Planning ahead for implementation of long-acting HIV prevention: challenges and opportunities

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Purpose of review
Broad-based access, uptake, and dissemination of daily oral HIV preexposure prophylaxis (PrEP) have been slow, despite strong evidence for efficacy. Effective and efficient implementation of long-acting HIV prevention products will require both analysis of the dynamics and determinants of daily oral PrEP implementation and identification of the distinct challenges and opportunities inherent in emerging technologies.

Recent findings
Evidence suggests the importance of addressing implementation issues at three levels: patient, provider, and system. Patient-level factors include targeted education and messaging, tailored supports to enhance acceptability and uptake, and effective strategies for promoting adherence/persistence and retention in care. Provider-level factors include engaging a broad mix of providers, while ensuring adequate training and support for patient assessment, counseling, and follow-up. Systems-level factors include optimal delivery modalities, resource allocation, and ensuring access to populations most in need of new prevention options.

Summary
Formative social/behavioral research must be undertaken proactively to prepare for and address future implementation challenges and reduce the gap between proving efficacy in clinical trials and assuring real-world effectiveness. Conceptualizing new HIV prevention technologies as behavioral interventions at the level of the patient, provider, and system will be paramount to effective and efficient implementation.

Keywords
HIV prevention, implementation, long-acting antiretrovirals, preexposure prophylaxis, sociobehavioral research

INTRODUCTION

Implementation of daily oral preexposure prophylaxis (PrEP) is a critical case study illustrating the gap between proving efficacy in clinical trials and achieving real-world effectiveness. More than 2.5 years after Food and Drug Administration approval of Truvada for daily oral PrEP, broad-based implementation and access remain low, with PrEP available largely in the context of open-label extensions or demonstration projects [1,2▪]. As long-acting HIV prevention products move along the development pipeline, effective implementation will require understanding the dynamics and determinants of past experiences with oral PrEP, while also identifying new challenges inherent to emerging technologies. There is growing acknowledgement of biomedical prevention as inherently behavioral, and of the need to understand social/behavioral variables in efficacy trials [3–5]. However, this understanding of behavioral influences is usually confined to a discussion of patient-level factors in acceptability, adoption, adherence, and persistence. This review extends the conceptualization of behavioral factors in biomedical prevention to include provider behavior and the ways in which both patient and provider behaviors are shaped by healthcare systems. Only by identifying barriers and opportunities to behavior at these three levels simultaneously – patient, provider, and system – will we be able to pave the way for efficient transition between efficacy and implementation of long-acting prevention products.

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KEY POINTS

- The experience of daily oral PrEP implementation offers important lessons for long-acting HIV prevention products currently in clinical development.
- To minimize the gap between proving efficacy in trials and achieving real-world effectiveness, clinical trials of long-acting HIV prevention agents should measure psychosocial and behavioral variables likely to influence later adoption and implementation.
- Social science research critical to understanding the political, economic, and social contexts, as well as the healthcare systems in which ARV prevention interventions may be provided, should be funded and conducted in parallel to efficacy trials to inform implementation planning.
- Providers who are likely to prescribe long-acting HIV prevention agents, including not only infectious disease doctors, but also those in adolescent medicine, primary care, reproductive health, and harm reduction/substance abuse, should receive training and education on these novel products at soon as efficacy is shown.
- Education and marketing of emerging long-acting prevention agents should be conducted to maximize interest and acceptability among populations most vulnerable to new infections.

PATIENT-LEVEL CHALLENGES AND OPPORTUNITIES

Perhaps the most exciting factor in the development of new long-acting HIV prevention products – including both injectable formulations and intravaginal rings – is their ushering in of a new era of user choice. Family planning research has shown that expanding the method mix has been a key factor associated with increasing contraceptive uptake and use over time [6], as different product profiles appeal to different individuals and individual preferences may change over the reproductive life course. Similarly, we might expect that an increase in the PrEP-method mix would result in greater acceptability and uptake, as users have a range of options and can choose one that best fits their overall and 'seasonal' HIV prevention needs [7].

However, the creation of new options requires complex and nuanced patient education to ensure that these options are truly accessible. In 2015, PrEP knowledge remains low, especially among the populations at greatest risk for infection in the USA and globally [8▪,9,10]. Developing optimal messaging strategies for long-acting formulations will be paramount, as oral PrEP uptake appeared to suffer from its association with a medication that was known to treat HIV-infected individuals [11]. Marketing of long-acting injectable PrEP must be creative, and perhaps veer away from the biomedical term 'PrEP' to something more comprehensible to target users. Research into target population lifestyles, values, and motivations should inform messaging and packaging. Educational materials will need to be tailored for low-literacy settings, and contexts in which access to healthcare are scarce. Messaging for men and women will need to differ, as will messaging tailored to different contexts. Long-acting agents will need to be described in different terms for individuals in serodiscordant relationships as compared with single people. Regardless of population, social-behavioral research suggests that effective messaging will focus on empowerment, intimacy, and sexual health, rather than risk, mistrust, and fear [12,13▪].

In addition, the availability of new prevention alternatives underscores the importance of attending to modality-specific factors in patient-level acceptability. For example, research on PrEP acceptability and adherence suggests a critical role of subjective risk perception in determining uptake and adherence [14,15▪]. In many cases, patients' subjective risk perceptions do not match more objective behavioral assessments of their behavior, but still determine PrEP-related attitudes and behavior. Long-acting agents may not be attractive to patients who perceive their own risk for HIV to be low, as they may believe that a product that remains active in the body for months is not necessary for their own level of risk. Similarly, long-acting injectable formulations will not be the right choice for those who have a phobia of needles [16], who report high perceived-sensitivity to medication [17], who are particularly concerned about side-effects, or who object to a long-acting agent that cannot be extracted or 'turned off' in their bodies. Intravaginal ring users must be comfortable with the process of insertion and removal, and must be willing to accept the possibility of the ring being felt by a partner or becoming dislodged during intercourse [18,19▪].

Conversely, long-acting agents might be a particularly good fit for patients with disclosure concerns, who would benefit from having a shot administered in the privacy of a doctor's office, without needing to store medication on their person or in their home [16]. Similarly, intravaginal rings may be inserted at home without the knowledge of a sexual partner. As such, long-acting products may be of particular interest to men and women who have little control over how and when sex takes place [16]. They may also be useful for people whose lives are chaotic or unpredictable in ways that could make the use of a daily oral medication more challenging. Although many of these factors appear

obvious in the abstract, the challenge of applying them to specific instances of patient-driven decision-making should not be underestimated. To truly engage and sustain patients on long-acting anti-retroviral (ARV) prevention, it will be critical for providers to understand individuals' motivations for choosing to protect themselves with ARV prevention. They will need to elicit enough information about the context and structure of patients' lives to best advise them on the most appropriate choice of product, recognize when and why a product is not working, and support discontinuation or product-switching processes.

Bridging the gap between efficacy and effectiveness for long-acting agents will require significant buy-in from populations who are at highest risk for HIV infection, but are often under-represented in randomized controlled trials. Adolescents and emerging adults, transgender individuals, people who inject drugs, and those who engage in sex work may benefit most from long-acting formulations, but are rarely engaged in formative or efficacy research in significant numbers. Effective long-acting implementation will require answers to three critical questions: are there biological or pharmacokinetic reasons to believe that long-acting agents might work differently for these populations (e.g., because of developmental factors, use of hormones, drug interactions) and how might we address those differences in product development and testing; what are the social or psychological reasons why long-acting agents might 'operate' differently for these populations, and what specific supports might our most vulnerable patients require; and how will highly vulnerable individuals and groups perceive long-acting trial results if they have not been included, and how will this influence future uptake. At present, PrEP uptake has been delayed among these populations because formative research was not undertaken to ensure they would be effectively engaged [20▪,21▪].

Finally, patient-level adherence behavior is a key factor in daily oral PrEP efficacy [22▪▪], but is significantly altered in the context of long-acting formulations. The contraceptive field distinguishes between user-dependent (e.g., pill, condom) and provider-dependent (e.g., injectables, intrauterine devices) methods, indicating a significant reduction in failure rates among provider-dependent methods because they are less susceptible to adherence differences between 'perfect use' and 'typical use' [23,24]. In the context of long-acting agents, adherence may be operationalized as 'retention in care,' and will not depend on day-to-day behavior, but on navigation of healthcare systems and related contexts. Factors associated with successful retention in care among diverse target populations in different contexts will need to be identified to design appropriate messages and persistence-support strategies.

PROVIDER-LEVEL CHALLENGES AND OPPORTUNITIES

As discussed above, one of the key benefits to long-acting formulations is their characterization as 'provider-dependent' methods, which are less susceptible to patient-based adherence challenges. At the same time, such methods are particularly dependent on the extent to which they are embraced by prescribing providers and offered to the patients who need them most. In implementation of daily oral PrEP, adoption by providers has been slowed in part by what has been termed the 'purview paradox,' in which HIV specialists believe that HIV prevention is the purview of primary care, whereas primary care providers believe that ARV prescription is the purview of HIV specialists. The main lessons from this paradox are four-fold.

First, the line between HIV prevention and care is continuing to blur, as are the lines between HIV-specific care and primary care that manages HIV as a chronic condition. This blurring of boundaries represents an opportunity to re-structure patient-focused care, re-imagining traditional boundaries in ways that may reduce HIV-specific stigma or exceptionalism. At the same time, such restructuring is bound to face tremendous challenges that must be addressed at the systems-level (see below) before they can be addressed by individual providers or in clinical settings. Lessons from countries in Africa that adopted WHO-recommended task-shifting from physicians to nurses and community-health workers to manage the scale up of ARV treatment could be usefully applied [25▪].

Second, it is critical to engage and educate a broad array of providers and specialties in ARV prevention, to ensure patient access at a variety of entry points. Some patients may be willing to access ARVs for prevention only through a primary care provider, and might be unwilling to engage in care through an HIV-specific healthcare setting because of concerns about associated stigma. Other patients may want to seek sexual healthcare in a setting separate from their primary care, and would be interested in a 'prevention-specific' practice to receive ARVs, and HIV/sexually transmitted infection (STI) testing, or in the case of women, integrated into reproductive health services.

Third, we must acknowledge the extent to which providers continue to struggle with sexual health conversations with their patients. Prescribing ARVs for prevention requires more than knowledge of the medications and their potential side-effects; it

requires the ability to competently take a sexual history, and identify patients who might benefit from particular biomedical and/or behavioral strategies. Most providers receive little if any training in these types of conversations and assessment, and many report concerns about their ability to effectively discuss such issues with their patients [26,27]. Even those providers who are comfortable discussing sexual health with their patients face barriers such as limited time with patients with multiple competing needs, or financial pressures that prevent adequate billing for prevention conversations.

And fourth, many providers may struggle with implicit prejudices that impact their willingness to prescribe long-acting ARVs for prevention. Daily oral PrEP acceptability among providers is directly related to PrEP knowledge [28], but even among providers who report being willing to prescribe PrEP, few actually have [29▪]. Providers report being most comfortable prescribing PrEP to serodiscordant couples [30,31▪], which may indicate an underlying bias toward the acceptability of condomless sex in the context of a committed relationship, even though data on treatment as prevention suggest that partners of virally suppressed individuals are not the highest-priority PrEP candidates [32,33]. In one study, when the race of the patient was experimentally manipulated, providers rated black patients as more likely to engage in risk compensation, and were therefore less likely to prescribe them PrEP [34▪]. Moving forward toward equitable access to long-acting agents for populations most vulnerable to infection will require considerations of similar implicit biases and the development of practice guidelines that help public health professionals to overcome them.

SYSTEMS-LEVEL OPPORTUNITIES AND CHALLENGES

Many of the provider-level challenges noted above have systems-level counterparts; the organization of the healthcare system will play a tremendous role in how long-acting agents are implemented across different settings. As mentioned above, long-acting formulations could be delivered in a variety of healthcare settings, and consideration should be given to the potential use of mobile medical units (MMUs). MMUs may be particularly effective for providing long-acting PrEP in rural areas or communities in which mobile units are already delivering other preventive healthcare services such as HIV/STI screening or clean needle exchanges. Mobile clinics in Kenya and Malawi have been effective in delivering healthcare services, including HIV treatment, to remote populations and could be leveraged for delivering PrEP [35,36]; however, adequate consideration would need to be given to the logistics of collecting and storing blood for laboratory tests to measure kidney and liver function.

One of the most important implementation issues will be the added burden of patient visits on the healthcare system. Current clinical guidelines for ARV prevention require HIV testing every 3 months and STI and creatinine screening every 6 months; for every 50 patients placed on PrEP, a clinical setting would have to accommodate an additional 200 visits by otherwise healthy individuals each year. Scaling up PrEP modalities of all kinds will require innovative strategies to deal with this visit burden, including the potential for home-based HIV/STI testing. At the same time, popularity of long-acting agents might increase the number of high-risk individuals who test for HIV and other STIs regularly, and may increase engagement in primary care among young, healthy individuals who might not otherwise seek out a medical provider.

Similar to systems-level issues related to implementation of daily oral PrEP, long-acting formulations for prevention will be subject to concerns about the 'zero-sum' nature of healthcare delivery and resources. As has happened with daily oral PrEP, advocacy for long-acting ARVs for prevention may be pitted against advocacy for increased availability of treatment, especially in resource-poor settings. It is critical that long-acting product availability not lead us to recapitulate historical tensions between treatment and prevention, but rather allow us to highlight the connections between these two goals and the extent to which the populations reached by both services represent individuals at different stages of the care continuum.

Difficult decisions will need to be made regarding the prioritization of long-acting PrEP for key populations and how the constellation of PrEP products will be allocated and funded. It will be important to funnel resources toward populations at highest risk without being paternalistic in pushing long-acting agents or biomedical modalities more broadly. When combination ARV treatment first became available, certain populations were deemed 'unsuitable' for treatment because of adherence concerns. Similar beliefs may cause these same populations to be targeted for long-acting formulations, with or without their full consideration or input. In the contraceptive field, a skewed method mix can simply be an indicator of social/cultural preferences, or signify a lack of choice, or provider bias [37]. Once several efficacious biomedical prevention modalities are approved, method mix in the HIV prevention field will need to be measured and a skew in the mix must be evaluated to ensure that it is not a reflection of compromised user choice or a paternalistic system

imposing specific modalities on specific populations. In the USA, young men of color who have sex with men may feel that ARV medication is being foisted upon them as a biomedical palliative to underlying dynamics of racism and classism that fuel disproportionate incidence rates in their communities.

CONCLUSION

Considerations of implementation challenges often raise more questions than they answer, as the complexities of real-world engagement, delivery, and retention shed light on inherent inequities and limitations of existing practice models. The review above suggests several key recommendations for proactive implementation work as long-acting formulations move forward in development. First, efficacy trials of long-acting agents should integrate psychosocial and behavioral variables likely to influence later adoption and implementation. Budgets for biomedical prevention trials should include appropriate funding for social and behavioral components so that this work is considered central to the research endeavor. Second, social science research critical to understanding the political, economic, and social contexts, as well as the healthcare systems in which ARV prevention interventions may be provided, should be conducted in parallel to efficacy trials to inform implementation planning. Third, preparatory research and education should be conducted with providers who are likely to prescribe long-acting agents. Consideration should be given to the importance of engaging providers from a variety of practice settings – primary care, sexual and reproductive health, harm reduction/substance use, adolescent medicine, among others. Finally, education and marketing of emerging long-acting agents should not be conceived based on a public health sensibility, but should be conducted to maximize interest and acceptability among populations most vulnerable to new infections. Conceptualizing new HIV prevention technologies as behavioral interventions at the level of the patient, provider, and system will be paramount to effective and efficient implementation with the potential for the greatest impact on the epidemic.

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Conflicts of interest

There are no conflicts of interest.

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