

THE EVOLUTION AND FUTURE OF HIV PREVENTION TECHNOLOGY

An HIV Policy Primer

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This paper serves as a primer on the evolution of HIV prevention efforts, innovative new technologies, and the outstanding barriers that keep critical tools from reaching those who would most benefit.

Introduction

The HIV pandemic has changed the face of global health, posing serious challenges to development and political, economic, and cultural stability in many countries and communities. Since the beginning of the pandemic in the early-1980s, an estimated 75 million people have contracted HIV, and 32 million have died of AIDS-related illnesses. Fueled by scientific advances and global political and financial will, more than 23 million people were on life-saving anti-retroviral treatment (ART) at the end of 2018. In stark contrast, prevention programs have struggled, and despite early declines, the annual number of new infections has hovered at or just below 2 million per year for the last decade. Dramatically reducing infections is essential to bringing the HIV pandemic under control, but it will require both ensuring innovative prevention technology reaches those who need it and the political and financial will to make prevention a global priority.

Over the last almost four decades, many prevention strategies and tools have been utilized to try to stymie the spread of HIV, with moderate success. The arsenal of prevention tools and approaches used over that period has enabled many gains, including the provision of treatment to mothers during pregnancy, childbirth, and breastfeeding. Known as prevention of mother-to-child transmission (PMTCT),

2018 KEY STATISTICS¹

- 1,700,000 new HIV infections
 - 61 percent occurred in sub-Saharan Africa
 - among adult infections, 47 percent occurred in women and 20 percent occurred in young women aged 15–24
- 37,900,000 million people living with HIV (PLHIV)
- 700,000 AIDS-related deaths

The Risk of Acquiring HIV Was:

- 22 times higher among men who have sex with men (MSM);
- 21 times higher for sex workers; and
- 12 times higher for transgender people.

At the time of publication, there were approximately 337,500 people on daily oral pre-exposure prophylaxis (PrEP).²

it has prevented an estimated 1.4 million HIV infections in children between 2010 and 2018. Combined with the introduction of other important advances such as voluntary medical male circumcision (VMMC), total annual numbers of new infections were reduced by more than 1 million per year from 1998 to 2011.

However, HIV prevention programs have been hindered by the absence of a robust mix of tools that meet the needs of different populations in different places. Two hard realities have profoundly impeded control of the global pandemic. Despite vaccine research starting in 1987, there is no vaccine candidate on the verge of coming to market, and there is no cure—and the prevention tools that are available have been insufficient to meet the variety of needs and vulnerabilities that put certain people at risk. In recent years, there has been hope that using HIV “treatment as prevention” (TasP) would drive the infection rate down, but that early promise has yet to be realized because existing tools, such as oral pre-exposure prophylaxis (PrEP), have not yet reached the scale needed to have an impact in many countries. Stigma—societal, institutional, and self-stigma—continues to be a formidable barrier to access to prevention information and tools around the world.

Prevention programs have faced a variety of structural barriers even as new tools have come to market, including inadequate financing, regulatory and guideline obstacles, and inefficient delivery of health services. There is an opportunity now to address critical implementation challenges for prevention tools with several novel HIV prevention tools at different stages of development. Further, as demonstrated in the 2018 global data presented by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in its July 2019 report, the continuing high rates of new HIV infections argues strongly in favor of significantly elevating the priority of prevention within the global HIV effort. Approximately 1.7 million people were newly infected in 2018, far from the desired levels of less than 500,000 annually targeted by the UNAIDS Fast Track goals. As long as the number of PLHIV continues to grow at high rates annually, the goal of bringing the global pandemic under control will remain elusive and the financial and political pressures to contain it will increase in intensity. Further, most new infections are occurring among young adults. With the youth population growing at a swift pace in many areas of the world, specifically sub-Saharan Africa, the sheer numbers of PLHIV—should prevention among that age group fail—could overwhelm health delivery systems and lead to a risk of disease resurgence.

This harsh reality comes at a time when aggregate money for the global HIV effort has been stagnant for a decade, with concerning declines in the last three years. There is a need to make hard choices within the envelope of available resources. Historically, primary prevention has not been equally prioritized with ART provision in global and country-level HIV programs, such as the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR). Elevating prevention now will have to be a political, policy, and financial choice that puts more resources toward accelerating access to important new HIV technology with the goal of driving down the infection rate. Fundamentally, governments will need to make their own choices, but the priorities of donors, such as the U.S. government and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund), are very important in shaping the decision-making and prioritization of those governments. As the U.S. government remains the leading funder of global HIV efforts, a systematic reassessment of U.S. prioritization of and commitment to prevention should be conducted before development of a new strategy for 2021 and beyond starts over the next year.

HIV Prevention Historical Challenges

HIV prevention has suffered from four main challenges: (1) reliance on biomedical prevention and behavior change approaches that do not fully account for societal and other factors that put certain people at acute risk; (2) lack of an effective mix of methods that account for different transmission circumstances; (3) an absence of discreet, easy-to-use methods under the direct control of the individual person seeking to prevent infection; (4) inconsistent use of available methods at every high-risk encounter or lack of adherence. The absence of effective programmatic platforms for prevention is a fifth challenge covered in the Health Systems section below.

New infections peaked in the late-1990s with annual estimated infections of 2.9 million for several years, rising to 3.8 million in 1998.³ Following the identification of the human immunodeficiency virus in 1983, creation of the first diagnosis test in 1985, and improved understanding of the transmission methods, the primary approaches to HIV prevention rested on behavior change messaging around avoiding risky sexual behavior and use of barrier methods. Uganda led the way in putting forward a unifying three-part message: Abstinence, Be faithful, and use Condoms (ABC). In 1986, the Ugandan government created the National AIDS Control Program in the Ministry of Health, the first national HIV/AIDS program in Africa, and began utilizing ABC as its prevention strategy. First and foremost, the message was to abstain from sex. If that was not possible, then one should be faithful to a single partner and practice “zero grazing” outside of that relationship. Finally, if one could not abstain, then they should use a condom. The ABC strategy was not perfect. Indeed, it was the subject of considerable controversy and debate at the time. Even so, it has been credited with dramatically reducing the rates of HIV/AIDS infection in Uganda at a time when other African countries were being ravaged by the disease.⁴

The ABC approach remained the leading prevention method through the 1990s. The advent of ART in 1996 offered another prevention tool to the arsenal. Subsequent research showed providing anti-retroviral (ARV) drugs to women while they are pregnant, giving birth, or breastfeeding could prevent transmission of the virus to their baby. The World Health Organization (WHO) first recommended the use of ARVs for PMTCT in 2000. The creation of the Global Fund in 2002 and PEPFAR in 2003 brought ART and PMTCT to countries worldwide. In 2007, the WHO recommended VMMC as another HIV prevention option for men.

VMMC provides men lifelong partial protection by reducing the risk of female-to-male HIV transmission by 60 percent, and modeling has suggested that achieving 80 percent coverage among 15-29 year old men in PEPFAR's priority countries would prevent millions of HIV infections.⁵ More than 19 million men underwent VMMC for HIV prevention between 2010 and 2018, with the largest proportion (46 percent) between the ages of 15 and 29.⁶ As a result of these combined approaches, annual new infection rates began to fall from the late-1990s.

Treatment as Prevention

By 2010, major progress had been made in bringing treatment to millions worldwide as PEPFAR and the Global Fund demonstrated that large treatment programs were possible and effective. The number of annual new infections also had plateaued, but the arsenal of prevention tools remained limited. There was clear need for tools that were discrete, easy-to-use, and highly effective at preventing infection. The inability to unlock dramatic incidence reductions was driven by the failure to meet the needs of those most vulnerable to or at risk of infection, including adolescent girls and young women (see text box) and members of key population groups, such as MSM, transgender people, sex workers, and people who use drugs.

The ABC approach relies on two components, neither of which are discreet nor allow the individual user to achieve protection without the knowledge of his or her partner. The first is behavior change, which must start with an acknowledgement of risk and an accompanying willingness to change one's sexual behavior to mitigate that risk. The second is correct and consistent use of a barrier method at every high-risk sexual encounter. However, for either approach to be effective, both partners must agree tacitly or overtly to abstain, be faithful, or use condoms. In situations where one of the sexual partners does not control the encounter or is not empowered to insist on fidelity or use protective measures, the approach is likely to fail. Women, in particular, may not be able to insist that their partners use a condom or stay faithful many countries. For example, in 2017, only 63 percent of men in South Africa aged 20-24 years who had two or more sexual partners in the past year reported using a condom at last intercourse.⁷ Women also may face sexual or gender-based violence that leaves them unable to control their sexual activity and may face stigma or violence if they seek HIV prevention methods, including the use of condoms.

The lack of discreet, user-driven prevention remained a critical gap for women and at-risk populations. Based on the success of PMTCT using ARVs to prevent infection, there was promise that use of ART could be expanded for greater protective benefits and help address those gaps. New research released in the early-2010s indicated TasP could be used in two ways. The first is to mitigate transmission of HIV by reducing the viral load of people already living with the virus through use of ART. The second is the use of ART as PrEP to prevent HIV acquisition by people who have not been infected but are at high risk.

TASP TO MITIGATE DISEASE TRANSMISSION

Use of TasP as a prevention tool gained traction first following the results of several important studies. In 2011, the HPTN 052 study looked at transmission among heterosexual serodiscordant couples, meaning one member of the couple was living with HIV and the other was not. The study showed that early initiation on ART by the HIV-positive partner reduced cases of transmission to the HIV-negative partner by 96 percent. In 2014, the PARTNER study added additional evidence that viral suppression was key. When the partner taking ART achieved and maintained viral suppression (i.e., the level of the HIV virus in their blood was undetectable), no transmission among serodiscordant couples occurred despite a reported 58,000 acts of condomless sex. The Australian-based Opposites Attract study additionally found HIV-positive men who are on treatment and maintain viral suppression do not transmit HIV to their partners. This concept that an undetectable viral load equates to being unable to transmit the virus is now known as U=U (undetectable=untransmittable) and is being used to educate about the effectiveness of TasP through public health and media campaigns.

UNAIDS, PEPFAR, and the Global Fund have adopted the TasP idea since 2014 as part of global messages and programmatic approaches to prevent and treat HIV. It is reflected in the global goals to bring HIV under control. However, use of TasP as a strategy to mitigate viral transmission has up to now not fueled dramatic reductions in new infections. To be effective at an individual level, those on ART must properly adhere to their treatment regimen and consistently and correctly take their medication even once their viral loads have been reduced to a level at which blood tests can no longer detect the virus. To be effective at a community level, initial models showed a large proportion of PLHIV in a given community would need to have achieved viral suppression. In

2014, UNAIDS announced its Fast Track goals with a target of having 73 percent of PLHIV virally suppressed by 2020. Achieving that goal would require 90 percent of all PLHIV to have tested and know their status, 90 percent of those who know their status to be on ART, and 90 percent of those on ART to have achieved viral suppression. While many cities and countries have made major progress toward achieving those goals, there have continued to be major hurdles to getting PLHIV diagnosed, on treatment, and virally suppressed globally. By the end of 2018, just over 60 percent of the estimated 37.9 million people worldwide were on ART, and only 89 percent of them were virally suppressed, which accounts for only 53 percent of all PLHIV worldwide.^{i,8} In the United States, the viral suppression rate is only 52 percent, which is the lowest among comparable high-income countries.

TASP TO PREVENT HIV ACQUISITION

Use of ART to mitigate HIV transmission added an important tool for the prevention arsenal, but it did not fill the missing gap of a user-friendly method that enables individuals to take control of their own prevention. However, research into the use of ART as PrEP offered promise for the first time that an individual could take control of his or her own HIV prevention in a discreet and user-friendly way. Initial research focused on taking a daily dose of oral ART to prevent infection. The first trial of “oral PrEP” in humans to show efficacy was the Iniciativa Profilaxis Pre-Exposición (iPrEx) study in 2010, which found that the HIV infection rate was reduced by 44 percent in HIV-negative MSM and transgender women who were given a daily pill containing tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) compared with men given a placebo.⁹ In 2011, results from the Partners PrEP and TDF2 trials among heterosexual men and women at risk of infection in Africa demonstrated even higher efficacy.

In 2012, the U.S. Food and Drug Administration (FDA) approved the use of Truvada, a TDF/FTC formulation previously approved for use as treatment for PLHIV in 2004, to reduce the risk of HIV infection in uninfected, high-risk individuals based on the comprehensive body of evidence.¹⁰ In 2014, the WHO first recommended the use of oral PrEP to prevent HIV acquisition for members of populations at higher risk of infection, including MSM. The following year, the WHO expanded the guidelines to include all populations at substantial risk of acquiring HIV.¹¹

“On the basis of further evidence of the effectiveness and acceptability of PrEP, WHO has now broadened the recommendation [from the 2014 MSM guidelines] to include all population groups at substantial risk of HIV infection. Offering PrEP should be a priority for populations with an HIV incidence of about 3 per 100 person-years or higher. PrEP should be an additional prevention choice in a comprehensive package of services that also includes HIV testing, counselling, male and female condoms, lubricants, ARV treatment for partners with HIV infection, voluntary medical male circumcision and harm reduction interventions for people who use drugs.”

PEPFAR began supporting PrEP demonstration projects in 2014 under the DREAMS Innovation Challenge, and Kenya and South Africa were the first countries in Africa to approve PrEP in 2015 (see text box).¹²

Mathematical models predicted that oral PrEP could have a large and fast impact for people at risk if introduced rapidly and at high coverage. For example, a simulation focused on high-risk MSM in the United States showed that oral PrEP use reduced the lifetime risk of HIV infection from 44 percent to 25 percent.¹³ Oral PrEP has already had an impact on HIV transmission in high-risk populations in places where it has been introduced at sufficient scale. The most notable example is from Australia. The Expanded PrEP Implementation in Communities–New South Wales (EPIC-NSW) study published in 2018 showed that targeted utilization of oral PrEP at a high coverage rate among MSM was associated with a reduction in HIV diagnoses by 25 percent in one year. The study dispensed oral PrEP to 99 percent of its participants at least once during follow-up, and only two men became infected with HIV during the study.^{14,15}

Unfortunately, oral PrEP has not been introduced at that same level of scale and coverage in other places with high HIV infection rates. It has been four years since the WHO expanded its guidelines and yet current estimates show that only 340,000 people in 72 countries are using oral PrEP. However, that is a small proportion of those estimated to be at risk worldwide, given the 1.7 million new infections annually. It also falls far short of the Fast Track target of enrolling 3 million people in low- and middle-income countries in PrEP. Further, most of the current oral PrEP users are concentrated in a few countries. An estimated 40 percent are in the United States alone, which increases to

ⁱ To understand the total number of PLHIV virally suppressed, you multiply the proportion of PLHIV who know their status (79 percent) times the proportion accessing treatment (78 percent), by those virally suppressed (86 percent). The total of all PLHIV virally suppressed at the end of 2018 was only 53 percent (79 x 78 x 86).

53 percent when including the United Kingdom, France, Australia, and Canada. Only eight countries worldwide have more than 10,000 people enrolled on oral PrEP, accounting for 83 percent of all enrolled, but only three of the eight are high-burden countries in Africa, and only two are among the 10 countries with the highest HIV prevalence worldwide. An estimated 34 percent of all oral PrEP users are in sub-Saharan Africa, where use is concentrated in four countries (Kenya, South Africa, Zimbabwe, and Uganda); most users are adolescent girls and young women.^{ii,16}

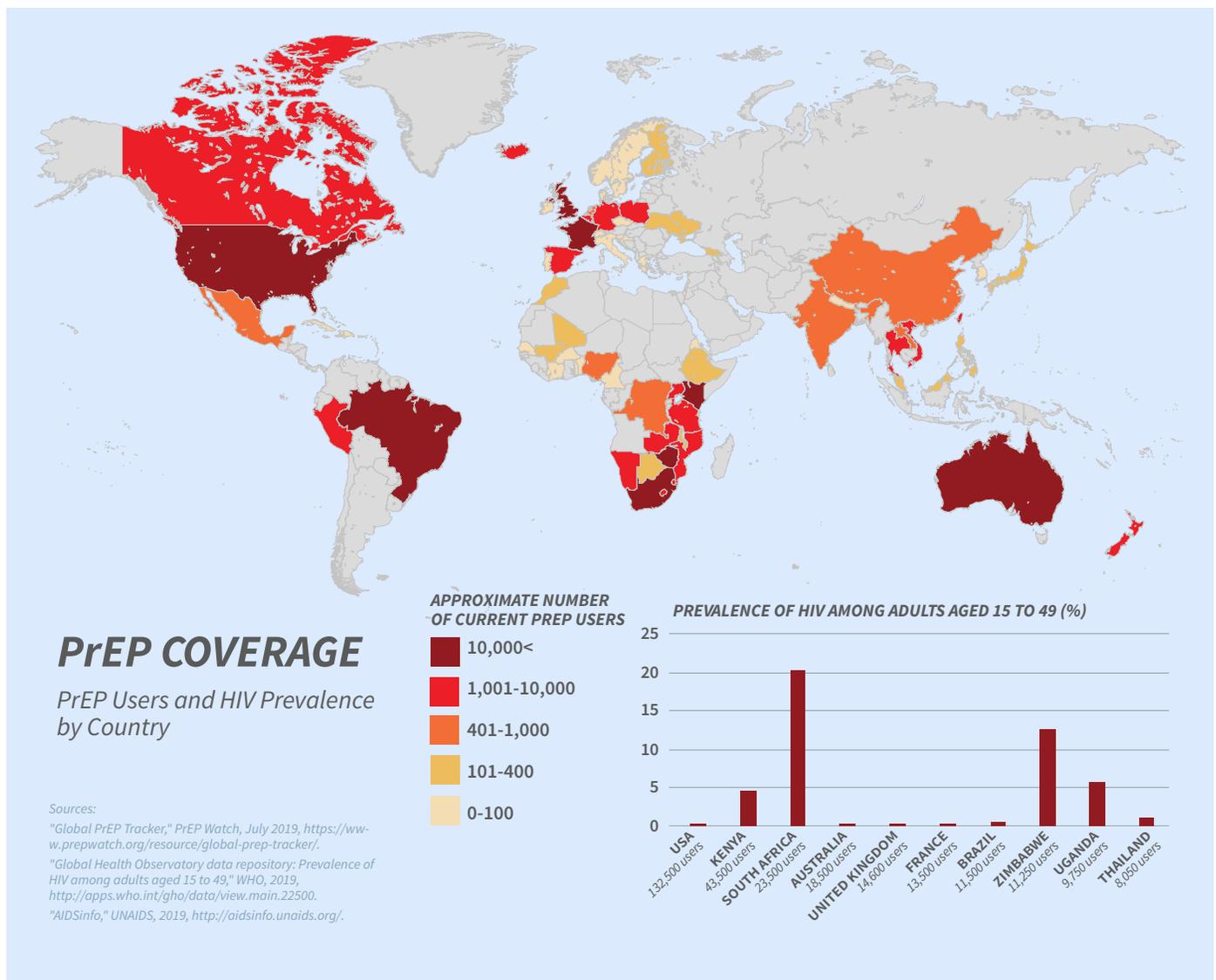
There are significant gaps in coverage worldwide. Even in the United States, where approximately 132,500 people are on oral PrEP, the Centers for Disease Control and Prevention (CDC) estimates that 1.1 million people are at high risk for HIV and should be using it.¹⁷ As of 2016, 93 percent of all oral PrEP users in the United States were male, and most were MSM. Worldwide, 64 percent of all oral PrEP

users were 25 to 44 years old, even though adolescent girls and young women ages 15-24 are particularly vulnerable in sub-Saharan Africa.¹⁸ Access remains a key barrier. More than 25 low- and middle-income countries were operating PrEP pilots or demonstration projects but fewer than 10 were implementing PrEP programs nationally. Even where PrEP is most accessible, less than 10 percent of those who would benefit from its use are on oral PrEP.

TASP LIMITATIONS

There are several reasons why TasP has yet to drive dramatic decreases in new infections. Both approaches require adherence to daily pill-taking for full effectiveness. For oral PrEP, otherwise healthy individuals must adhere to taking pills and may face barriers to use, including stigma, familial objections, and legal challenges. Low personal perception of risk and stigma are perhaps the main factors of non-adherence in both low- and high-income settings. Many

ii Data collection on PrEP users is challenging as PrEP use is not static.



participants in PrEP trials have reported having a low risk, or even no risk, of HIV, despite being members of high-risk populations.¹⁹ In many communities with high HIV rates, such as South Africa, pill-taking is associated with being sick. Potential PrEP users may decline use over concern their families or communities may believe they have HIV.

Offering long-acting drug formulations and delivery options that do not require daily dosing is likely to help facilitate better adherence. There are several options currently in development or clinical trials. An intravaginal silicone ring that releases dapivirine over the course of a month has been shown to be safe and effective; it is currently under review with the European Medicines Agency and could be available in 2020. There are also two trials testing the efficacy of a long-acting injectable PrEP. If found safe and effective, injectable PrEP may be a preferable method of PrEP for those who struggle to take pills, or fear the stigma related to taking PrEP. Results from efficacy trials of injectable cabotegravir are expected in 2021 and 2022.^{20,21} Another option in development is PrEP delivery through an implant, which offers the additional potential to be longer lasting than injectable PrEP and may be removed in the event of adverse reactions. There are several long-acting PrEP implants in preclinical trials, and it will take some time before they are ready for approval and market introduction. In the interim before these new tools come to market, offering on-demand PrEP will allow those who do not want to be on daily oral PrEP for an extended period to still have some protection when they need it. There is more that needs to be understood about risk perception and why some individuals start and stop PrEP use. Guidance around the efficacy of on-demand use could help address adherence issues for some, as users would not need to remember to take a pill every day. In addition, those who face financial barriers could spend less on PrEP if only using it intermittently.

Regardless of the PrEP method, implementation of it and ART at scale remains a barrier to achieving the full impact of TasP, and neither is a miracle option on its own. Experience with use of TasP has demonstrated the importance of having a robust multi-method arsenal of prevention tools and methods. Several recent studies that looked particularly at the impact of TasP as a transmission mitigation tool provide evidence that use of ART alone will not dramatically bring down new infections. One study, HPTN 071, known as the Population Effects of Antiretroviral Therapy to Reduce HIV Transmission or PopART study, examined the impact of a package of HIV prevention interventions on the rate of new infections at

the community level.²² PopART demonstrated that ART must be used in tandem with VMMC and oral PrEP, as well as other social and behavioral approaches, in order to achieve an accelerated decline of infections.²³

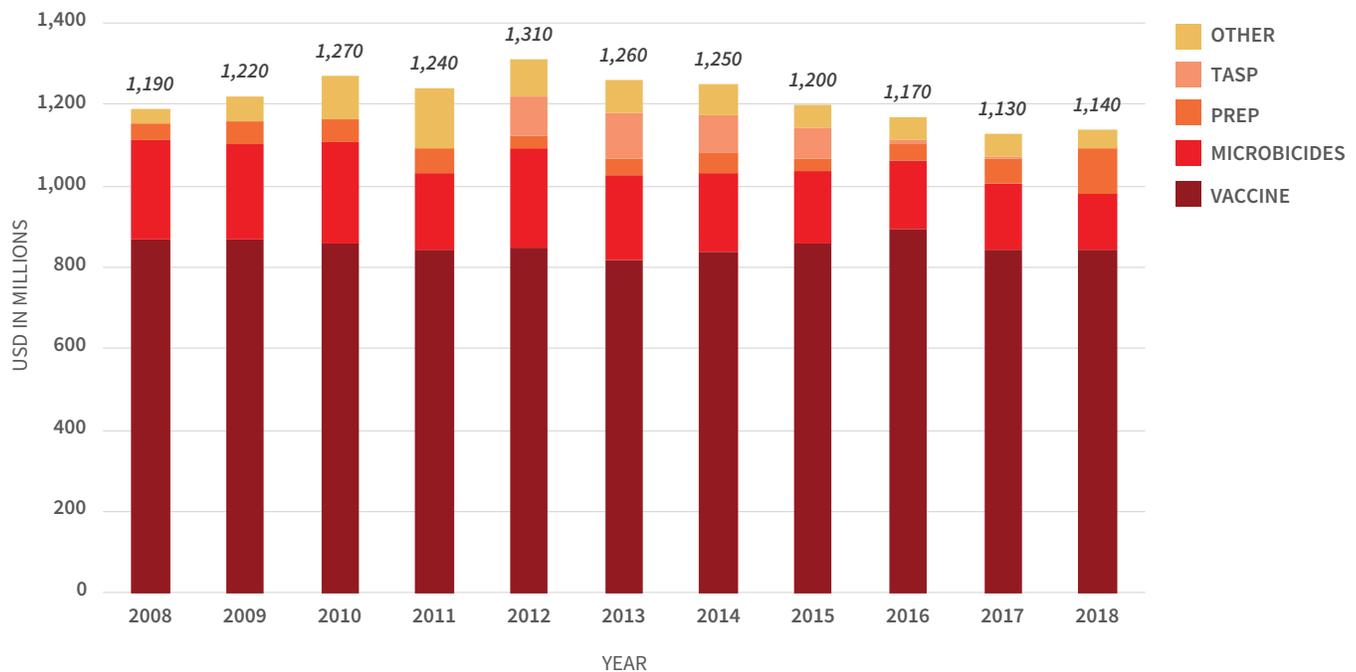
Critical Systems and Implementation Challenges

There remain many systematic barriers to achieving scale and coverage of prevention approaches globally, as evinced by the introduction of oral PrEP over the last five years. With a number of new products and approaches in various stages of clinical trials (see text box), these barriers will need to be addressed to ensure innovative technology reaches those who need it most. Among the most critical implementation challenges are: insufficient overall financing for the global HIV response and lack of prioritized programming for prevention within the available funding envelope; regulatory and enabling guideline hurdles that delay or prevent utilization of prevention tools; and weak health systems that inhibit access and availability. Insufficient demand creation among potential product users also can inhibit uptake of tools even when available. In addition, stigma continues to be a formidable barrier to access and use of prevention tools.

HIV PREVENTION INVESTMENTS AND PRIORITIZATION

Funding and programmatic prioritization remain limiting factors in ensuring that prevention tools are developed and that those approved for use reach scale and coverage sufficient for impact. Global resources for HIV have stagnated over the last decade. From 2002-2011, annual resources increased rapidly through bilateral and multilateral programming primarily by PEPFAR and the Global Fund. Since 2017, there have been concerning declines in the resources allocated to HIV, particularly by other traditional donor countries, and in global investment in HIV prevention research and development (R&D). For the 2017-2019 period, the Global Fund allocated almost half of its approximately \$10.2 billion to HIV.²⁴ In October 2019, the Global Fund's Sixth Replenishment Conference sought to raise at least \$14 billion to carry forward Global Fund operations through 2022. In total, \$14 billion was pledged, including \$4.68 billion from the United States, which represents an almost 9 percent increase from the Fifth Replenishment Conference, at which the United States pledged \$4.3 billion.^{25,26} In 2018, the total global investment in HIV prevention R&D was \$1.14 billion. While this is a \$10 million increase from the year prior, investment levels decreased annually for the previous six years, and the 2017 investment was the lowest since 2005.²⁷

GLOBAL HIV PREVENTION R&D INVESTMENT BY TECHNOLOGY CATEGORY



Source: HIV Prevention Research & Development Investments, 2018: Investing to End the Epidemic, www.hivresourcetracking.org.

The U.S. government remains the leader in financial support for the global HIV effort through R&D funding, its bilateral PEPFAR program—the largest commitment by any nation to HIV in the world, and contributions to the Global Fund. The U.S. government funded approximately 73 percent of HIV prevention R&D resources, or \$835 million, in 2018. In addition, PEPFAR has invested more than \$90 billion to global HIV efforts since fiscal year (FY) 2004, including U.S. contributions to the Global Fund. PEPFAR's annual funding peaked in FY 2010 at \$5.57 billion and then subsequently fell by over \$800 million between 2010 and 2013. Annual appropriations have remained relatively flat since FY 2011. For FY 2019, PEPFAR's \$6.8 billion (including \$1.35 billion to the Global Fund) represented 62 percent of U.S. global health funding.²⁸

Due to the sheer magnitude and reach of PEPFAR funding, its spending directives and programming investments dramatically influence the global HIV agenda. Since inception, PEPFAR's core goals have centered on provision of lifesaving medication to PLHIV, care and support for those affected by the virus, and prevention of new infections. Earmarks for funding specific programmatic interventions have been included since the original 2003 authorizing legislation and subsequent iterations in 2008, 2013, and 2018.ⁱⁱⁱ Current mandates in the 2018 legislation require that more than half

of annual bilateral resources be used for HIV treatment, care, and nutrition for PLHIV and at least 10 percent for activities supporting orphans and vulnerable children. There is no funding requirement for prevention, but Congress requires balanced funding for prevention activities; a report must be submitted to Congress if less than half of annual prevention funds are spent on behavior change programming, including abstinence programming, in high-prevalence countries.²⁹

PEPFAR provides ongoing support to more than 14.7 million people on ART and in 2018 allocated 42.6 percent of its total country and regional operational plan budget to treatment. Although it has had a heavy treatment focus, PEPFAR has advanced new prevention approaches based on emerging science, rapidly adopted new WHO guidelines, and supported demonstration projects of new tools within its country programs. For example, PEPFAR has adopted and prioritized the Option B+ lifelong treatment approach for pregnant women, VMMC, and more recently oral PrEP. In addition, the PEPFAR-led DREAMS partnership has created a comprehensive prevention approach for adolescent girls and young women in 13 African countries to address their risks and vulnerabilities to HIV infection. In contrast to the treatment investment though, only 15.6 percent of its 2018 country budgets was allocated to prevention activities.³⁰

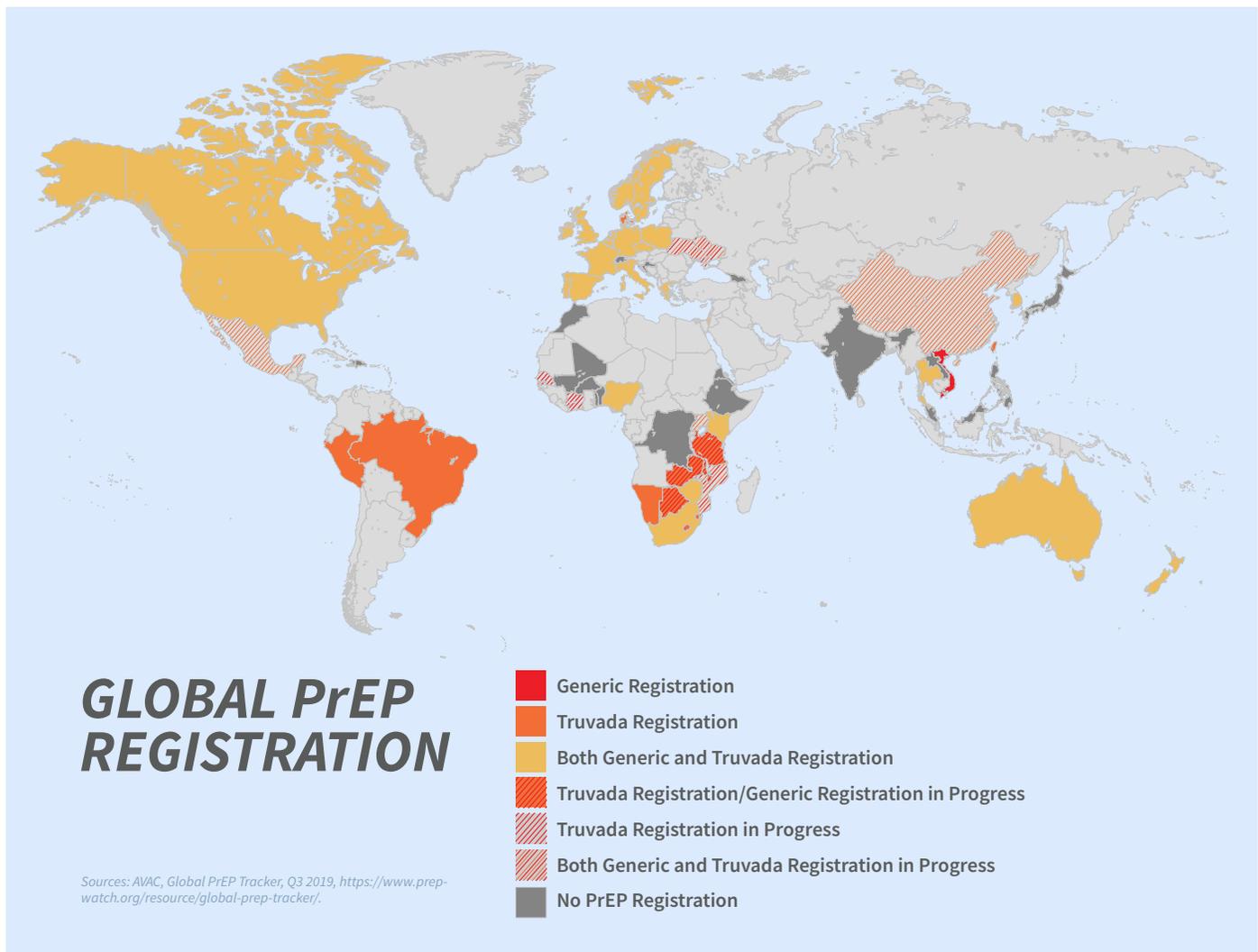
iii To learn more about these programmatic earmarks and the changes to PEPFAR legislation over time, see the Kaiser Family Foundation's report titled "PEPFAR Reauthorization: Side-by-Side of Legislation Over Time."

REGULATORY APPROVAL AND IMPLEMENTATION GUIDELINES

Even with sufficient funding and prioritization, introduction and uptake of new prevention technology can be slow, in part due to the many steps a drug or tool must move through before reaching the end user. Drug regulation varies by country, but in general new drugs that have completed the necessary trials must be approved by a given country's regulatory agency, which reviews the drug for quality, safety, and efficacy. The timing of these approvals can vary depending on the country's rules and the capacity of the regulatory agency.³¹ In addition, each country's ministry of health has different requirements and regulations that tools and drugs must meet in order to be registered in-country. Once registered, ministries typically must issue guidelines and directives to health facilities for the product to be used. The timelines and requirements for issuing national guidelines again vary by country.

Oral PrEP provides a current example of how the regulatory process can delay access to those who need new

HIV technology the most. As noted above, the WHO first recommended the use of oral PrEP for selected groups at high risk of HIV infection in 2014 and expanded the guidelines to include all populations at substantial risk of acquiring HIV in 2015.³² Despite the WHO's recommendations, oral PrEP is not available in all countries. At the time of publication, only 36 countries have national guidelines on PrEP use, although either Truvada or a generic oral PrEP is registered for prevention use in 44 countries.³³ Many countries with high burdens of HIV do not have national guidelines. Thus, despite the availability of a highly effective tool to enhance the existing arsenal of prevention methods, the inability for those at high risk to access oral PrEP in many countries puts their own health at risk and inhibits the ability to contain the global pandemic. Addressing these regulatory and guideline obstacles is an urgent need not only to ensure rapid availability and uptake of oral PrEP but to streamline procedures ahead of the introduction of new products.



LESSONS LEARNED

ORAL PREP INTRODUCTION IN SOUTH AFRICA AND KENYA

South Africa and Kenya were the first two countries in Africa to approve the use of ARVs for prevention, and Truvada and generic versions of TDF/FTC are currently approved in both countries. The two countries took different approaches to rolling out oral PrEP, and as a result, their programs have had very different outcomes and impacts.

In November 2015, South Africa became the first country on the continent to approve the use of ARVs for prevention, and it was the first to offer oral PrEP outside of studies and demonstration sites. Just six months later, in June 2016, the South African National Department of Health introduced guidelines authorizing use of oral PrEP by female sex workers (FSW). Oral PrEP was made available at 11 existing sites providing services to FSWs in five provinces, with a twelfth site added three months after initial introduction. Over time the program was expanded to include other populations at risk of infection, including MSM in April 2017, and at other sites, including at universities for young students in October 2017. The 2017-22 National Strategic Plan includes PrEP for young women 18 years of age and older but not adolescent girls or young men. The South African plan also included sensitization trainings for health care providers working with FSW, and with oral PrEP more generally, as well as job aids and information, education, and communication materials for facilities providing oral PrEP.

Kenya approved oral PrEP less than a month after South Africa. The National AIDS and STI Control Program (NASCOP) systematically reviewed evidence from clinical trials and demonstration projects to inform the Kenya PrEP Implementation Framework and national PrEP program, which were launched in May 2017. The framework recommended oral PrEP for all HIV-negative people with a high risk of contracting HIV. Unlike South Africa, key populations were not explicitly prioritized in this framework. The national program integrated oral PrEP into other sexual and reproductive health services; trained service providers on knowledge, attitudes, and perceptions of oral PrEP; and developed a communications and advocacy

plan aimed at increasing oral PrEP awareness, knowledge, and acceptability. The plan initially targeted the general population, including religious leaders, community leaders, and media. Later, the focus narrowed to groups embedded in HIV work, such as health care workers, researchers, and key population networks, and finally to current and potential oral PrEP users.

Kenya has almost twice as many oral PrEP users than South Africa despite having a much smaller epidemic. As of July 2019, an estimated 23,500 people were on oral PrEP in South Africa and 43,500 people in Kenya. Comparatively, there were 7.7 million PLHIV in South Africa in 2018, and nearly a quarter million were newly infected. In Kenya, there were only 1.6 million PLHIV and 46,000 were newly infected.

The reasons for the disparity in the number of oral PrEP users despite concurrent programs offer lessons for other countries. While both countries had strong political buy-in, they utilized very different methods of introducing oral PrEP to the market. South Africa opted to focus on specific key populations, while Kenya opted to market oral PrEP to the total population and focus on counties with high prevalence rates. As a result, a larger percentage of the population in Kenya has started on oral PrEP, and uptake is widely accepted. In South Africa, on the other hand, scale up has been a challenge. Because of the initial introduction to FSW, oral PrEP use has been stigmatized as associated with sex work, which has alienated many adolescent girls and young women, who are at particularly high-risk of HIV infection in South Africa.³⁴ These two early examples have shown the importance of considering and combatting the stigmatization of oral PrEP by offering oral PrEP to the general population, strategic demand creation, and involving communities in the design, implementation, and communication of PrEP programs.

HEALTH SYSTEMS

Even where oral PrEP is approved and in the national guidelines, the absence of effective programmatic platforms for prevention in which new tools can be integrated as they become available can limit access and availability. Unlike delivering treatment, which generally uses health facilities to test, treat, and care for PLHIV, a similar singular platform does not exist for prevention. By default, healthy people generally do not go to health facilities. Prevention messages are delivered through the media and in settings such as community centers, schools, and workplaces. VMMC has often been provided through targeted outreach to places where young men congregate including schools and workplaces. Condoms are available in a variety of locations. As a result, oral PrEP implementation has faced a daunting challenge of how and where to provide access. Most country guidelines require that it be provided in a medical facility by a trained provider who can test to ensure the individual has not yet acquired HIV, write a prescription, and manage follow-up. Many facilities in high-burden countries already have large numbers of patients on ART to manage, so adding in additional patients seeking or on PrEP can overload providers. As new prevention tools hit the market over the next few years, consideration should be paid to how individuals can access them, including potentially from non-clinical providers or at different venues. Allowing non-clinicians to prescribe oral PrEP, or even offering it without a prescription, would lower the barriers to access. In October 2019, California became the first U.S. state to allow pharmacists to provide 60-day supplies of oral PrEP without a prescription if the individual can show a negative HIV test within the previous seven days.³⁵ With special training, pharmacists also will be able to provide post-exposure prophylaxis (PEP), which is the use of ART to prevent HIV acquisition possible exposure to the virus. Many of the long-acting PrEP options in development, such as injectables, will allow people to visit health clinics less often and might possibly be administered by pharmacists, community health workers, or nurses. Other tools, such as implants, may require a clinical interface.

Strong supply chains globally and in countries also are important to ensure the availability of HIV treatment and prevention, as drug and condom shortages and stock-outs occur periodically—or sometimes habitually—in many countries.³⁶ A weak supply chain and commodity forecasting system, or interruptions to commodity production, can inhibit access, as well as consumer confidence that their medicine or prevention products will be available when needed.

Availability is also affected by pricing and how products are procured and by whom. The cost of individual products to

the procurer and onward to the user can vary widely between countries depending on country-specific patent laws. In many countries, commodities provided by bilateral and multilateral organizations are distributed for free or at low cost through the public health system. Cost also can vary within countries with those accessing commodities in the private health sector or through health insurance paying different prices or co-pays.

There has been particular controversy about the cost of Truvada for oral PrEP in the United States as a barrier to access and use. Truvada can cost up to \$2,000 a month in the United States, whereas a month's supply of generic oral PrEP in Australia costs \$8 per month or is available for free in some high-burden countries because Gilead Sciences donated doses.^{37,38} Accelerated use of oral PrEP by those at high risk of HIV infection is core to the plan to end the HIV epidemic in the United States by 2030, which President Trump announced in his State of the Union address in February 2019. Gilead has pledged to donate up to 2.4 million bottles of oral PrEP to the CDC through 2030; however, this will not fill the full need, with an estimated 1.1 million at risk in 2019.³⁹

In addition to price, advocates have raised concerns about the lack of oral PrEP options in the United States. Currently Truvada is the only oral PrEP product available, although Gilead has agreed to allow a generic version to be produced by 2020. Gilead also has a second tenofovir-based daily oral HIV PrEP product called Descovy, which the FDA approved for use in October 2019.⁴⁰ The DISCOVER trial, which included approximately 5,300 mostly MSM in the United States, Canada, Australia, and Europe, began in 2016 to assess whether Descovy was as safe and effective as the TDF/FTC formulation. In addition, Merck is developing an oral PrEP product using the drug islatravir. Phase 2 clinical trials are underway following preclinical trials that demonstrated effectiveness at a low weekly dose.⁴¹

Price is only one factor in determining who has access to which HIV treatment and prevention products. Not every product is approved for all users, which can limit the method mix available. For example, the primary findings from the DISCOVER trial, announced in early 2019, showed that the drug formulation, FTC and tenofovir alafenamide (TAF), also referred to as FTC/TAF, was safe and effective for MSM and transgender women, with slightly different side-effects.^{42,43} The FDA did not approve Descovy for women due to lack of data. Women historically have been underrepresented in health research making it difficult to extrapolate findings. Even when products are approved for use by all, certain individuals or groups may be prioritized in the implementation process or in marketing, which can affect overall uptake.

HIV PREVENTION TOOLS IN DEVELOPMENT

INTRAVAGINAL RING

The International Partnership for Microbicides (IPM) has developed an intravaginal silicone ring which releases dapivirine over the course of a month. Beginning in 2012, there have been a number of trials assessing this intravaginal ring. The Ring Study and ASPIRE assessed the effectiveness of the ring and showed that proper use of the ring reduced the rate of new HIV infections by 56 percent.⁴⁴ The subsequent DREAM and HOPE studies found a higher rate of adherence than the Ring Study and ASPIRE trials. These studies also found that the overall HIV incidence rate among women in the study was 54 percent lower than would be expected without use of the dapivirine ring.⁴⁵ The IPM ring is currently under review with the European Medicines Agency. IPM is also conducting clinical trials on a 3-month dapivirine ring, as well as a 3-month dapivirine and levonorgestrel ring used for both PrEP and contraception. CONRAD has an ongoing clinical trial assessing 3-month multipurpose prevention rings as well. This trial is comparing the safety of a combination TFV and levonorgestrel against a TFV only ring.⁴⁶

INJECTABLE PREP

A long-acting injectable PrEP produced by ViiV Healthcare is currently in efficacy trials. The HPTN 083 and HPTN 084 trials are evaluating the safety and efficacy of injectable cabotegravir every two months for PrEP in HIV-uninfected people. The results of these trials are expected in 2021 and 2022.^{47,48}

PREP IMPLANTS

Two types of implants are being explored: inert, where the delivery device stays in the body until the time of removal, and bioerodable, where the delivery device dissolves, leaving the active drug in place. The Centre for the AIDS Programme of Research in South Africa (CAPRISA), RTI, Oak Crest, and Northwestern University are all assessing the safety and acceptability of a sustained-release TAF sub-dermal implants for HIV prevention. CONRAD and Northwestern University are assessing similar implants using cabotegravir. Merck is assessing the efficacy of islatravir for PrEP using implant devices designed to provide prolonged islatravir. To date, these implants have been studied in rodents and nonhuman primates and have shown positive results.⁴⁹

MICROBICIDES

Topical microbicides have been the subject of research for many years. The CAPRISA 004 microbicide trial assessed the effectiveness of a vaginal microbicide gel used before and after sexual intercourse. This gel showed a 40 percent reduction in the risk of HIV infection in women.⁵⁰ A number of medicated vaginal and rectal gels, lubes, and douches are also in trial and have been showing promising results. An anal gel being developed by the Population Council that uses PC-1005 and an enema being developed by Johns Hopkins University that uses TFV are both in phase 1 trials. One study found that 63 percent of the HIV-negative MSM were willing to use a rectal microbicide for HIV prevention.⁵¹ There is also an MPT fast-dissolve insert being developed by CONRAD that uses elvitegravir and TAF in phase 1 trials.

OTHER

There are a number of novel delivery methods in preclinical trials. CONRAD is developing an MPT intrauterine device using elvitegravir. PATH is developing an MPT microarray patch using cabotegravir and progestin. CONRAD, PATH, the Population Council, and Kessel are jointly developing an MPT diaphragm using PC-1005. The Population Council is developing a nano-fiber using griffithsin. A dual-purpose pill with TDF/FTC and the contraceptives levonorgestrel and ethinyl estradiol is also in development.⁵²

VACCINES

In 2016, the HVTN 702 study began assessing the efficacy and safety of a new version of the HIV vaccine candidate from RV144. The trial includes men and women in South Africa, and results of the study are expected in July 2021.⁵³ In 2017, another trial, HPX2008/HVTN 705, began assessing the preventive vaccine efficacy of a new HIV vaccine candidate. This trial includes women in sub-Saharan Africa, and its results are anticipated sometime after 2022.⁵⁴

ANTIBODIES

The Antibody Mediated Prevention (AMP) Study is testing a manufactured antibody called VRC01. This study differs from vaccine studies in that instead of administering a vaccine and waiting for the patient to produce antibodies, researchers are administering the antibodies directly. The AMP study is comprised two “sister” trials, HVTN 704/HPTN 085 and HVTN 703/HPTN 081. Participants receive an infusion of the antibody every two months. Results from the trials are expected in late 2020.^{55,56}

For example, in the United States and Europe, oral PrEP is widely used among and marketed to MSM. In South Africa, the phased oral PrEP introduction approach targeted use by FSW, which resulted in mixed messaging that has been hard to overcome as marketing and availability was expanded to others. In other African countries, oral PrEP is portrayed as a tool for women, leading men to be skeptical of uptake.

DEMAND CREATION

As new prevention technologies are made available, users ideally see them as useful and make informed choices across a range of options so that they can find the right product that works for them at the right time in the right places. However, just because a product is available and priced correctly does not mean it will be used for greatest impact. There is a tendency for public health officials to think new tools targeting a disease or health issue will be instantly welcomed and utilized by consumers. HIV is no exception. However, when there is limited or no demand creation among potential product users coupled with the introduction of a new product, the result can be low uptake or, worse, stigmatization of the tool. One challenge is balancing the messaging about a prevention tool to those most in need while not stigmatizing the product to the larger population.

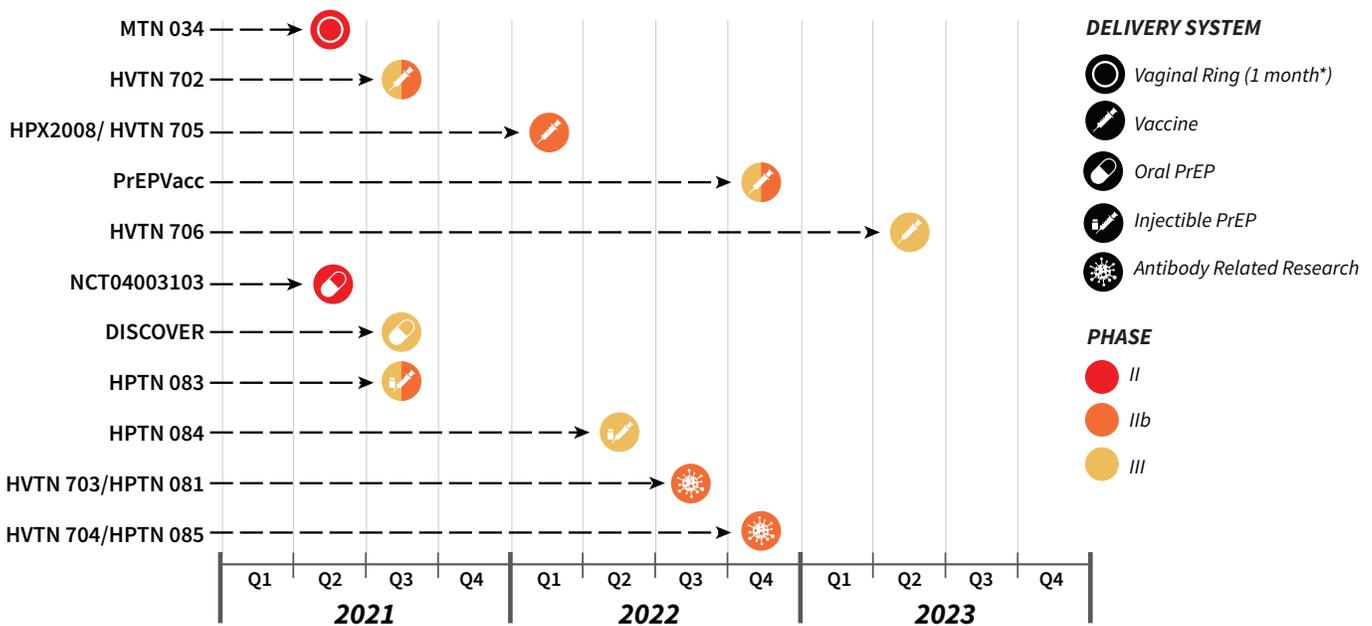
Framing oral PrEP, for example, and general prevention around positive living and protecting individual health has been seen as valuable. Among MSM in the United States, research has shown that clients responded more positively to messaging around protection and health than to messaging around risk.⁵⁷ Market segmentation, a process of grouping people according to their characteristics and then developing targeted marketing strategies for each group, has been a mainstay of social marketing tactics for many years. By grouping populations by risk, habit, and attitudes and targeting appropriate tools with the right messaging to these segments, the uptake of new tools can be made quicker and more effective. The approach has been used quite effectively with condoms and VMMC.⁵⁸

THE PERSISTENT CHALLENGE OF STIGMA

Stigma remains a formidable barrier to HIV prevention, treatment, and care and can manifest in several forms: legalized discrimination against groups at risk of HIV infection and PLHIV; societal stigma against PLHIV, groups at high risk, and high-risk behavior; stigma in health settings and among health workers; and self-stigma among those at risk or living with HIV.

Institutionalized discrimination, in the form of laws criminalizing certain behavior, such as homosexuality, sex work,

HIV Prevention Tools in the Pipeline: Clinical Phase II, IIb, and III Trials



*Currently under review by the European Medicines Agency; Will be submitted to the South African Health Products Regulatory Authority and the US Food and Drug Administration.

Source: "HIV Prevention Research & Development Database," AVAC, 2019, <https://www.avac.org/pxrd>.
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and drug use, promotes stigma and makes it difficult or even criminal to reach those engaged in that behavior with HIV services. Many countries with a high HIV burden have such laws, which may be amplified by rhetoric from political leaders condemning certain behaviors and threatening individuals with prison or worse. Even when no formal law exists, such rhetoric can create a de facto policy.⁵⁹ Often, political rhetoric is a reflection of broader societal stigma against certain behavior. Societal stigma may echo cultural or religious norms and manifest in bias in the places where health education and services are most critical, such as schools and health facilities. MSM, transgender women, sex workers, and others may be turned away from services or opt out of

facility-based care if they perceive or experience stigma. Adolescent girls frequently face opposition and harassment for seeking out HIV prevention because of perceptions that they should not be sexually active.

Ensuring non-discriminatory access to a wider variety of discrete, user-friendly prevention methods is critical to those facing such stigma and vulnerable to HIV infection. For example, oral PrEP enables women to take control of HIV prevention discreetly to minimize fear of stigma or violence. Long-acting prevention tools, such as injectables and implants, currently in development will provide additional options in the future. As these tools become available, they will meet the gaps that have persisted in HIV prevention.

ADDRESSING THE HIV PREVENTION NEEDS OF WOMEN

Women are highly vulnerable to HIV infection for social and biological reasons that can complicate their prevention needs. A woman's ability to advocate for herself, control her sexual interactions, and protect herself against gender-based violence all impact her HIV risk and her ability to access prevention tools. In many HIV high-burden countries, it is not uncommon for women's first sexual experiences to be forced or coerced. Women may face increased barriers to health service access and face stigma and abuse for using preventative methods. Women are not always able to ask their partners to wear condoms, or if they do ask, their partner may refuse.

In addition, because of the greater mucus area exposed to HIV during vaginal sex, women are more vulnerable than men to infection. There is also evidence that an imbalanced vaginal microbiome or infection with a sexually transmitted infection can increase a woman's risk of HIV acquisition and can impact the effectiveness of a TFV gel microbicide. In a clinical trial, TFV was three times as effective for women who had Lactobacillus-dominant vaginal microbiomes as it was among women with Gardnerella vaginalis-dominant vaginal microbiomes.⁶⁰

As a result of these factors, an estimated 6,200 young women between the ages of 15-24 become infected with HIV every week. Four in five new infections among adolescents aged 15-19 years in sub-Saharan Africa are in girls. Women need discreet, highly effective HIV prevention options. Up until the introduction of oral PrEP, such an option did not exist on the market. However, there is

more that needs to be done to meet the HIV prevention needs of women and ensure that their infection rates significantly decline. Women are underrepresented in clinical studies, specifically for HIV. As evinced by the FDA's decision not to approve Descovy for women, the absence of data limits understanding of how medications and dosing affect women and, by extension, provision of appropriate information to women about their risk and protection.⁶¹ For example, evidence suggests that in order to get protective effects of TDF/FTC, women need to take daily oral PrEP much more consistently than men. There is research showing that men can achieve consistent protection from HIV infection even if they take two to four doses per week. On the other hand, women may need to take at least six doses of oral TDF/FTC per week to achieve protection.

Women also need tools that address more than just their HIV prevention needs. Because pregnancy is visible, and HIV status is not, women are often more concerned about becoming pregnant and will seek out contraceptives before PrEP or other HIV prevention tools. A range of multipurpose prevention technology (MPT) products that address multiple sexual and reproductive health issues are currently in development. Currently, male and female condoms are the only MPTs on the market, preventing pregnancy, STIs, and HIV. Additional MPTs would accentuate the HIV prevention method mix and potentially also help fill the widespread unmet need for contraceptives.

There are a wide variety of delivery methods being explored for MPT, including daily combined pills, on-demand options, such as gels and inserts, and longer-action methods, such as implants and intrauterine devices. Some of these are coformulations of PrEP and

contraception, while others address multiple STIs.⁶² There are several clinical trials testing a 3-month dapivirine and levonorgestrel ring used for both PrEP and contraception.⁶³ A dual-purpose pill with TDF/FTC and the contraceptives levonorgestrel and ethinyl estradiol is also in development. This pill may be ready for market introduction in as little as 12 months, and because the individual drugs have already been approved by the FDA, approval of the coformulation will likely be expedited.⁶⁴ There are also preclinical trials on an MPT intrauterine device using elvitegravir, an MPT microarray patch using cabotegravir and progestin, and an MPT diaphragm using PC-1005.

also must be made to put more emphasis on driving down the infection rate. Governments will need to make their own choices, but the U.S. government and the Global Fund should also consider how to use their influence and re-prioritize prevention to ensure that these tools reach those who need them at greater scale and coverage.

How to Ensure Successful HIV Prevention

We have no choice but to get HIV prevention right. The global pandemic is at an important tipping point right now. Without a sharp decrease in infections, the growing youth population in countries with high HIV burdens in sub-Saharan Africa, where the overall population could increase from 1 billion to 4 billion before the end of the century, could fuel a dramatic resurgence in the virus.⁶⁵ Such a resurgence would undermine decades of progress and investment and make it ever more difficult to get the global pandemic under control. The world has at its disposal the best mix of HIV prevention methods it has ever had, with more innovative products on the way. However, those products can only have maximum impact if they are financially and programmatically prioritized, expeditiously made available, and delivered in a non-stigmatizing and non-discriminatory manner to those who need them the most. The obstacles inhibiting oral PrEP from reaching those at highest risk should be addressed and mitigated by global and country-level stakeholders. The potential of PrEP, used in combination with other prevention tools and methods, to kickstart a dramatic reduction in infections is there if we choose to use it.

We are now at a critical juncture. The Fast Track target of fewer than 500,000 new HIV infection annually comes due in 2020. To meet it, the number of infections would need to drop by 1 million over the next year. That can only happen if fighting HIV is elevated as a political and financial priority of governments and access to HIV prevention technology is accelerated. Within the envelope of available resources, political, policy, and financial choices

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Acknowledgements

This primer draws on consultations with experts, a review of the relevant literature, and independent analysis of available data. Many thanks to J. Stephen Morrison, senior vice president and director of the CSIS Global Health Policy Center, and Mitchell Warren, executive director of AVAC, who provided advice and comments on earlier drafts.

This report was made possible by the generous support of the Bill & Melinda Gates Foundation.

This report is produced by the Center for Strategic and International Studies (CSIS), a private, tax-exempt institution focusing on international public policy issues. Its research is nonpartisan and nonproprietary. CSIS does not take specific policy positions. Accordingly, all views, positions, and conclusions expressed in this publication should be understood to be solely those of the author(s).

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