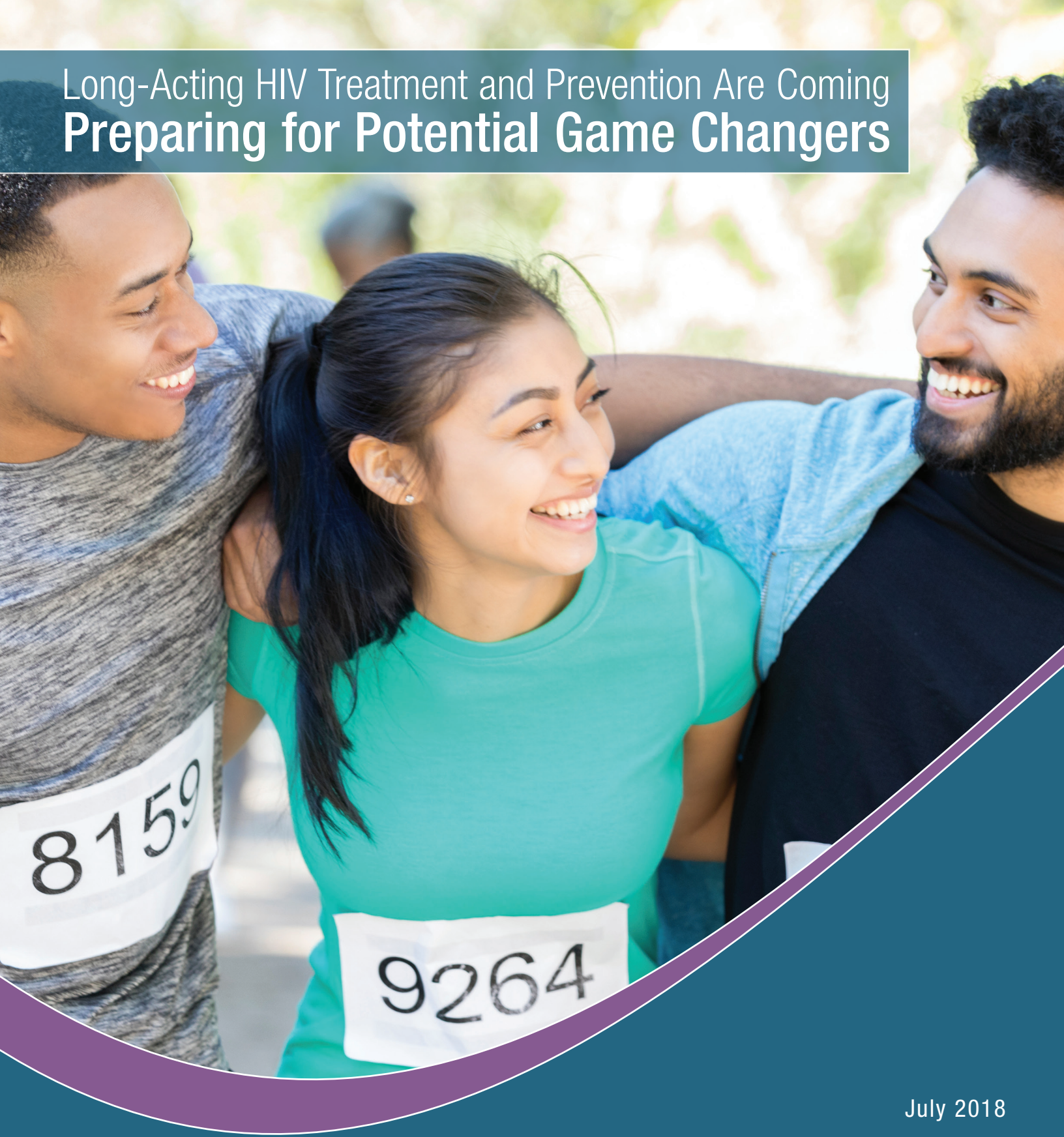
Long-Acting HIV Treatment and Prevention Are Coming

Preparing for Potential Game Changers



July 2018

DEFINING THE INTENDED MARKET FOR NEW PRODUCTS

amfAR
MAKING AIDS HISTORY
The Foundation for AIDS Research

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.

DEFINING THE INTENDED MARKET FOR NEW PRODUCTS

Several pharmaceutical manufacturers are developing innovative new therapies both to treat and prevent HIV infection. If successful, long-acting products that do not require daily dosing could become available within the next few years. Moving beyond questions of whether products are safe and effective, policy makers will need to assess a range of critical issues that will influence whether and when individuals can and will choose to use them.

Now is the time for all stakeholders to begin to grapple with some fundamental questions. Many people living with or at risk for HIV infection struggle with regular adherence to treatment and prevention regimens. Large inequities also exist in that certain communities have the most unmet needs for HIV treatment and prevention services, and others tend to benefit most from innovative products and therapies. To use innovative long-acting therapies to improve health outcomes while also reducing population-level disparities, the following critical questions must be addressed:

Do individuals want long-acting products for HIV treatment and/or prevention?

The promise of new long-acting products is that they will facilitate greater adherence in ways that improve health and quality of life. This potential will only be realized if people find them acceptable and want to use them. These products raise numerous issues related to ease of use, consumer perceptions of safety and effectiveness, stigma, and other factors.

The promise of new long-acting products is that they will facilitate greater adherence in ways that improve health and quality of life.

Another issue is the extent to which quality of life considerations are met. Quality of life is of primary importance to individuals, and it is therefore important to understand how long-acting products affect a person's quality of life. Considerations include the possibility of side effects, therapeutic and non-therapeutic benefits, affordability, privacy, and convenience, including the need for prescription refills and frequency and duration of medical appointments.

A clear benefit of long-acting products is that individuals would not have to take a pill every day. For some, such as those who lack stable housing, there may be a benefit in not having to store medications since long-acting regimens could involve a medical provider administering an injection every four or eight weeks or placing an implant under the skin. Such delivery mechanisms could provide a

Who Are New Long-Acting Products Intended to Benefit?

In addition to safety, effectiveness, and other regulatory considerations, key questions must be addressed such as who could benefit from new long-acting products and how to overcome barriers to accessing them. Issues that all stakeholders must consider include:

Consumer Demand and Acceptance: For new products to be successful and useful in meeting public health goals, people who could benefit from them will need to want to use them. This raises numerous issues related to comfort and ease of use, perceptions of safety and effectiveness, privacy, stigma, and other factors. Interest, acceptance, and demand may vary by product, and different groups and individuals may express varying levels of interest in these products. Stakeholders should begin work to understand consumer perspectives and engage diverse communities in an ongoing dialogue as products pass through various phases of development. Ongoing education and dialogue with community stakeholders, well before new products are marketed, are essential to building trust and support for them.

Provider Attitudes and Willingness to Prescribe: New long-acting products have the potential to help address longstanding inequities in access and health-related outcomes across various populations. Reducing inequities will require proactive steps including understanding provider questions and concerns and forthrightly addressing provider bias in prescribing.

Impact on Adherence: A rationale for long-acting products is to offer new options that can assist individuals in improving adherence to help them achieve their own health and quality of life goals. It will be important to assess whether non-daily dosing actually improves adherence and to identify the different types of support that will be needed to promote adherence and maintain engagement in care.

Cost-Effectiveness for Payers, Providers, and Individuals: Cost pressures are an ever-present factor in health care decision-making for payers, providers, and individuals. Since it is anticipated that innovative new products will be priced above the level of current therapies, if we are to avoid widening disparities in access, conversations with all stakeholders must begin about which populations stand to benefit most and how to appropriately factor cost into coverage decisions.

greater degree of privacy for individuals as well. Depending on how people are able to access long-acting products, quality of life could vary. People who have difficulty scheduling medical appointments or face long waiting times in clinics could have a lower quality of life. Similarly, the cost of long-acting products could negatively influence quality of life. As shown by studies of long-acting reversible contraception, out-of-pocket expenses can greatly influence the rate at which people fill their prescriptions.[1]

Depending on how people are able to access long-acting products, quality of life could vary.

It is also important to understand attitudes and preferences of different populations (e.g., gay and bisexual men, transgender people, communities of color, people who engage in commercial sex, people who use drugs, young people, and women) toward different types of long-acting products (e.g., pills, injectables, implants, intravaginal rings). Further, it is necessary to acknowledge the history of marginalization and longstanding discrimination experienced by many people of color and other communities heavily impacted by HIV. To obtain the type of engagement needed to grapple with a complex constellation of issues, deliberate efforts are needed to create multiple opportunities for these communities to actively work with federal policy makers, scientists, providers, and others to sort through these issues.

Many individuals may have questions about drug-drug interactions, such as with other prescribed medications or recreational drugs. These questions may be especially prominent for some women and transgender people as they relate to interactions with and the safety of using long-acting products along with various forms of contraception and hormone therapy, as well as during pregnancy and breastfeeding.

The development of long-acting products with new methods of delivery has created significant interest among many people living with HIV. One study found a high degree of interest in long-acting products among persons with HIV taking daily oral antiretroviral therapy (ART), especially among young people and those who use recreational drugs.[2] This interest varied by the

The development of long-acting products with new methods of delivery has created significant interest among many people living with HIV.

frequency of dosing, with 61%, 72%, and 84% indicating that they would definitely or probably try injectable ART for dosing weekly, every two weeks, or once a month, respectively. Yet 48% indicated that they were very concerned about possible side effects, and 35% were very concerned about needle use for injectable ART.

Similarly, in a study comparing short cycle therapy (five days on medication/two days off) to continuous therapy, young people with HIV expressed a strong preference for short cycle therapy, and 98% of young people in the study took part in a two-year follow-up study.[3] Results from the LATTE-2 study provide the strongest evidence that people living with HIV prefer long-acting regimens to daily oral therapy.[4] Although injection-site reactions were common, almost all participants receiving injections (99%) reported they would be highly satisfied to continue their long-acting regimens.

Studies also have documented high acceptability of long-acting pre-exposure prophylaxis (PrEP) for HIV prevention. Several studies have been based on hypothetical questions put to gay and bisexual men. In a national study of gay and bisexual men, 43% and 54% of men reported a willingness to use long-acting injectable PrEP every month and every three months, respectively.[5] A study of gay and bisexual men in Washington, DC, found that 62% were very likely and 25% were somewhat likely to use long-acting injectable PrEP,[6] while 81% of a sample of gay and bisexual men aged 18–19 in New York City stated that they would definitely or probably be willing to use long-acting injectable PrEP.[7] Among gay and bisexual men taking daily oral PrEP, one-third would prefer a long-acting injectable formulation and an additional third would prefer it if it was shown to be the most effective dosing against HIV transmission.[8]

Other studies asked about actual acceptability in the context of clinical trials that involved injections. In the ECLAIR study, 74% of men at low risk for HIV infection who received long-acting cabotegravir injections were willing to continue with the study product after receiving three injections in three-month dosing intervals.[9] Despite the majority of men reporting anxiety before their first injection and pain during or following injections, 62% preferred the injectable formulation to daily pill taking.[10] Moreover, in a study involving women in the U.S. and Africa, at their last injection, 68% of women strongly agreed that they would definitely use and 80% would think about using long-acting injectable PrEP in the future.[11] Across these studies, participants voiced concerns about the potential side effects, long-term health effects, and the level and duration of protection from long-acting agents. Future research is needed to better understand these issues and to inform strategies for communicating about concerns and for scaling up long-acting injectable PrEP.

Another key acceptability consideration includes how easy long-acting products will be to use, how products will be administered, and how difficult it will be to schedule clinical appointments. Many of the long-acting products that are furthest along in development require intramuscular or intravenous injections. For example, in clinical trials, cabotegravir and rilpivirine are injected intramuscularly in a clinic-based setting. Injections for HIV prevention are administered on two occasions four weeks apart and then once every eight weeks, though current Phase III clinical trials involve four-week dosing intervals.

Studies have documented high acceptability of long-acting pre-exposure prophylaxis (PrEP) for HIV prevention.

If these products are approved for marketing to the public, various issues could affect their acceptability in the real world. Some people may prefer to access long-acting products through a primary care provider rather than through an HIV-specific provider because of concerns about stigma. It may be more convenient if nurses and other medical providers can administer the injections in addition to doctors. Injections every four weeks could mean that some people with HIV have medical appointments more often than they have now with daily oral ART. Careful attention should be paid to what these medical appointments involve, how they are scheduled, their financial and time burden, and whether there is sufficient medical workforce capacity.

Products that can be implanted under the skin could potentially reduce the need for frequent clinical contact. The same is true for subcutaneous injections currently in development if they can be self-administered or administered by family members or friends. An array of effective long-acting products available in easily accessible settings could facilitate broad consumer acceptance and uptake. Multipurpose technologies, which combine protection against multiple risks, such as unintended pregnancy, HIV, and other sexually transmitted infections, could include long-acting products and have even greater appeal.

A related issue that could impede acceptability of long-acting products relates to what is called "the tail," which refers to the length of time when measurable levels of drug remain in the body below levels of effectiveness for either treatment or prevention. This creates the conditions under which drug resistance could develop, and also may cause difficulty reversing any drug-related injury or other side effect (e.g., drug-drug interactions with a new medicine the person must start for another reason, such as an anticoagulant, antibiotic, or anticonvulsive) and is thus a major concern for researchers and the Food and Drug Administration (FDA). Because of the tail of some of the earliest products being tested, persons who initiate therapy with long-acting products must commit to taking a daily oral version of the product for up to a year after they discontinue the long-acting product, in order to ensure effective levels of drug remain in circulation to avoid the development of resistance. Research is continuing to shrink the length of time that drug remains below the level of effectiveness, but the commitment required following discontinuation of a product likely will be a major factor in any product's uptake.

Which questions must be addressed for providers to prescribe long-acting products?

The perspectives of both potential users and providers of these products are critical for the uptake of long-acting products. To make new products available to various populations that can benefit from them, we need providers with up-to-date knowledge of national guidelines and the latest research on long-acting agents, and who are willing to offer these products in the context of clinical care.

Little is known about provider attitudes toward long-acting products for HIV treatment and prevention, but lessons can be learned from provider research related to other HIV and long-acting products, including long-acting reversible contraception. For example, a recent study finding that black patients have lower rates of obtaining sufficient medication as part of their ART regimens may reflect racial bias among providers in prescribing practices.[12] Provider bias also has been shown to play a role in long-acting reversible contraception recommendations, with many women, especially women of color, reporting that their preferences regarding contraceptive selection or removal were not honored.[13] The willingness of providers to prescribe long-acting reversible contraception is further influenced by confusion about eligibility criteria and negative perceptions of long-acting formulations for adolescents.[14] Research suggests a need for provider training, practice protocols, and other strategies that address provider bias, promote patient-centered care, and improve future provider-patient interactions.

Long-acting PrEP may raise issues of sexual morality for providers, and the reluctance of some providers to prescribe may be tied to homophobia and transphobia.

PrEP, whether in a once-daily or long-acting formulation, raises various provider-level challenges. Providers continue to struggle with sexual health conversations with patients. This is a potential barrier to providers prescribing long-acting PrEP because it requires the ability to competently take a sexual history. In addition, long-acting PrEP may raise issues of sexual morality for providers, and the reluctance of some providers to prescribe may be tied to homophobia and transphobia. For long-acting formulations, as with once-daily formulations, racial biases may also affect providers. In one study of medical students, for example, when the race of a hypothetical patient was changed in clinical vignettes, medical students rated a black patient as more likely to engage in sexual risk behavior while using PrEP and were therefore less likely to prescribe it.[15] Factors that may affect providers' knowledge of and willingness to prescribe long-acting products, including conscious or unconscious racial bias and sexual stigma, must be better understood so that they can be effectively addressed.

Will less than daily dosing strengthen or weaken adherence?

Much of the excitement over the potential of new long-acting products is that they could be helpful tools for improving adherence both for people living with HIV on ART and for HIV-negative individuals using PrEP. Therefore, it is important to understand whether and what types of adherence challenges exist for people living with and at risk for HIV infection and to explore whether less frequent dosing is useful for improving adherence and quality of life.

Significant research has been conducted to examine engagement in HIV care from diagnosis to maintenance of viral suppression among people on ART. This includes studies of adherence patterns and behaviors. Adherence is a significant challenge for some people living with HIV. Researchers at the Centers for Disease Control and Prevention (CDC) using national HIV surveillance data found that 86% of people with HIV self-reported taking all ART doses in the preceding 72 hours and only 60% self-reported adhering to dose time and other dose requirements.[16] Moreover, the researchers estimate that one in ten people with HIV on ART is nonadherent, but does not perceive him- or herself to be in need of professional assistance with adherence support.

The CDC identified the following factors associated with lower adherence to ART in the U.S.: younger age, female gender, experience of depression, use of stimulants, binge alcohol drinking, greater than once daily medication dosing, and longer time since HIV diagnosis.[17] They also found that patient beliefs are associated with reduced adherence to ART. A meta-analysis of international studies on adherence to ART found that the factor most strongly associated with improving adherence was adherence self-efficacy, which is an individual's belief in their ability to adhere to their ART regimen. Trust in their HIV care provider and personal belief in the necessity of adhering to ART also were positively associated with improving adherence. Current substance use and concerns about taking ART were the factors most strongly associated with poor adherence.[18] This information provides insights into how best to tailor adherence supports to specific subpopulations.

Factors Associated with Lower ART Adherence in the U.S.

- Young Age
- Female Gender
- Experience of Depression
- Use of Stimulants
- Binge Alcohol Drinking
- Greater than Once Daily ART Dosing
- Longer Time Since HIV Diagnosis

Researchers estimate that only 54% of adolescents and young adults who initiate ART achieve viral suppression.

Many of the factors linked to lower adherence are associated with populations most heavily impacted by HIV. Certain groups face significant barriers to adherence and engagement in care. Researchers estimate that only 54% of adolescents and young adults who initiate ART achieve viral suppression and fewer than 6% of youth living with HIV are virally suppressed.[19] Few groups in the U.S. have been more heavily impacted by HIV than black gay and bisexual men. Contrary to popular assumptions, researchers have long understood that behavioral factors (e.g., number of sex partners, consistency of condom use, etc.) do not explain their disproportionately high infection rates compared to white gay and bisexual men and other groups.[20] A 2012 meta-analysis of disparities in rates of infection among black gay and bisexual men in the U.S., Canada, and the United Kingdom extended these findings and demonstrated that the largest disparities in infection rates between black gay and bisexual men and gay and bisexual men of other races were associated with clinical indicators, including ART access and adherence, suggesting that improved access to ART and better adherence could potentially help to reduce these disparities.[21]

Several studies have demonstrated the link between homelessness or unstable housing status and reduced adherence or access to ART.[22] Transgender people and cisgender women also have been shown to have lower adherence and require tailored interventions.[23,24,25] A range of factors, from stigma, self-efficacy, mental health, and substance use to insurance access, financial constraints, and

caretaking responsibilities, affect the ability of women, including transgender women, to adhere to ART.[26,27,28] Among cisgender and transgender women, trauma has been associated with treatment non-adherence and failure.[29,30] While not exhaustive of all groups that need tailored adherence support, numerous studies have documented differential adherence to ART and unique barriers to adherence that are amenable to intervention. Simplified dosing and newer regimens with fewer side effects have improved adherence.[31] Many providers recommend multiple targeted strategies,[32] including a focus on non-medical supportive services that help to remove barriers to engagement in care and adherence to an ART regimen.[33,34] Significant work also has been done to examine adherence from a social-behavioral perspective, and a number of social-behavioral models have been developed and evaluated that help to identify core drivers of medication adherence.[35]

In examining whether less than daily dosing will contribute to improved adherence, experience in other areas of medicine also may offer insights. A study of Medicaid claims data from six states found that beneficiaries with schizophrenia receiving treatment via long-acting injectable products had better adherence to and persistence on therapy over 12 months than beneficiaries taking oral antipsychotic medications.[36] Long-acting reversible contraception is widely perceived as a significant clinical advance. One study of the effectiveness of long-acting forms of contraception found that they were significantly more effective than traditional, short-acting therapies.[37] Moreover, one component of the same study found that other forms of contraception (pills, patch, and ring) had higher failure rates than long-acting therapy for women under age 21, and that failure rates for these young women were double the rate for women over 21.

Long-acting products may play a larger role in assisting some key populations than others, and understanding who could benefit most should play a role in assessing how to deploy new products for HIV treatment and prevention.

What is the appropriate role of drug cost in determining who can access long-acting products?

Under the current drug development and financing system in the U.S., innovative new products are expected to be priced higher than existing therapies. Frequently, the greater the innovation or the size of differential health outcomes, the higher the price. Thus, if long-acting HIV treatment and/or prevention products are approved and they greatly diminish adherence burdens, pricing of such products could be significantly higher than existing therapies. This raises the question of when people should have access to such breakthrough products, and what is the role of drug price in determining access.

Modeling the Cost-Effectiveness of Long-Acting HIV Treatment

Estimated cost of current first-line ART regimen is $25,000/year (average wholesale price, AWP)	
	Price Below Which Long-Acting Therapy Remains Cost-Effective
Multiple Prior Failures	$48,000/year
Second-Line Therapy	$26,000–31,000/year
First-Line Therapy	<$24,000/year

Source: Ross EL, Weinstein MC, Schackman BR, et al. The clinical role of cost-effectiveness of long-acting antiretroviral therapy. *Clinical Infectious Diseases*. 2015;60(7):1102-1110.

There is a rich field of cost-effectiveness research that aims to assess tradeoffs and quantify the overall benefit of providing more expensive therapies for various medical conditions. Modeling studies have begun to be developed to examine the cost-effectiveness of long-acting ART. One study sought to project the clinical impact of long-acting ART for HIV treatment in order to define the cost thresholds at which long-acting ART would become cost-effective in the U.S.[38] Researchers explored daily ART only and compared its use to long-acting ART for persons with multiple prior virologic failures, as a second-line therapy after a person has failed on a first-line therapy, and as a first-line therapy for all patients. Their model assumed an annual cost of $25,000 for daily ART (as the average wholesale price, AWP, for the regimen) and set a maximum of willingness to pay $100,000 per quality-adjusted life year gained, which is a standard benchmark in the cost-effectiveness research literature. Not surprisingly, their model

showed that the price of long-acting ART can be higher and remain cost-effective as its use is more tailored to specific populations. Indeed, for persons with multiple prior virologic failures, the annual cost of long-acting products could reach $48,000 per year and remain "good value." Moreover, when applying the model more narrowly to the REACH cohort consisting of marginally housed people living with HIV,[39] long-acting ART would be cost-effective if its cost was as much as $70,000/year.[40]

Further research is needed, not only to replicate this model and test alternate assumptions, but to explore the differential impact on specific subpopulations. For example, given the poor adherence to therapy observed in youth across health conditions, what is the specific role of long-acting products for both HIV treatment and prevention for youth? And what would be the differential cost-effectiveness threshold for providing PrEP to all young people versus just sexually active young gay and bisexual men of color? Moreover, such modeling studies do not offer definitive answers as much as introduce a needed input into the policy dialogue that must entail new conversations with all stakeholders, including affected communities, prescribers, payers, and pharmaceutical manufacturers over acceptable ways to tailor outreach and to provide differential access to ART for both treatment and prevention.

Policy Development Should Begin Now

Determining who should be prioritized for access to new products is challenging, as our health system is not well equipped for making decisions that may not rely solely on objective clinical factors. Nonetheless, non-clinical factors will determine whether or not long-acting products are embraced by key populations and have an impact on population-level health and the reduction of health disparities. Therefore, work should begin now to study key issues and bring together diverse stakeholders to take collective action, including:

1. **Federal agencies need a coordinated plan to navigate the policy issues that do not fit squarely within the purview of a single agency.**

The challenge for federal policy makers is that while the issues raised by new long-acting products impact many federal agencies and require the specific expertise of various federal officials, no single agency has been tasked with addressing them all. The National Institutes of Health (NIH) funds significant research and plays a role in promoting the development of promising products; the FDA must determine that products are safe and effective. Payers, including the Centers for Medicare and Medicaid Services (CMS) and the Health Resources and Services Administration (HRSA), must determine whether and when to cover new products. The CDC conducts surveillance and monitoring activities and often provides critical data on viral suppression rates and other metrics of adherence to therapy. Several other agencies could contribute to studying related questions or helping to resolve policy issues.

But, at the end of the day, who is responsible for overall coordination? The Secretary of the Department of Health and Human Services (HHS) should delegate responsibility for policy coordination to an office or HHS operating division that is best positioned to grapple with the complex and diverse issues presented by these new products. The Office of HIV/AIDS and Infectious Disease Policy is a natural leader of this initial effort, though it may not have adequate staff capacity or be the best situated to contend with these types of issues. Nonetheless, it may be able to initiate a policy process that will determine who will take the lead for HHS, how the range of stakeholders can engage with HHS, and how critical research that may be either cross-cutting or outside the primary responsibility of any single agency will be funded.

2. **Proactive steps are needed to develop collaborative partnerships with the groups and communities with the most to gain from long-acting products.**

Communities will not benefit from new products if they do not know about them and if they do not trust them. We must ensure that the communities that face large disparities in access to treatment are included in discussions of implementation and access. Therefore, as important as it is to develop new products, investments are needed in preparing communities for new therapies and engaging in meaningful dialogues so that individuals and providers accept them. There are many unanswered questions that will play out differently for specific products. For injectable products, in addition to concerns over injection-site pain or other factors that could impede a product's desirability, the volume of injection could limit demand for a product or render it not an option for some people, such as those with a high body mass index or persons with buttock implants, including some trans women. Further, keloid scarring (smooth hard growths on the

skin resulting from scar tissue) could potentially result from injecting a large volume into the buttocks, and this type of scarring is more common in people of color.

Additionally, we have ample evidence that supports are often needed to bolster adherence to ART and other therapies. The types of supports needed for new long-acting products may be very different from supports needed for daily pill taking. Moreover, the information and adherence supports needed may vary dramatically from one group to another, with young gay and bisexual men, for example, seeking different supports than heterosexual women. Federal agencies and pharmaceutical manufacturers should begin working now with community stakeholders and providers to educate them about products in the research pipeline and to understand their questions and concerns, both to set the stage for future products and to shape policy decisions that will be made before any products are marketed to the public.

3. More research and dialogue are needed on the role of cost in determining access to new products.

Cost already plays a significant role in determining which groups benefit from innovative new therapies. Too frequently, the consequence of avoiding tough questions of equity or assuming that the health system will automatically extend access to every new product is that the communities with the greatest needs are the last to fully benefit from them. Therefore, we need to more fully embrace the type of modeling studies described above and seek to better understand how to use therapeutic breakthroughs to reduce disparities, prioritizing access to those persons and communities with the greatest needs. This will require continued investments in modeling and other studies to help inform the policy dialogue around cost and access.

Moreover, more work is needed to model the financial and other impacts not only on payers, but also on the people who will use these products and the providers who will prescribe and/or administer them. This concern is heightened by recent trends among some private insurers that do not count co-pay assistance provided by pharmaceutical manufacturers toward meeting a person's deductible and annual out-of-pocket limit.[41] Insurers are often responding to concerns that such assistance programs can steer people to more expensive products, yet other financial incentives may drive people to physician-administered products or in other cases to cheaper products, without fully considering individual preferences, clinical appropriateness, or patient affordability. While no perfect approach to balancing the legitimate interests of patients, providers, and payers exists, more focused attention is needed before new long-acting products are marketed for HIV prevention and treatment.

Conclusion

HIV may not be front-page news on a regular basis, but the country is making major progress toward reducing the scope of the epidemic and improving health outcomes for people living with HIV. Nonetheless, significant barriers remain that expose the inequities of our health system and the unmet needs of many communities heavily impacted by HIV. The development of innovative long-acting products for HIV treatment and prevention offers the potential to strengthen adherence to therapy and further improve population-level outcomes. If we get this right, these products also may help to reduce disparities so that HIV becomes less deeply entrenched in specific groups and communities.

Prepared for amfAR by Sean E. Bland and Jeffrey S. Crowley
O'Neill Institute for National and Global Health Law, Georgetown Law, July 2018

The authors thank and acknowledge the following individuals who offered insights into relevant policy issues or reviewed drafts of documents produced for this project: Rivet Amico, Dawn Averitt, Lindsey Dawson, Rick Elion, David Evans, Michael Horberg, Tim Horn, Naina Khanna, Ann Lefert, Britten Pund, Ace Robinson, Andrea Weddle, along with numerous federal agency staff members.

REFERENCES

1. McCain J. The effect of removing financial barriers on the use of long-acting reversible contraceptives. *Managed Care*. 2016;25(8):21-25.
2. Williams J, Sayles HR, Meza JL, et al. *Long-acting parenteral nanoformulated antiretroviral therapy: Interest and attitudes of HIV-infected patients*. Nanomedicine (London). 2013;8(11):1807-1813.
3. Butler K, Inshaw J, Ford D, et al. BREATHER (PENTA 16) short-cycle therapy (SCT) (5 days on/2 days off) in young people with chronic human immunodeficiency virus infection: An open, randomized, parallel-group Phase II/III trial. *Health Technology Assessment*. 2016;20(49):1-108.
4. Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomized, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017;390(10101):1499-1510.
5. Parson JT, Rendina HJ, Whitfield TH, Grov C. Familiarity with and preference for oral and long-acting pre-exposure prophylaxis (PrEP) in a national sample of gay and bisexual men in the US. AIDS and Behavior. 2016;20(7):1390-1399.
6. Levy ME, Patrick R, Gamble J, et al. Willingness of community-recruited men who sex with men in Washington, DC to use long-acting injectable HIV pre-exposure prophylaxis. *PLoS One*. 2014;12(8):e0183521.
7. Meyers K, Rodriguez K, Moeller RW, Gratch I, Markowitz M, Halkitis PN. High interest in a long-acting injectable formulation of pre-exposure prophylaxis for HIV in young men who have sex with men in NYC: A P18 cohort study. *PLoS One*. 2014;9(12):e114700.
8. John SA, Whitfield THF, Rendina HJ, Parsons JT, Grov C. Will gay and bisexual men taking oral pre-exposure prophylaxis (PrEP) switch to long-acting injectable PrEP should it become available? *AIDS and Behavior*. 2017;epub ahead of print:28913659.
9. Murray MI, Markowitz M, Frank I, et al. Tolerability and acceptability of cabotegravir LA injection: Results from ECLAIR study. Presented at: Conference on Retroviruses and Opportunistic Infections 2016; February 22-25; Boston. Abstract 471.
10. Meyers K, Rodriguez K, Brill AL, et al. Lessons for patient education around long-acting injectable PrEP: Findings from a mixed-method study of phase II trial participants. *AIDS and Behavior*. 2018;22(4):1209-1216.
11. Bekker L-G, Li SS, Tolley B, et al. HPTN 076: TMC278 LA safe, tolerable, and acceptable for HIV preexposure prophylaxis. Presented at: Conference on Retroviruses and Opportunistic Infections 2017; February 13-16, 2017; Seattle; Abstract 421LB.
12. Landovitz RJ, Desmond KA, Liebowitz AA. Racial disparities among publicly insured Californians with HIV. *Journal of Health Care for the Poor and Underserved*. 2017;28(1):406-429.
13. Higgins JA, Kramer RD, Ryder KM. Provider bias in long-acting reversible contraception (LARC) promotion and removal: Perceptions of young adult women. *American Journal of Public Health*. 2016;106(11):1932-1937.
14. Murphy MK, Stoffel C, Nolan M, Haider S. Interdependent barriers to providing adolescents with long-acting reversible contraception: Qualitative insights for providers. *Journal of Pediatric and Adolescent Gynecology*. 2016;29(5):436-442.
15. Calabrese SK, Earnshaw VA, Underhill K, Hansen NB, Dovidio JF. The impact of patient race on clinical decisions related to prescribing HIV pre-exposure prophylaxis (PrEP): Assumptions about sexual risk compensation and implications for access. *AIDS and Behavior*. 2014;18(2):226-240.
16. Beer L, Skarbinski J. Adherence to antiretroviral therapy among HIV-infected adults in the United States. *AIDS Education and Prevention*. 2014;26(6):521-537.
17. Beer L, Skarbinski J. Adherence to antiretroviral therapy among HIV-infected adults in the United States. *AIDS Education and Prevention*. 2014;26(6):521-537.
18. Langebeek N, Gisolf EH, Reiss P, et al. Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: A meta-analysis. *BMC Medicine*. 2014;12:142.
19. Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: Exaggerated health disparities. *AIDS Patient Care and STDs*. 2014;28(3):128-135.
20. Millett GA, Flores SA, Peterson JL, Bakeman R. Explaining disparities in HIV infection among black and white men who have sex with men: A meta-analysis of HIV risk behaviors. *AIDS*. 2007;21(15):2083-2091.
21. Millett GA, Peterson JL, Flores SA, et al. Comparisons of disparities and risks of HIV infection in black and other men who have sex with men in Canada, UK, and USA: A meta-analysis. *Lancet*. 2012;380(9839):341-348.
22. Milloy MJ, Marshall BD, Montaner J, Wood E. Housing status and health of people living with HIV/AIDS. *Current HIV/AIDS Report*. 2012;9(4):364-374.
23. Sevelius JM, Carrico A, Johnson MO. Antiretroviral therapy adherence among transgender women living with HIV. *Journal of the Association of Nurses in AIDS Care*. 2010;21(3):256-264.
24. Sevelius JM, Saberi P, Johnson MO. Correlates of antiretroviral adherence and viral load among transgender women living with HIV. *AIDS Care*. 2014;26(8):976-982.
25. Beer L, Skarbinski J. Adherence to antiretroviral therapy among HIV-infected adults in the United States. *AIDS Education and Prevention*. 2014;26(6):521-537.
26. Factors affecting antiretroviral therapy adherence among HIV-positive pregnant and postpartum women: an adapted systematic review. *International Journal of STD and AIDS*. 2013;24(6):427-432.

27. Holstad MM, Spangler S, Higgins M, Dalmida SG, Sharma S. Psychosocial characteristics associated with both antiretroviral therapy adherence and risk behaviors in women living with HIV. *AIDS and Behavior*. 2016;20(5):1084-1096.

28. Mizuno Y, Beer L, Huang P, Frazier EL. Factors associated with antiretroviral therapy adherence among transgender women receiving HIV medical care in the United States. *LGBT Health*. 2017;4(3):181-187.

29. Hatcher AM, Smout EM, Turan JM, Christofides N, Stöckl H. Intimate partner violence and engagement in HIV care and treatment among women: A systematic review and meta-analysis. *AIDS*. 2015;29(16):2183-2194.

30. Machtinger E, Haberer J, Wilson T, Weiss D. Recent trauma is associated with antiretroviral failure and HIV transmission risk behavior among HIV-positive women and female-identified transgenders. *AIDS and Behavior*. 2012;16(8):2160-2170.

31. Schaecher KL. The importance of treatment adherence in HIV. *Am J Manag Care*. 2013;19(12 Suppl):S231-S237.

32. Beer L, Skarbinski J. Adherence to antiretroviral therapy among HIV-infected adults in the United States. *AIDS Education and Prevention*. 2014;26(6):521-537.

33. Langebeek N, Gisolf EH, Reiss P, et al. Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: A meta-analysis. *BMC Medicine*. 2014;12:142.

34. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: Evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Annals of Internal Medicine*. 2012;156(11):817-833.

35. Amico KR, Mugavero M, Krousel-Wood MA, Bosworth HB, Merlin JS. Advantages of using social-behavioral models of medication adherence in research practice. *Journal of General Internal Medicine*. 2018;33(2):2017-215.

36. Pilon D, Tandon N, Lafeuille MH, et al. Treating patterns, health care resource utilization and spending in Medicaid beneficiaries initiating second-generation long-acting injectable agents versus oral atypical antipsychotics. *Clinical Therapeutics*. 2017;39(10):1972-1985.

37. Winner B, Peipert JF, Zhao Q, et al. Effectiveness of long-acting reversible contraception. *New England Journal of Medicine*. 2012;366(21):1998-2007.

38. Ross EL, Weinstein MC, Schackman BR, et al. The clinical role of cost-effectiveness of long-acting antiretroviral therapy. *Clinical Infectious Diseases*. 2015;60(7):1102-1110.

39. Bangsberg DR, Ragland K, Monk A, Deeks SG. A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. *AIDS*. 2010;24(18):2835-2840.

40. Ross EL, Weinstein MC, Schackman BR, et al. The clinical role of cost-effectiveness of long-acting antiretroviral therapy. *Clinical Infectious Diseases*. 2015;60(7):1102-1110.

41. *Copay Accumulators: Costly Consequences of a New Cost-Shifting Pharmacy Benefit*. January 3, 2018. Available at: http://www.drugchannels.net/2018/01/copay-accumulators-costly-consequences.html.

amfAR

MAKING AIDS HISTORY

www.amfar.org

amfAR Public Policy Office 1100 Vermont Avenue, NW • Suite 600
Washington, DC 20005 • T: +1 202.331.8600 F: +1 202.331.8606