

# 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.<sup>4</sup>

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.

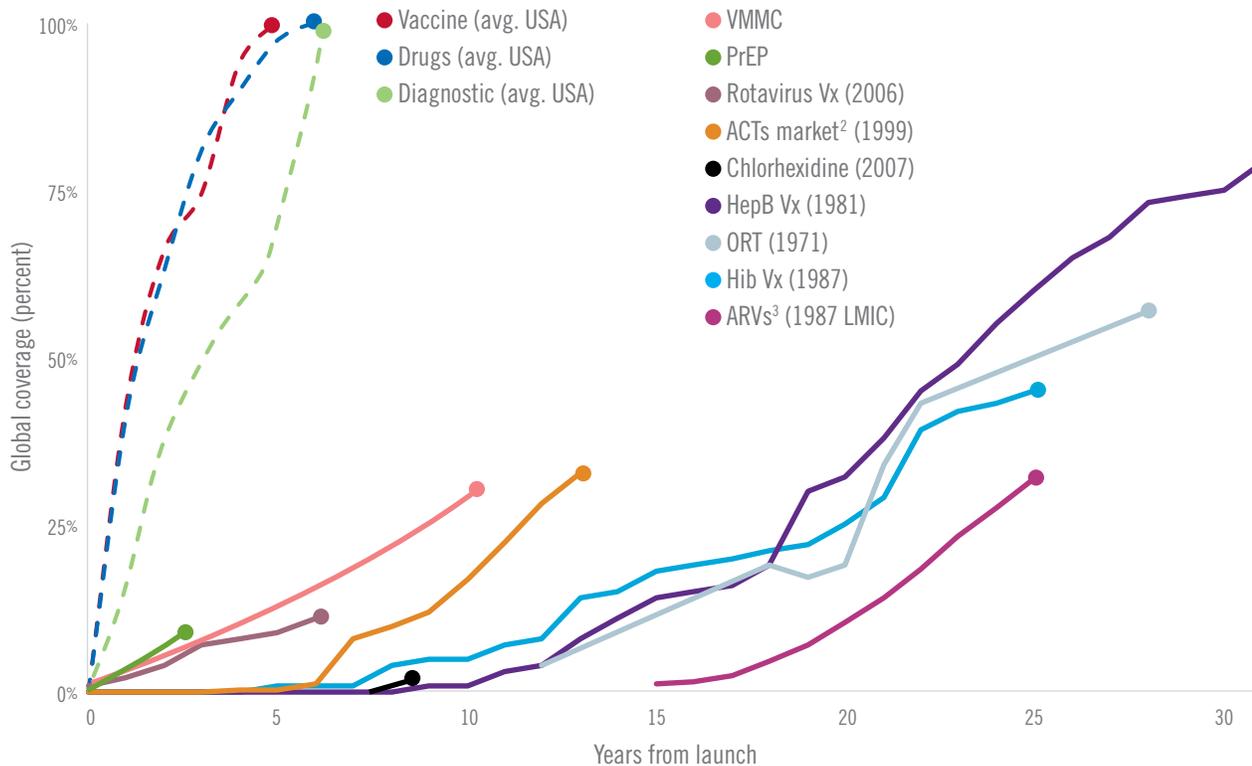
Everyone's right, of course. All different kinds of methods are needed. But the conclusion that daily oral PrEP doesn't have a role in sub-Saharan Africa based on the information collected to date is wrong and must be corrected.

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

<sup>4</sup> 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:

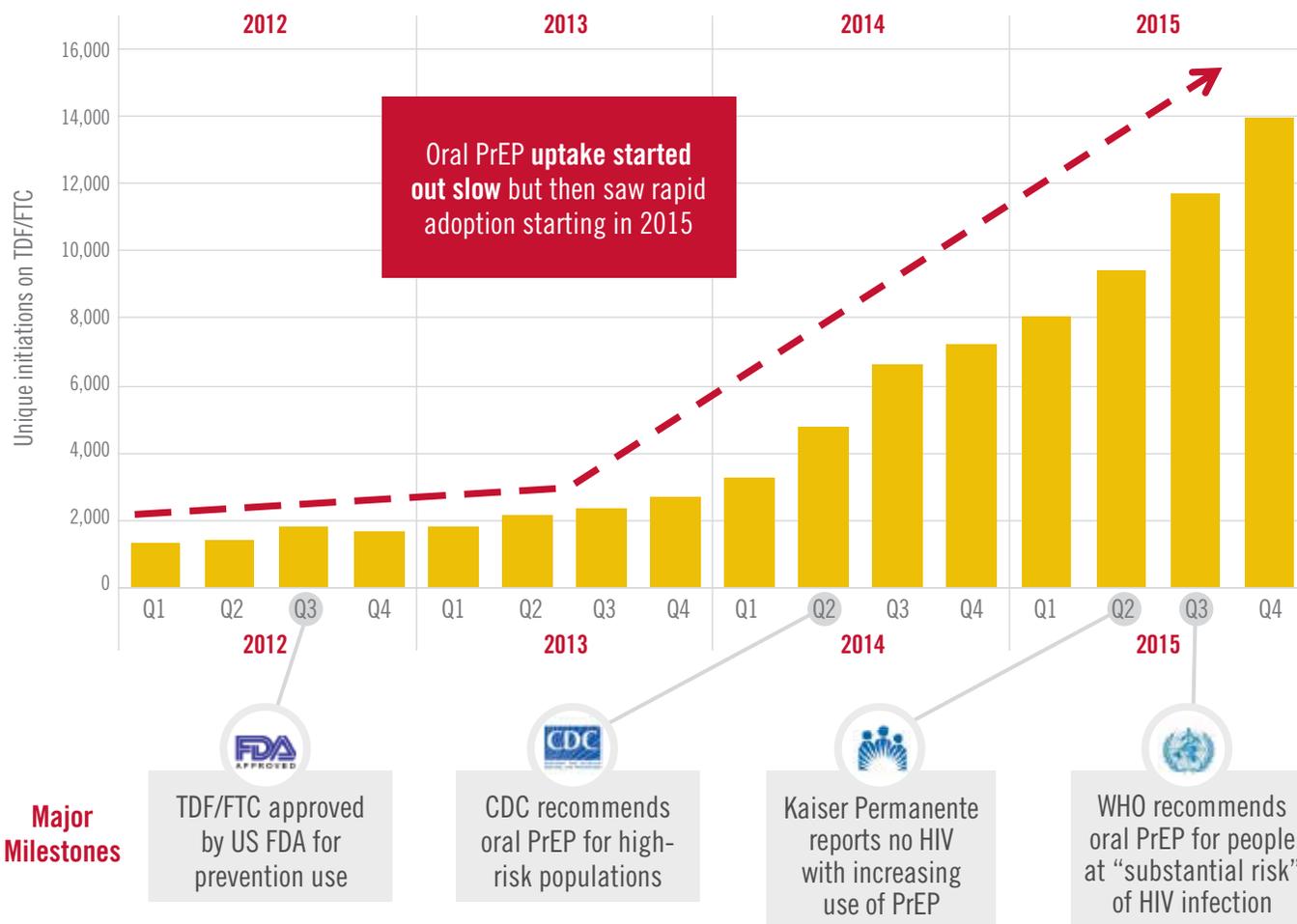
- **Introduction takes time, and PrEP is following familiar patterns.** In the US and the UK, there is powerful evidence that PrEP use is slashing rates of new HIV diagnoses among gay men and other men who have sex with men. But it was just a few years ago that PrEP was being described as too slow and 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

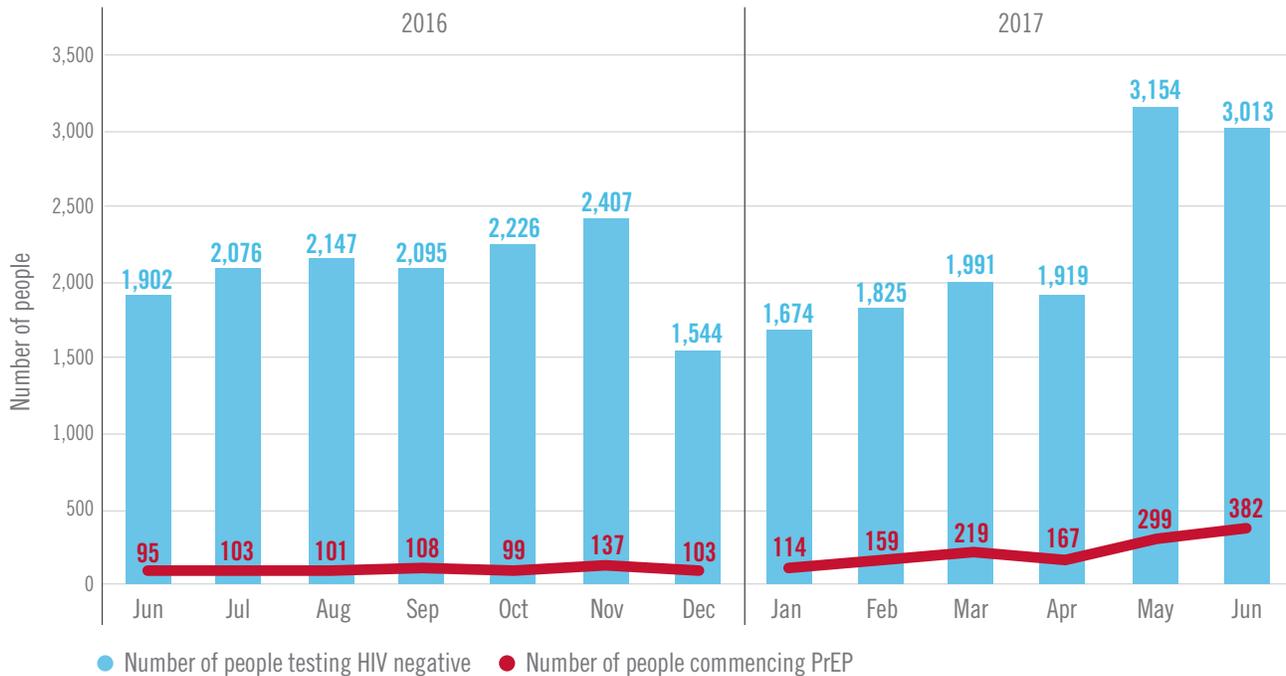
higher uptake number using the same calculation—or it might not. But if uptake is calculated using broad categories, then the percent uptake will almost certainly look artificially low.

- **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.

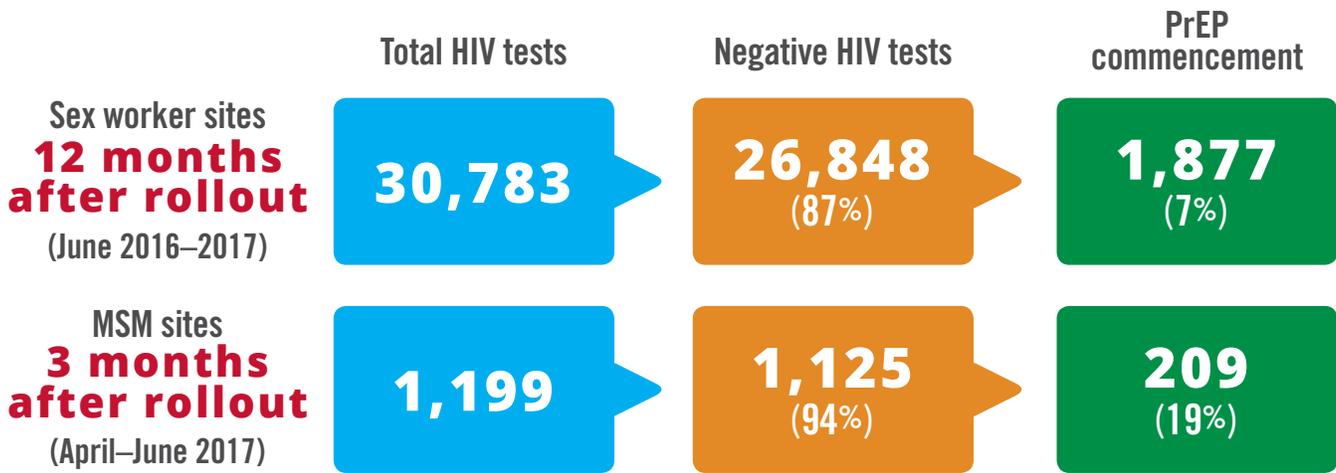
When it comes to oral PrEP, variations on these positions exist today, and that’s to be expected. What’s more surprising is that an additional thread of today’s debate is calling into question the efficacy of PrEP with direct and elliptical statements suggesting that the available data raise questions

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**



**LESSONS LEARNED**

- PrEP incorporated well into combination prevention delivered by NIMART trained nurses.
- Since implementation, clients’ views of PrEP have evolved; there are increased levels of cycling on and off PrEP due to risk profile changes.
- Peer outreach, convenient operating hours and mobile services drive higher service uptake.
- Strong adherence support is critical, especially in the first few months of PrEP use.

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.

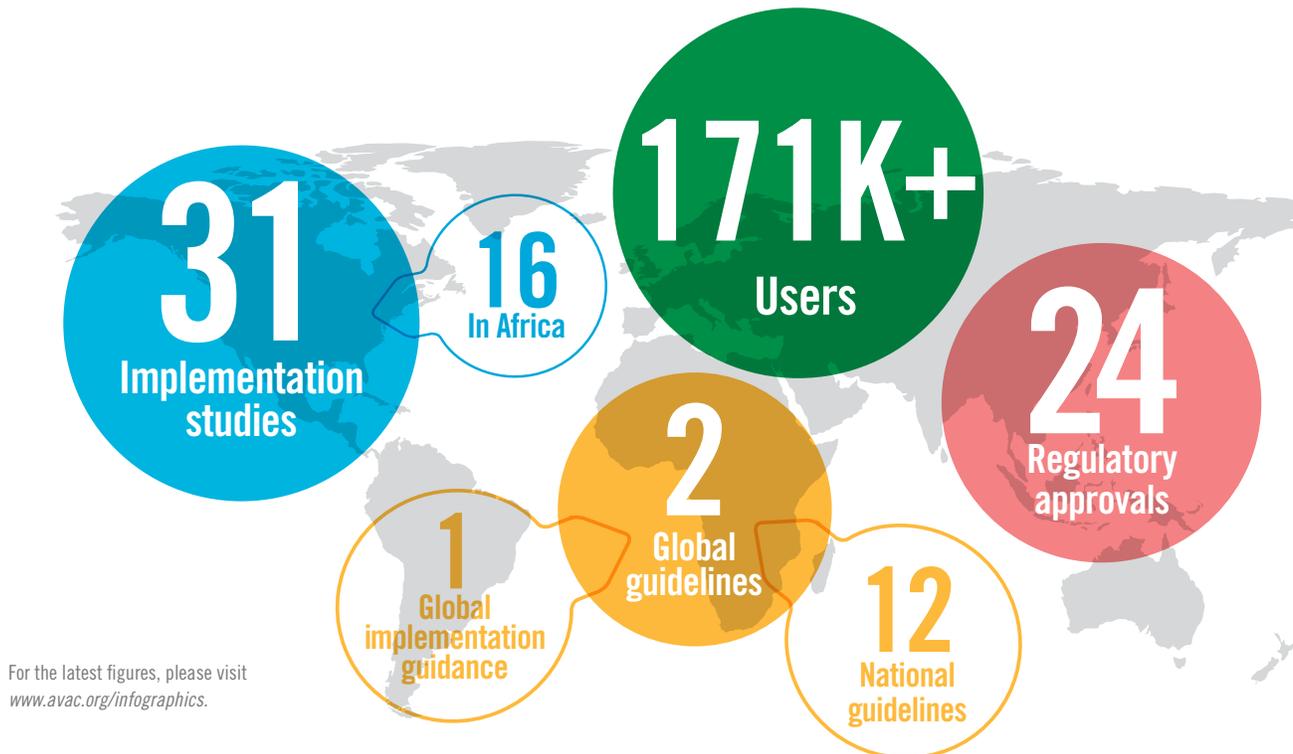
To be clear, there are many questions about oral PrEP using TDF/FTC that need to be answered, particularly about how to deliver it in programs that meet people’s needs and support them in choosing to start and stay on PrEP safely. Biology *does* impact HIV treatment and prevention. For example, far more 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 (FHCRC) 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 at 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

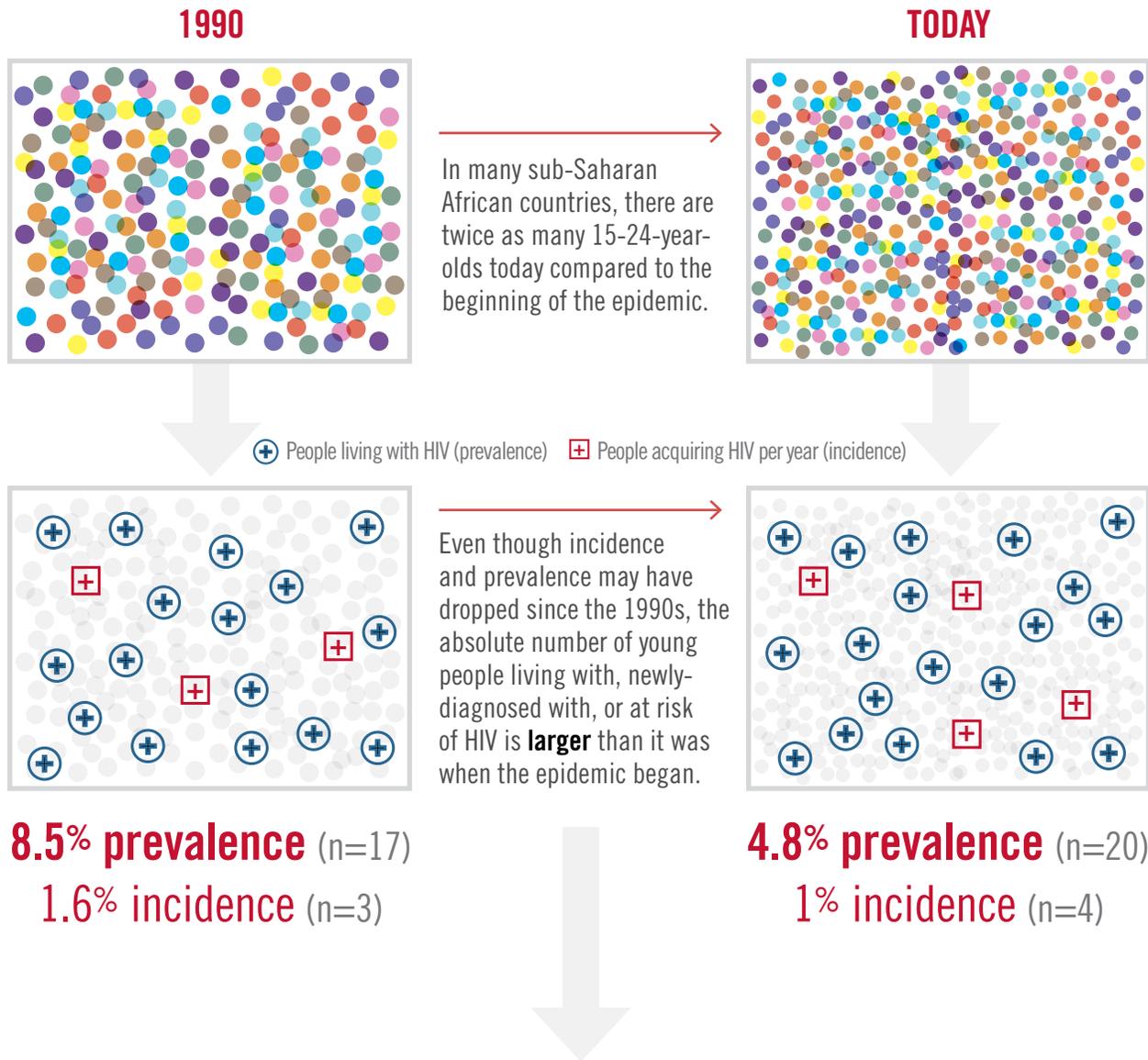
ART and are virologically suppressed. But not all indicators are created equal, and not all reports can be taken at face value. In the context of early PrEP rollout, it's essential for advocates to engage and, where needed, challenge the indicators in use today.

	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.