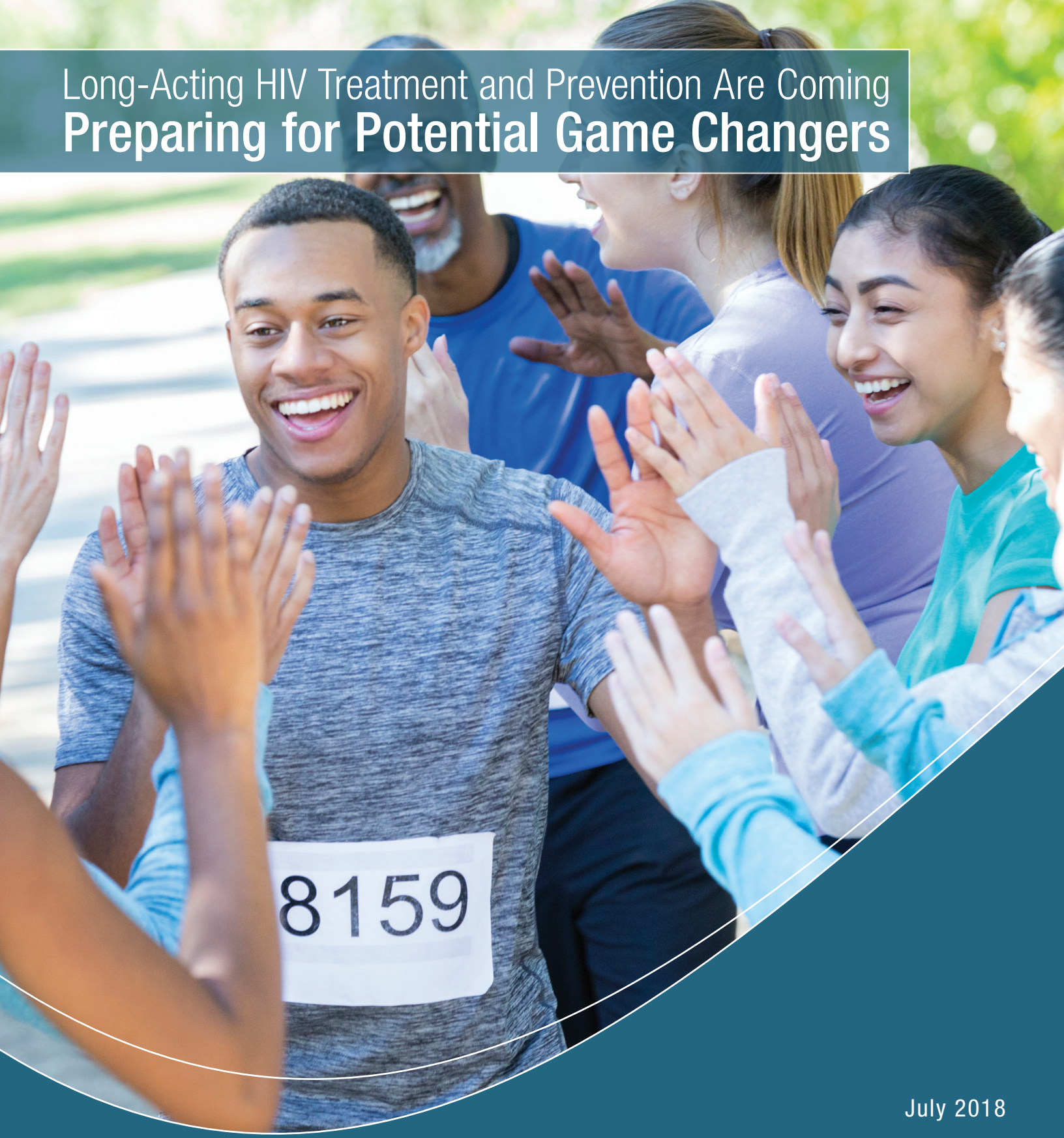

Long-Acting HIV Treatment and Prevention Are Coming
Preparing for Potential Game Changers

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Innovative products for treating and preventing HIV infection are under development. Sometimes called long-acting agents, such products may take different forms ranging from injections to implants to oral medications. If determined to be safe and effective, what could make these new products transformative is that they would not require daily dosing. Some products may require monthly dosing and others may require administration only a few times a year. Taking an idea and turning it into a desirable, effective, affordable, and accessible product is a long and difficult process. To facilitate the analysis and policy decisions needed to advance the process, we describe here some of the issues that must be considered to make durable new HIV treatment and prevention options available for individuals.

LONG-ACTING HIV TREATMENT AND PREVENTION: THE OPPORTUNITY, THE OBSTACLES, AND A PATH FORWARD

Several pharmaceutical manufacturers are actively engaged in developing innovative new therapies both to treat and to prevent HIV infection. If successful, new long-acting products that do not require daily dosing could become available within the next few years. Only one product is currently available, but several agents are in various stages of the research pipeline. Many people living with HIV and other stakeholders are excited by these new products, wondering if they could be a game changer in our ability to move much closer to ending the HIV epidemic in the United States and around the world. For individuals to benefit, however, new products will be subject to a complex maze of policy decisions.

Some may wonder whether new therapies are needed given the broad array of safe, effective, and easily administered therapies currently available. For all of the people with HIV in care and on treatment, however, there are many more who are not in care, not on antiretroviral therapy (ART), or do not achieve durable viral suppression.

Policy makers must assess and navigate a variety of issues:

FDA Review and Approval: The Food and Drug Administration (FDA) must determine that new products are safe and effective. They also will need to consider unique questions related to long-acting products such as the potential to spur drug resistance. Policy makers should bring together relevant parts of the FDA to consider the range of potential delivery mechanisms (e.g., pills, injectables, implants, intravaginal rings) and work to expeditiously review new drug applications and provide clear guidance for manufacturers and the public on key issues. Learn More

Defining the Intended Market for New Products: Innovative products that may be more expensive than existing therapies raise complex questions over how to define their role in relation to current treatment and prevention options. Related questions about the uptake of long-acting therapies and their impact on adherence also must be considered, as well as factors that will influence consumer demand and provider willingness to prescribe them. Policy makers should plan to proactively monitor and invest in necessary studies to document impact and identify unresolved issues. Learn More

Payer Coverage and Access Decisions: Medicaid, Medicare, the Ryan White HIV/AIDS Program, and private health insurance programs operate under different laws and rules regarding pharmaceutical coverage. Federal agencies should begin to consider, in advance, how they will evaluate new long-acting products and how they can provide early guidance for purchasers, prescribers, and the public on how new products will be evaluated and integrated into drug formularies. Learn More

People whose HIV is durably virally suppressed do not transmit infection sexually to their partners. People living with HIV and scientists from all over the world have endorsed a public education campaign called U=U, which stands for undetectable equals untransmittable.[1,2] In 2017, the Centers for Disease Control and Prevention (CDC) examined durable viral suppression in 33 jurisdictions in the U.S.[3] The study found that in 2014, only about half (48%) of people living with diagnosed HIV and on ART had durable viral suppression, i.e., all viral load measures were suppressed (<200 copies/mL) during the defined time period. Poor adherence to medication is not the only cause of lack of durable suppression, but it is a leading contributor to these results.[4,5] These data demand greater attention to supporting engagement in HIV care and maintaining adherence to achieve durable viral suppression. Continued adherence to ART or any course of therapy over an extended period of time is challenging. Even persons who are generally able to take their medication daily may experience periods when they miss doses. The more missed doses, the more likely people are to experience viral breakthrough whereby they are no longer effectively virally suppressed.

Great progress is being made at increasing viral suppression rates of people in care, although too many are diagnosed late and enter care long after infection. For a variety of reasons, too many diagnosed individuals are not in care, and not all of those in care achieve durable viral suppression.

Pre-exposure prophylaxis (PrEP) is a relatively new and very potent method of preventing HIV infection. The FDA approved the first product in 2012, which remains the only product with an on-label indication for PrEP. As used in the U.S., PrEP involves taking a daily pill containing two antiretrovirals (ARVs), whereas the treatment of HIV infection typically involves regimens of three or more ARVs. PrEP is highly effective and is an important preventive tool, in addition to treatment as prevention, condoms, and behavioral interventions for preventing HIV transmission.[6,7,8,9,10,11] Adherence challenges may be different, but no less severe, for people who are HIV negative than for people living with HIV.[12] In fact, some have posited that people who are HIV negative may have fewer motivators to continually adhere to a regimen because they are not motivated by the desire to control an existing infection.[13]

Which issues will need to be considered regarding new long-acting products used for HIV treatment and/or prevention?

FDA Review and Approval: The Food and Drug Administration (FDA) is responsible for assuring the safety, efficacy, and security of drugs, biologics, and medical devices. Once a pharmaceutical manufacturer has a product to submit for review, the FDA will assess the safety and effectiveness of the product and consider relevant commercialization issues.

While the FDA has well-established procedures, long-acting therapies may raise new or unusual questions. For extended-release products that remain in the body and bio-active for long periods of time, different chemistry, manufacturing, and control (CMC) measures will be required to assess long-term safety and effectiveness. Moreover, for ART as with other drugs, a significant concern of the FDA and treating physicians will be to ascertain the potential for the use of long-acting therapies to lead to drug resistance. One circumstance in which resistance develops is when levels of drug remain in the body for significant periods of time, yet at a level below the level of effectiveness. There is often an unavoidable degree of uncertainty involved in the FDA's determinations, especially with respect to novel classes or delivery mechanisms of drugs and biologics. Therefore, pharmaceutical manufacturers, prescribers, and consumers all will depend on a transparent review process that establishes clear standards for how the FDA will evaluate different products and the standards that new products will be required to meet for approval.

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FIGURE 1. WHAT IS ON THE HORIZON?

CURRENT		IN DEVELOPMENT		
		Injectables	**Implants**	**Oral**
HIV Treatment	**40** single-agent antiretroviral and combination antiretroviral products approved for use in the U.S., including 1 injectable product	The FDA approved Ibalizumab in March 2018. **At least 9 more** products are in development that could be injected. Dosing frequency could be approximately **every 8 weeks**.	**At least 2** products are in development that could be implanted under the skin or in the body. Dosing frequency could be as little as **once a year**.	**At least 1** product is in development that could be taken orally. Dosing frequency could be around **once a week**.
HIV Prevention	**1** combination antiretroviral product approved for use in the U.S.			

Policy makers should begin planning to bring together relevant parts of the FDA to consider the range of potential delivery mechanisms (e.g., pills, injectables, implants, intravaginal rings) and work to expeditiously review new drug applications and provide clear guidance for manufacturers and the public on key issues.

Defining the Intended Market for New Products: A new product will benefit individuals if they want it, their treating provider recommends and prescribes it, and they are able to access it. For consumers, personal preferences vary. Some people can effectively adhere to daily oral therapy; for others it's a challenge. These types of issues and perceptions may not be fully understood when new products come in different forms, such as injections or implants. In early studies of some long-acting injectables, research subjects have reported temporary injection site pain that is generally not severe and resolves within a couple of days.[14,15] It will be important to understand a range of critical issues that will influence demand for new products and the ability to adhere to therapy. Moreover, a major rationale for introducing long-acting products is to support adherence. More research is needed to understand whether infrequent dosing actually strengthens adherence.

New HIV infections are concentrated among young gay and bisexual men. This is a group that does not commonly visit medical providers, and if they do, it is often related to sexual health. Thus, ongoing monitoring of HIV infection or regular provider visits associated with PrEP monitoring also serve as opportunities to assess for and provide services ranging from sexual health screenings to primary care and mental health. By introducing long-acting products that may require fewer health care encounters, how does the health system guard against weakening bonds between individuals and their health care providers? Providers also have their own questions and concerns. Access to new products will be contingent on a provider prescribing them. Therefore, it will be important both to understand provider concerns about issues such as safety or drug resistance, and to educate them on how to determine which patients would benefit from the therapy.

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Federal agencies and others should fund efforts to actively engage with community partners and to assess consumer and provider attitudes, questions, and information needs well before individual products are marketed.

Payer Coverage and Access Decisions: Once drug products are approved for use, payers — meaning the various public and private programs that pay for health care, such as Medicaid, Medicare, the Ryan White HIV/AIDS Program (including the AIDS Drug Assistance Program, ADAP), private insurance, and other programs — will have various levels of discretion to determine whether and when to make these products available. Each of these programs operates under different provisions of law. Unlike the FDA, whose analysis is focused on whether a product is safe and

effective, coverage decisions by payers turn on whether a product is "reasonable and necessary." While what is reasonable is highly subjective, medical necessity determinations often have multiple components, including whether a therapy is needed for a specific condition (e.g., to treat HIV infection or to prevent HIV acquisition), and whether better or equivalent, yet cheaper products are already available. There are related costs that must be covered in addition to the medication, such as laboratory tests and monitoring by a health care provider. If a product involves something that requires physician administration, however, how these related services and how the therapy itself is paid for may change. In Medicare, for example, the Part B program covers physician-administered drugs and the Part D program covers most outpatient prescription drugs; each has its own coverage requirements. Therefore, different long-acting products could be covered by different parts of Medicare and could have different access rules.

Establishing the standards by which payers determine whether a therapy is medically necessary for an individual patient will be critically important.

While some consumers may want access to all approved therapies, the need to control costs in our health system creates an important role for health plans and payers to restrict access to therapies to when they are medically necessary. Therefore, establishing the standards by which payers determine whether a therapy is medically necessary for an individual patient will be critically important, as well as determining which policy and financial tools to use to manage access.

The Centers for Medicare and Medicaid Services (CMS), the Health Resources and Services Administration (HRSA), and relevant other agencies, as well as the Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents and the U.S. Public Health Service (PHS), should begin to review their evidence standards for new coverage policies and how they can provide early guidance for purchasers, prescribers, and the public on how to implement new products.

There is no glide path for bringing innovative long-acting HIV treatment and prevention products to people who could benefit from them. Important policy work must be done to navigate complex issues. Even in advance of products being available, the time to start working on these issues is now.

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2 "Scientists never like to use the word 'Never' of a possible risk. But I think in this case we can say that the risk of transmission from an HIV-positive person who takes treatment and has an undetectable viral load may be so low as to be unmeasurable, and that's equivalent to saying they are uninfectious. It's an unusual situation when the overwhelming evidence base in science allows us to be confident that what we are saying is fact." Anthony S. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, quoted in Cairns G. International study of gay couples reports no transmissions from an HIV-positive partner on treatment. *NAM Aidsmap*. July 25, 2017. http://www.aidsmap.com/page/3159177/. Accessed April 2, 2018.

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