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EDITORIAL

The Potential of Long-Acting, Injectable PrEP, and Impediments to its Uptake

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In December 2021, the U.S. Food and Drug Administration approved the first injectable, long-acting HIV pre-exposure prophylaxis (PrEP) medication, cabotegravir, an integrase strand transfer inhibitor [1]. A randomized double-blind study demonstrated that injectable cabotegravir was superior to oral PrEP in preventing HIV infections in men who have sex with men and transgender women [2], and a parallel study in cisgender women had similar results [1]. The new PrEP medication, which will require healthcare provider-administered intragluteal injections every 2 months following two loading doses 4 weeks apart, offers an alternative to daily, oral PrEP. Injectable PrEP uptake in the USA has the potential to reduce HIV infections, especially for individuals for whom taking daily oral medication is unwanted, challenging, or unrealistic [1]. However, injectable PrEP's considerable potential to impact the HIV epidemic cannot be realized without understanding and addressing impediments to its implementation.

Perhaps the most critical advantage of injectable PrEP relative to oral PrEP may be its periodic, rather than daily, administration [1]. Some individuals forget to take their PrEP medication and would benefit from taking PrEP less often. For others, PrEP adherence is complicated by multifaceted and intersecting factors, including underestimation of personal HIV risk and behavioral health challenges, particularly depression and substance use [3]. Less frequent PrEP administrations, coupled with appropriate behavioral health supports, might be preferable to the challenges of maintaining a daily PrEP routine. "On-demand" dosing of oral PrEP, in which two tablets are taken 24 h before sex, one tablet 24 h later, and then another tablet 24 h later can similarly mitigate the need for daily oral PrEP. However, "on-demand" dosing requires an individual to have foresight into when they next anticipate having sex, which is not always possible. Furthermore, robust data are still lacking regarding the efficacy of "on-demand" PrEP dosing in transgender people and cisgender women. In addition, engaging in daily preventive health behaviors may be more difficult for individuals with significant social challenges, such as persons lacking stable housing, employment, food affordability, and basic safety.

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Consequently, administering PrEP 6–7 times a year, rather than daily, may therefore increase the number of PrEP users and assist them in remaining in long-term use.

Another key advantage of injectable PrEP is its potential ability to circumvent certain challenges imposed by social stigma [1]. Some individuals decline oral PrEP out of fear that their family, partners, or peers may discover that they use PrEP by finding their pills. This could reveal their elevated risk for HIV and inadvertently "out" them as LGBTQ + or someone who uses drugs [3]. Participants in multiple studies reported experiencing PrEP-associated stigma in diverse ways, including stereotyping, rejection, transphobia, and homophobia [3]. Though removing the necessity to have PrEP medication in one's possession will not eliminate PrEP-related stigmatization, it may decrease stigma's contribution to PrEP non-uptake and non-adherence by making PrEP usage easier to conceal if desired.

Despite the considerable benefits, many of the same barriers impacting oral PrEP usage will likely hinder injectable PrEP uptake. Awareness and knowledge deficits about PrEP among potential users are prominent barriers to utilizing PrEP. In addition, concerns about side effects that impact oral PrEP usage may also inhibit the uptake of injectable PrEP, even though both modalities have been well tolerated. Distrust of healthcare systems reflects another significant barrier to PrEP uptake [3]. This can stem from historic population-level maltreatment of people living with HIV, substance use disorders, or racial, sexual, and/or gender minorities, as well as personal experiences of discrimination and stigmatization by healthcare providers. Access barriers further limit PrEP uptake [3]. Monitoring PrEP entails routine clinic visits, and some patients have transportation or time constraints. Others lack access due to geographic limitations if there are no local providers who prescribe PrEP or offer LGBTQ + -sensitive care. These barriers may become more pronounced with injectable PrEP, as clinic visits are required every 2 months and must be held in-person, as opposed to the quarterly visits required for oral PrEP and the opportunity to have some appointments via telemedicine. These logistical barriers may disproportionately affect populations that maintain elevated HIV risk and can further PrEP access disparities. Although injectable PrEP may be an appropriate choice for many, including those with significant renal disease, it is contraindicated for patients taking rifampicin, rifapentin, carbamazepine, oxcarbamezapine, phenytoin, or phenobarbital due to drug interactions, and should not be taken concomitantly with these medications [4].

As PrEP is a medical intervention, healthcare provider buy-in is a *sine qua non* for the success of PrEP utilization. However, provider-level barriers may hinder PrEP uptake. Providers' lack of knowledge or discomfort speaking about sexual health and substance use impede a patient's ability to learn about and access PrEP. Patients may be caught in a "purview paradox," which occurs when primary care providers and HIV specialists each abnegate responsibility to prescribe PrEP, instead believing the other is responsible for its provision [5]. Healthcare providers who prescribe PrEP may have concerns about patient adherence, medication side effects, or that the prescription will lead to increases in condomless sex, numbers of sexual partners, or other sexually transmitted infections [3], potentially reducing their willingness to promote a new approach to PrEP. It is also important to underscore the challenges injectable PrEP will impose on providers. Injectable PrEP will require more frequent clinic visits, adding to the scheduling and time demands of providers. In addition, providers will need a mechanism to track the injection schedules of their patients. Effective implementation will demand quick identification of those who are late for their injections.

Recognizing these potential barriers can lead to the development of effective implementation strategies as injectable PrEP becomes widely available. Healthcare providers can play a critical role in counteracting the many barriers facing the utilization of PrEP. Providers should have access to more training about PrEP, including patient-specific challenges to PrEP usage and the medications' updated prescribing guidelines and side effect profiles. Providers should be proactive in obtaining sexual and substance use histories and discussing PrEP with their patients, which aligns with C.D.C.'s current recommendations for providers to discuss PrEP with all sexually active adolescents and young adults [4]. In addition to increasing PrEP knowledge and access, normalizing patient-provider conversations about PrEP can improve provider comfortability in prescribing PrEP and reduce the stigma associated with PrEP usage. Public health campaigns

should be implemented to increase PrEP awareness, particularly in communities with PrEP underutilization, augmenting healthcare provider education efforts.

Lastly, steps must be taken to ensure injectable PrEP's affordability, ensuring equitable access for individuals with fewer financial resources [6]. With the availability and efficacy of generic, oral PrEP, a large price difference between the two PrEP modalities may create financial barriers to switching from oral to injectable PrEP [7]. The Affordable Care Act mandates that preventive interventions with grade A ratings by the U.S.P.T.F. should have no cost-sharing requirements for patients with commercial insurance. In 2019, oral PrEP was given a grade A rating, which should apply to injectable PrEP as well. Notably, this may not reduce costs for those without insurance, and the impact on those with Medicare and Medicaid remains unclear. Governmental and corporate programs are needed to ensure that the costs of injectable PrEP, clinic visits, and ancillary services are affordable for those who are underinsured. In addition, steps need to be taken to ensure global communities have equitable access to injectable PrEP.

Despite advances in HIV testing, treatment, and prevention, HIV continues to affect many U.S. populations. Some of the barriers limiting oral PrEP uptake may similarly impact injectable PrEP, and steps should be taken to mitigate these obstacles. Currently, real-world data are lacking, and future research should assess the effectiveness and patient perspectives regarding injectable PrEP. In addition, more research surrounding injectable PrEP is needed to ensure equity in reaching, engaging, and retaining all populations with elevated HIV prevalence and risk. Nevertheless, injectable PrEP should reflect a positive addition to HIV prevention, enhancing patient choice, potentially increasing PrEP usage, and ultimately decreasing new HIV infections.

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