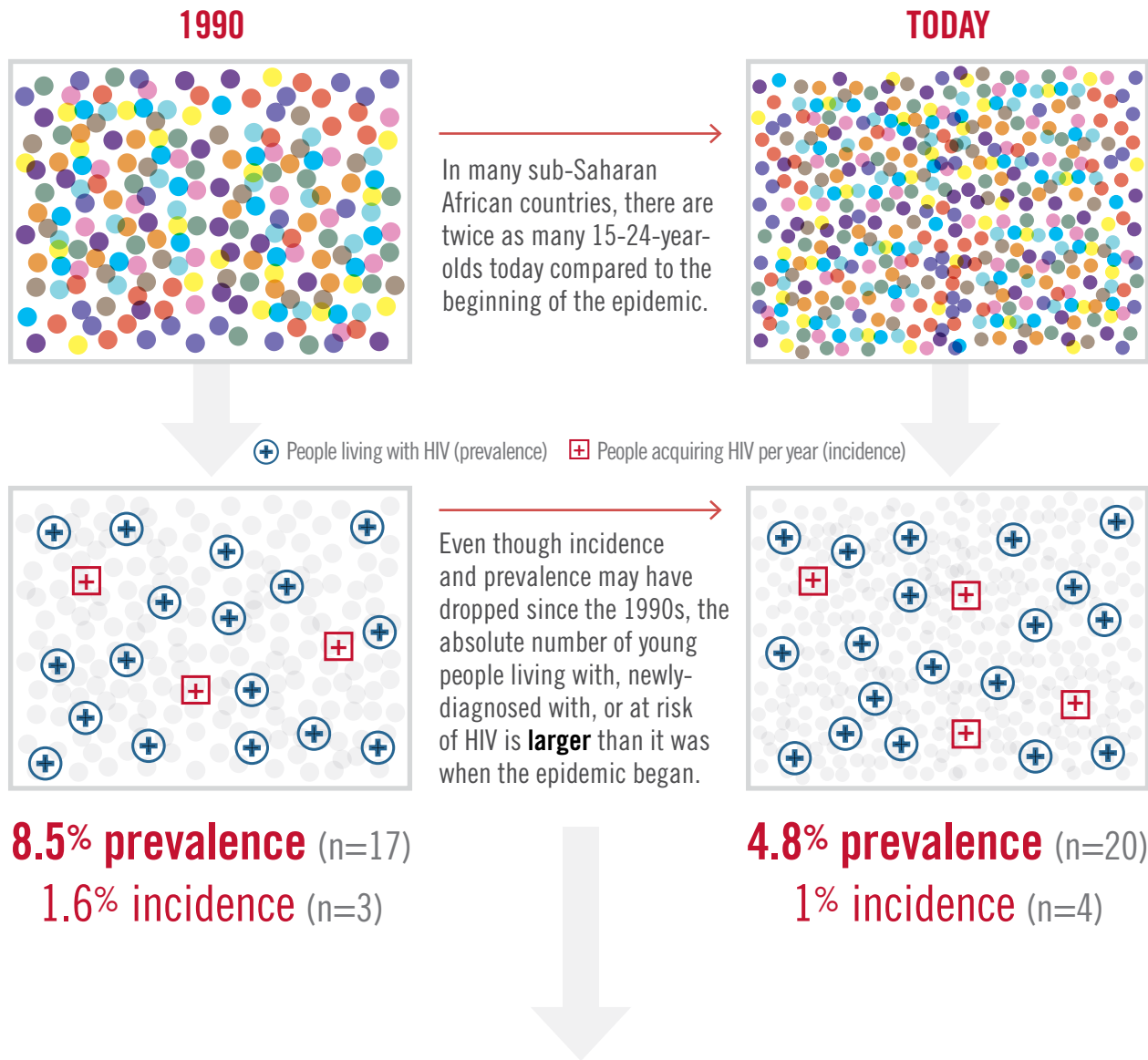
ART and are virologically suppressed. But not all indicators are created equal, and not all reports can be taken at face value. In the context of early PrEP rollout, it's essential for advocates to engage and, where needed, challenge the indicators in use today.

	Numerator	Denominator	Inside the indicator	Engaging the indicator	Challenging the indicator
PrEP uptake	Number of people initiated on PrEP.	Number of people assessed as eligible for PrEP.	<p>Setting the denominator too high will make overall uptake look artificially low.</p> <p>Eligibility isn't as straightforward as the number of people who meet the criteria in the guidelines. Some sex workers may have high rates of condom use and may not want to use PrEP even though they are technically “eligible” for the intervention. Stratification within demographic groups—such as adolescents and young people—is essential. Not all people of a certain age need PrEP, even in countries with a high prevalence.</p>	<p>At this stage of product introduction, uptake isn't low, it's slow. There's a big difference between the two.</p> <p>If the absolute number of people using PrEP in a given country or program is small—in the double or triple digits—this can be seen as evidence that uptake is low or that people don't want it. But in the first years of a new and unfamiliar product, that's exactly what is expected. It takes time for a product to become familiar and acceptable. If the denominator and the expectations are too high, then uptake looks low when it might actually be slow—and right on schedule.</p>	<p>Today's PrEP uptake figures seldom, if ever, reflect macro, community- and facility-based factors that might be in play. What is uptake like in a country where homosexuality and same-sex marriage are illegal? What is it like in a place where providers scold patients for fitting the risk criteria that brought them into the clinic in the first place? PrEP uptake can't be evaluated in a vacuum.</p>
Loss to follow-up and rates at which people stop using PrEP during periods of high risk	Number of people who initiated on PrEP for the first time who do or do not return for prescribed refill or follow-up visits.	Number of people newly initiated on PrEP.	<p>For PrEP to work, retention in programs is key. A simple loss in follow-up figures can mask a lot of variables.</p>	<p>The schedule of follow-up visits matters. One study in South African young people found that retention drops off when clinic visits change from monthly to quarterly. Looking at summaries of retention figures, it's important to ask: what was the schedule for follow-up visits? How was it set, and are there data suggesting that this is the right timing for this population?</p>	<p>Policy inconsistencies around PrEP use in pregnancy are still being ironed out in many countries. Even though women with HIV can use tenofovir-based drugs throughout pregnancy, some programs will still ask women to stop PrEP use when pregnant. Such mixed messages cannot wholly explain low retention, but they should not be discounted when considering rates of discontinuation.</p>

Eligibility for PrEP includes all of the following: 1) testing HIV-negative; 2) no signs or symptoms of acute HIV and 3) at substantial risk per country or program definition.

Figure 15 The Math Behind the “Bulge”

Whether it’s called the “youth bulge” or “wave” or even “tsunami”, the fact remains that there are many more young people today than there were 30 years ago. This has profound implications for the HIV response, as these same young people—especially females aged 15-24—are at highest risk of HIV in East and Southern Africa. But while the math can seem simple—more people means more HIV—it’s actually not that straightforward. HIV prevalence and incidence have gone down across the board since the epidemic started. This graphic explains why the bulge is the most important demographic issue facing HIV prevention today and why efforts to date are only barely holding the problem at bay. The incidence and prevalence figures used below are Zambian data from the time periods in question.



The fact that incidence and prevalence are stable or dropping in today’s 15- to 24-year-old African men and women is good news. Much of this success is due to ART. But there is clear evidence that young people are not being diagnosed and linked to care or prevention nearly as often as those over 24. Strategies that have worked so far cannot keep a new epidemic in young Africans at bay. There needs to be a sustained, ambitious and innovative effort to build and finance programs that find young people, meet their needs and provide key services including sex and sexuality education, safe spaces for peer support and skills-building and much more. Saturation coverage of VMMC, PrEP and other tools is also essential to the future.

The Slippery Slope

RECOMMENDATION

3

Make this your message: *We're on track to epidemic control if and only if the funding gap is closed, rights infringements and violations are addressed, civil society is involved and comprehensive prevention and research are prioritized in a way that has never been seen before.*

Stop saying: *A country or community's progress to date is the same as its future path.*

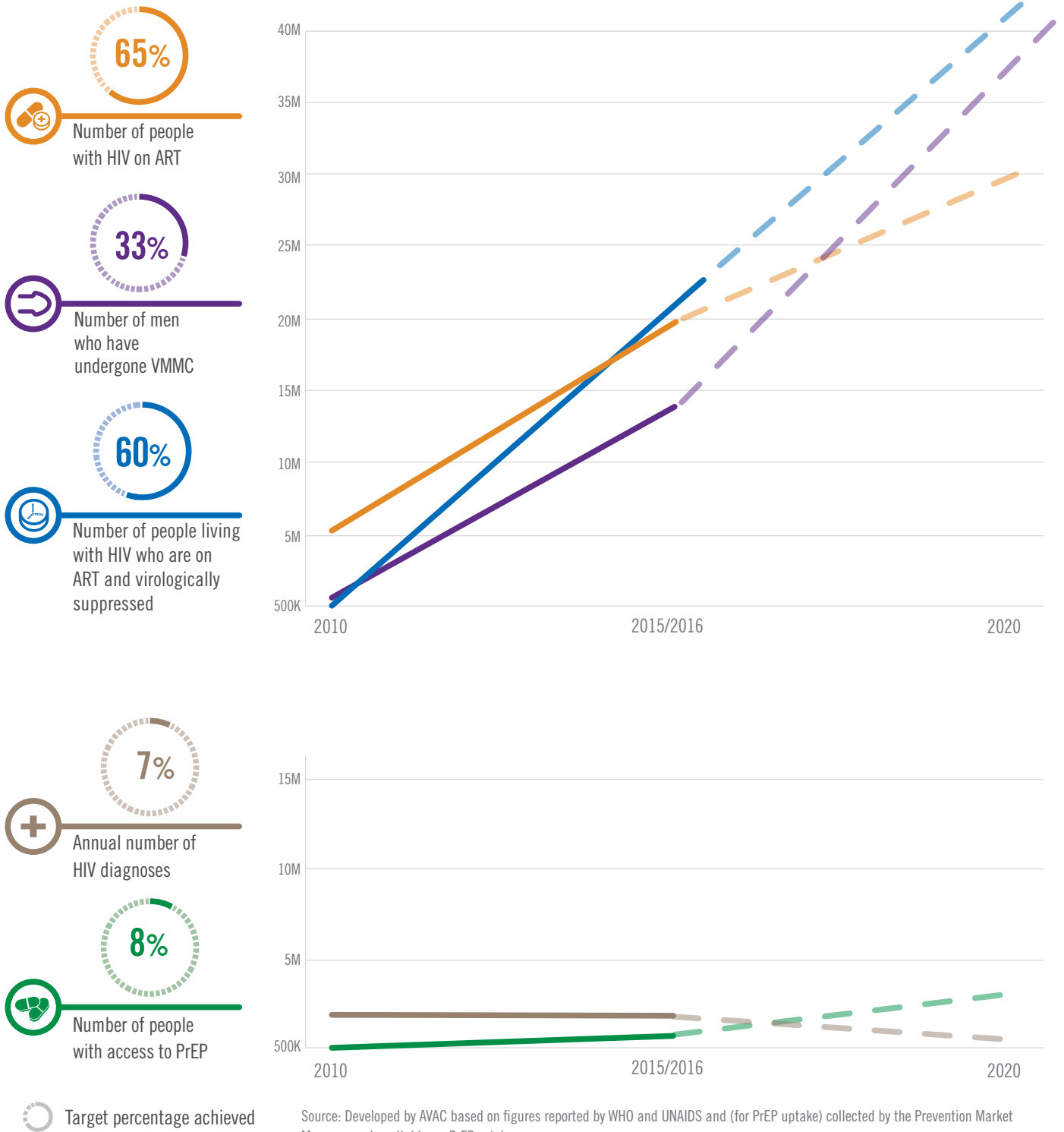
Today there are only a few countries that are even possibly on track to achieve epidemic control. This good news leaves raging epidemics elsewhere, particularly in places where human rights are in shambles and HIV is concentrated in key populations. This isn't the kind of partial progress we can settle for.

When it comes to mixed messages, the fuzziest phrase of 2017 just might be “on the path to epidemic control”. PEPFAR used the phrase to identify 13 focus countries in its updated strategy, released in September 2017. UNAIDS has used it, but more recently seems to be moving away from it. Whether you love it or want to lose it, it's hard to think of another handful of words that carries such a combination of promise and peril. The promise is that some countries have seen rates of new diagnoses plummet as antiretroviral treatment access has scaled up. PEPFAR funded detailed household surveys, known as the Population-based HIV Impact Assessments (PHIA), which provide data of unprecedented quality in mapping these declines. Based on these downward slopes, PEPFAR predicts that a select handful of countries can achieve epidemic control (which PEPFAR defines as a context in which there are fewer new cases of HIV than AIDS deaths) by 2020. It's a tantalizing possibility. It's also where the peril comes in.

Countries that have achieved dramatic incidence reductions are indeed “on a path” to epidemic control. That path, though, is all projection. In most places, the pace at which incidence must decline to meet a 2020 goal of “epidemic control” is faster than the pace at which new diagnoses have declined to date. (The technical term for this is an R_0 , or basic reproductive ratio of less than one, meaning that the number of people that a single person with HIV would pass the virus on to is on average less than one.) Countries that are on the path to a place where R_0 is less than 1 have to step up—and change—their game: reaching young people and men, mixing in more effective primary prevention and striving for

Figure 16 Target Tracking, 2010–2020

As the figure below shows, progress has been made toward some, though by no means all, of the UNAIDS Fast Track Goals for 2020. Calculating progress is also complex: rates of new HIV diagnoses aren't dropping, the overall number of people living with HIV is bigger than forecasted when the Fast Track initiative launched. One reason is limited change related to discrimination, stigma and gender inequality. AVAC has long argued that ambitious targets are the best kind. They propel action even if they aren't met. But when it comes to achieving epidemic control, progress must be properly calculated, and can never be confused with success.



Source: Developed by AVAC based on figures reported by WHO and UNAIDS and (for PrEP uptake) collected by the Prevention Market Manager and available on PrEPwatch.org.

saturation coverage of VMMC and ART, all in the context of true cultural and legal shifts that protect rights and undo sexism, homophobia and state violence. In other words, it's going to be at least as hard—if not harder—to cover that final kilometer than it was to arrive at the present state.

In every country that has provided sex and age disaggregated data, rates of HIV diagnosis, linkage to ART and virologic suppression among those on treatment are lower among young men and women aged 15 to 24 than the general population. This is the precise age group that has swelled in size over the past twenty years. As the figure on page 23 shows, the math behind the “youth bulge” is clear: even with decreases in incidence, there are more young people with and/or at high risk of HIV than there were 30 years ago. Today's best efforts are keeping rates of new HIV diagnoses from going up, but the steps that put countries on the path to epidemic control aren't enough to finish the job.

Perhaps paradoxically, hope for the future lies in the fact that, to date, most countries haven't thrown everything they've got at their epidemics.

The gains so far in countries like Swaziland and others with PHIA data are estimated by PEPFAR to be about 90 percent attributable to antiretroviral treatment leading to virologic suppression in people living with HIV. That's an extraordinary achievement. It's also an indictment of a slow global response that waited far too long to act on the evidence that immediate ART could preserve individual health and reduce onward transmission when the person with HIV was able to make an informed choice to begin.

The downward trends in countries “on the path” to epidemic control don't reflect fully scaled-up VMMC programs. These incidence slopes don't even reflect all of the benefit of the VMMCs performed during the period when incidence was declining, as many of the African males undergoing medical male circumcision are under age 24, so the benefits in terms of infections averted are in the future, when they reach the period in which they are at highest HIV risk, between 25 and 34.

The downward slopes also don't reflect the introduction of oral PrEP or meaningful progress towards addressing the structural factors that put adolescent girls, young women, men who have sex with men, transgender people and sex workers—among others—at such substantial risk. Work on these fronts is just getting underway—or hasn't started in earnest. So we can only imagine what might happen if these pieces of the prevention puzzle were put in place. Indeed, the dominant story coming from UNAIDS and some donors is the progress that's been made with ART. As Figure 16 shows, there is a reason for this: access is rising around the world. But new diagnoses are not falling. The goals for the protection of human rights and levels of discrimination are even further off track. And funding levels continue to move in the exact opposite direction of what is required to meet—and sustain—any or all of these targets for the long term.

The dotted lines that project paths towards epidemic control or global targets trace steep and, we would argue, slippery slopes. The spaces between those dots might as well be chasms, for all the ways that it's possible to fall off course. The resources that are currently invested in primary prevention (prevention for people at risk of acquiring HIV) remain paltry and siloed by strategy, rather than integrated into the kind of comprehensive approach articulated by MSMGF and the other authors of *Reconsidering Primary Prevention of HIV: New steps forward in the global response* (see Figure 2, p. 5).

Moreover, a framework for meaningfully implementing and measuring progress toward primary prevention goals has only just been released by UNAIDS, and it's not going to be simple to implement for many reasons: oral PrEP is a new strategy (see Section Two), young women and adult men are hard to reach with existing strategies and yet are among those at the highest risk and many testing programs have been urged to measure “yield” solely in terms of number of people with HIV diagnosed and linked to care. This is a missed opportunity, as testing programs that identify people

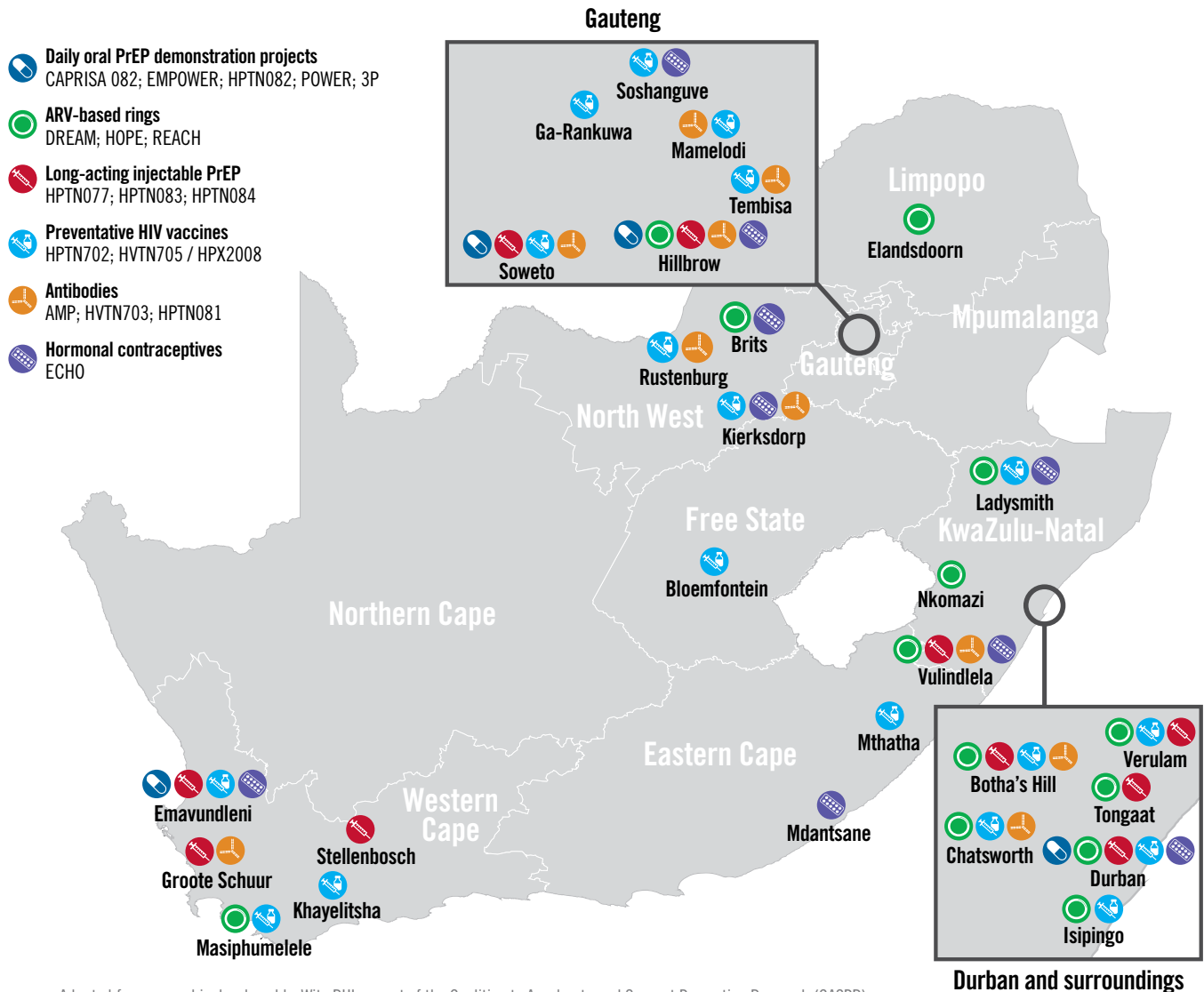
with HIV are also seeing many people at risk who should be linked to effective, tailored prevention. This is going to take resources, innovation and clear directives to redirect and reorganize testing programs so that they serve people with HIV and those at risk for HIV equally well.

At the same time, demographics, decisions about how to spend existing prevention dollars and optimistic graphics about countries on track to achieve epidemic control are a distraction from the core issue: there isn't enough money available for the global AIDS response to achieve the 2020 targets, and the money that is available is increasingly being allocated by PEPFAR to countries that have made progress. Struggling countries, countries whose economic status is shifting and countries where the epidemic is localized in marginalized groups are all going to be left behind. The world is not on a path to epidemic control—not even close. We need the stories of progress to make the case for why more resources are needed, but to confuse progress with ultimate success is dangerous, if not irresponsible. The message that countries are on the path to epidemic control suggests that our work is close to done. It is not.

To get the job done—whether it's achieving R_0 , an AIDS-free generation or “control”—there are five things that need to happen differently:

- ▶ **Increase the resources available for fighting HIV/AIDS.** The progress to date has been phenomenal in some countries—and it hasn't been achieved by accepting the rhetoric that “flat is the new normal.” Low- and lower-middle-income countries must continue to increase contributions to health budgets and HIV spending, high-income countries must continue to ante up and the private sector must pitch in to a wholly achievable and high-return investment in existing and future tools—such as an effective preventive HIV vaccine—which have a crucial role to play in decisively ending the epidemic.
- ▶ **Take the funding that is presently available for primary prevention and spend it better.** *AVAC Report* makes this point every year. And every year it bears repeating: HIV testing that isn't linked to referrals and services for HIV-negative people should not be coded as an HIV prevention investment. Provision of an HIV test and a brochure about safe sex should not qualify a program for recurring, substantial investments of prevention dollars. PrEP programs that roll out without community partners and civil society buy-in are wasting some or all of their investments. New and exciting interventions should not displace core investments in VMMC and condom programs. There are efficiencies and shifts in policies that can help advance primary prevention even in today's constrained environment.
- ▶ **Model the impact of different strategies on the path to epidemic control—and then act on this information.** During the years when ART coverage soared and incidence plunged in Swaziland, funding for VMMC fluctuated, and the coverage crept up by a measly 16 percent. Even if it had been substantially higher, though, the impact in HIV infections wouldn't have shown up in the five-year window. VMMC prevention at the population level accrues over time; the cost of not having hit more ambitious targets will be seen in years to come. Countries, funders and civil society all need better information about the relative contribution of different strategies—and of different forms of inaction—if we are to have any hope of programming toward true epidemic control.
- ▶ **Leave no country, community or epidemic behind.** The most pernicious use of the “path to epidemic control” phrase is in the context of PEPFAR's current strategy, which highlights real progress in 13 countries while sidelining 37 other countries that receive PEPFAR funding. This includes countries like Ukraine, one of many countries with an epidemic related to injection drug use and driven by the absence of

Figure 17 **HIV Prevention Research and Demonstration Sites in South Africa (December 2017)**



Adapted from a graphic developed by Wits RHI as part of the Coalition to Accelerate and Support Prevention Research (CASPR).

comprehensive rights-based harm reduction. In the context of constrained resources, funders are using the category of “on the path to epidemic control” to allocate funding away from geographies with entrenched, key population-based epidemics—and to slash resources in middle-income countries where there is no evidence that governments plan to step up and fill the gap. We all want nothing more than for the world to be on the path to epidemic control. But this can’t happen without investment, honesty and clarity. Mixed messages won’t cover the final kilometer. They never have.

Conclusion

By the time AVAC brings out our next annual report, we will be within 18 months of the deadline for the Fast Track goals. Today the world is only halfway to achieving its treatment target and less than halfway to the 2021 VMMC target. Progress towards coverage of male and female condoms and reductions in stigma and gender-based violence are all too slow. Daily oral PrEP is slowly gaining traction, and stigma and discrimination are more entrenched than ever. In the coming months we will track progress—stay connected on www.avac.org—and will also work to influence outcomes via a range of advocacy efforts.

Join us.

MANY APPROACHES, ONE MESSAGE

PREVENTION MATTERS

When AVAC was founded in 1995, we were called the AIDS Vaccine Advocacy Coalition. Our singular goal was to advance swift, ethical research for a vaccine that was then—and is today—essential to bringing the epidemic to a conclusive end.

Over twenty years later, AVAC is still focused on swift and ethical research, but our scope has expanded. Along with vaccines, we advocate for PrEP, microbicides, voluntary medical male circumcision and more.

And we've evolved with the field. As positive results have delivered new tools, AVAC has expanded its high-impact advocacy, focusing on programs, policies and payers for HIV prevention at the country level. In recent years, we have also begun work with partners to accelerate access by working to meet the information and planning needs of the global prevention “market”. Advocating for and doing the work at the same time can seem like a mixed message; through robust and rigorously honest partnerships, transparency and full information sharing we are making it work—and, we hope, making HIV prevention work better for the people who need it most.

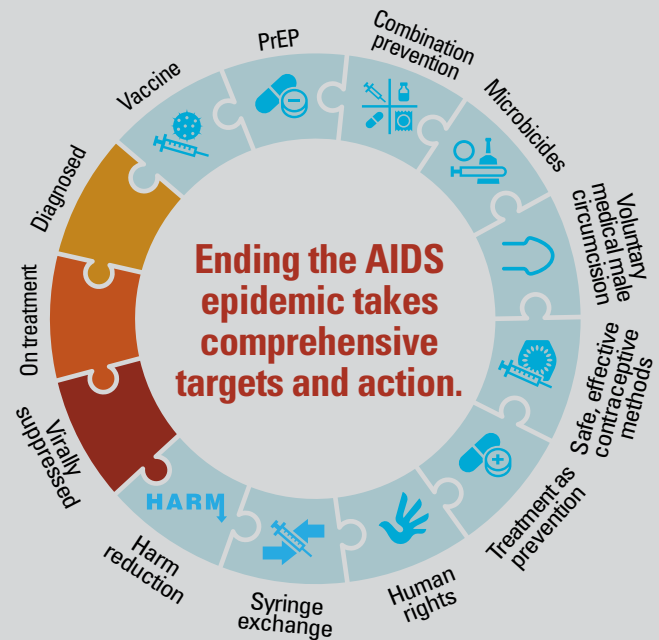
Over the years and across all our workstreams, our message is the same: prevention is the center of the AIDS response. Not just any prevention, but smart, evidence-based, community-owned, rights-based strategies.

We do this work because it's essential. We will keep doing it—with your help—until the epidemic has, finally, come to an end.

OUR PRIORITIES

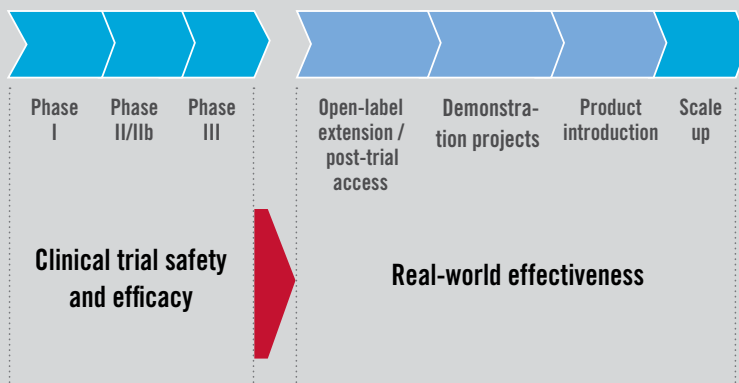
Keeping the field on track—no matter what.

We've experienced 20 years of breakthroughs and disappointments in prevention research. A vaccine that many had given up on was the first to provide modest protection. One microbicide everyone hoped for didn't pan out. Male circumcision and PrEP studies overcame skepticism and, together with antiretroviral therapy, paved the way for a prevention revolution. Through it all, AVAC has worked with partners to maintain the field's focus and press for continued research into an AIDS vaccine, a cure and more.



Defining the path from research to rollout.

Research to Rollout: A schematic road map



For the first decade of AVAC's existence, most prevention advocacy focused on actions to the left of the red arrow above. But with results come new challenges. We now work on research *and* on ensuring that products cross the gap between efficacy and real-world use.

When AVAC was founded, the only biomedical HIV prevention options for adults were male and female condoms. The pathway for introducing any new strategy was largely unmapped. No one knew where the gaps would be—between trial result and country action, between guidance and financial support. Now we do. Over two decades, AVAC has not only identified the gaps; we've worked to bridge them, so that products reach people in programs that work—without delay.

Creating a global network of prevention advocates.

When we started this work in 1995, advocacy for HIV prevention hardly existed. So AVAC helped build a global network of advocates equipped with effective advocacy strategies and the latest evidence. With our support, they are putting prevention on the agenda in countries and communities around the globe.

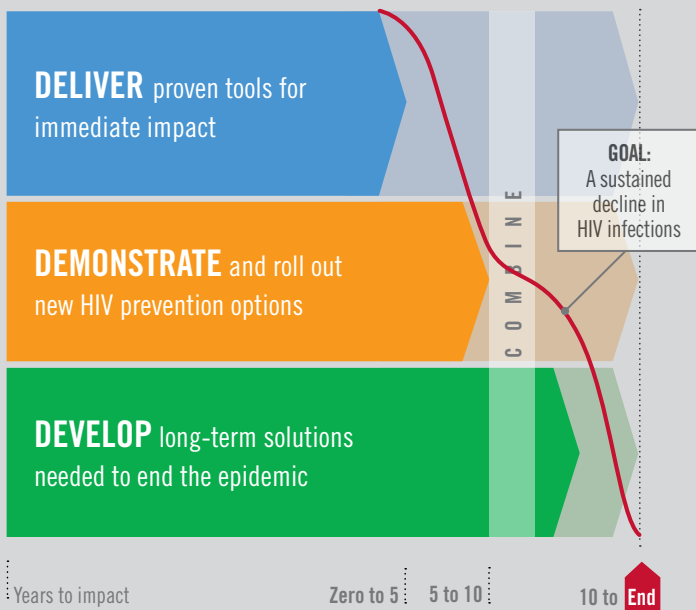
Through coalition-building, strategic convening, training and other support, AVAC partners with stakeholders throughout the world to increase awareness and understanding of the current state of HIV prevention research and implementation. Together, we hold decision-makers accountable and press for smart investments and sound policies in all aspects of HIV prevention.

Partnering for a Prevention Revolution



Demanding action on an agenda to end AIDS.

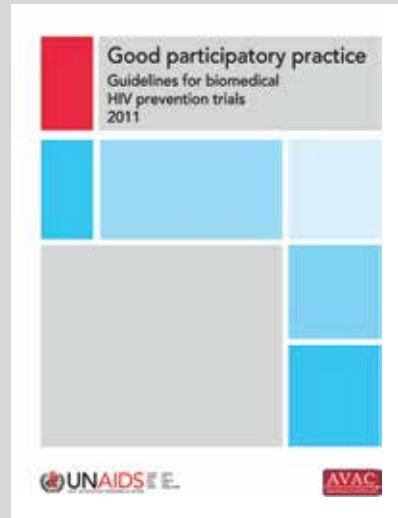
A Three-Part Agenda for Ending AIDS



When the world lacked a plan for ending AIDS, we helped to create one. Now we're holding global leaders accountable for results—demanding the resources, policies and evidence-based plans needed to deliver all of today's prevention options to the people who need them, and to plan for the rapid rollout of new options as they emerge.

Managing through controversy.

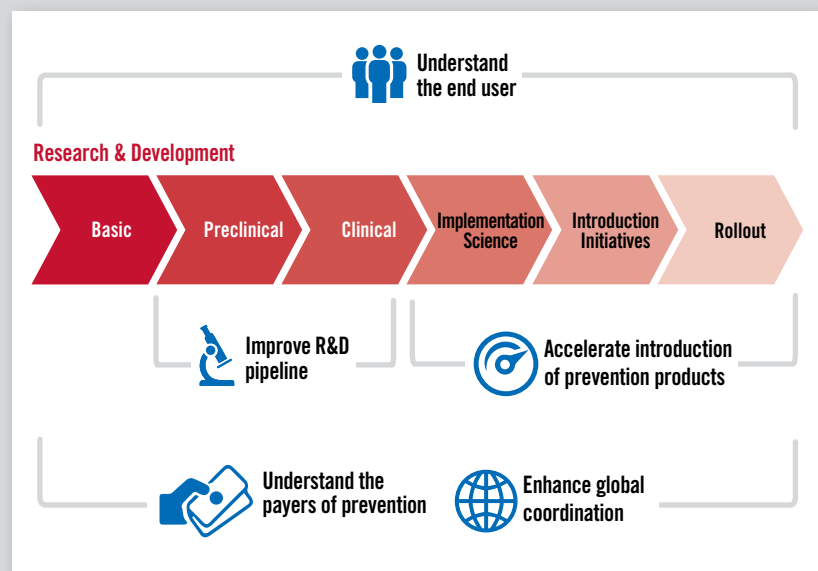
Communities' support for prevention research can never be taken for granted—it has to be earned. We've helped build trust among researchers, funders and communities to speed the ethical development and rollout of new prevention options. And when controversy threatened to derail those efforts, AVAC provided leadership and resources to help get them back on track.



The Good Participatory Practice (GPP) Guidelines provide trial funders, sponsors and implementers with systematic guidance on how to effectively engage with all stakeholders in the design and conduct of biomedical HIV prevention trials.

Driving product introduction and access.

AVAC has always advocated for closing critical prevention gaps. Now we're taking our mission further. With African and global partners, we're stepping beyond advocacy to generate the knowledge and tools that countries need to more quickly deliver new advances. We're engaging directly with national decision-makers to identify and overcome delivery hurdles for PrEP. We're examining the preferences and experiences of people at high risk for HIV, so that future tools—long-acting injectables, vaginal rings and others—can be optimized to meet their needs.



From research to rollout, evidence drives AVAC's advocacy. By expanding the evidence base for action, we're making HIV prevention advocacy more powerful than ever before.

Learn more and support our work.

Your gift to AVAC will support our efforts to accelerate the development and delivery of HIV prevention options to men and women worldwide. With your help, we can continue to convene, collaborate and communicate a strong, clear and cohesive vision for HIV prevention today, tomorrow and to end the epidemic.

It will take all of us working together to end AIDS. Please join us.

To learn more about AVAC, including our history, our focus and our team, please visit www.avac.org. And to support this work, please go to www.avac.org/donate.



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, documents that explore the issues of trial participants and affected communities, and a lively blog, *P-values*, which features voices from across the HIV prevention advocacy arena.



DATABASES www.avac.org/pxrd, www.avac.org/resources-search and www.avac.org/infographics

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



MAILING LISTS

www.avac.org/maillinglists

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



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

SOCIAL MEDIA

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twitter.com/hivpxresearch

[youtube.com/hivpxresearch](https://www.youtube.com/hivpxresearch)

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