

# Making an Impact With Preexposure Prophylaxis for Prevention of HIV Infection

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Five years ago, pivotal evidence emerged from clinical trials that preexposure prophylaxis (PrEP), using oral tenofovir disoproxil fumarate in combination with emtricitabine, was effective and safe for prevention of human immunodeficiency virus (HIV) infection [1, 2]. Subsequent work has shown high uptake and use of PrEP in demonstration settings worldwide [3–6]. Regulatory approval of a label indication by the Food and Drug Administration (FDA) in 2012 was a first for HIV prevention and has been followed more recently by similar approvals in some of the countries most heavily affected by HIV [7, 8]. PrEP works for HIV prevention, reducing individual risk by >90% [9], and early adopters are already achieving real benefits [10]. Normative guidance documents from the Centers for Disease Control and Prevention (CDC) in 2014 and the World Health Organization (WHO) in 2015 have carved out a role for PrEP as a global strategy to protect individuals at risk [11, 12].

Reducing the burden of HIV globally with PrEP and other effective strategies requires defining how to prioritize delivery for greatest impact. An important challenge for PrEP has been identifying those at risk for HIV acquisition for

whom PrEP could be a prevention choice. The WHO has proposed a standard termed “substantial risk,” defined as an anticipated HIV infection incidence in the absence of PrEP of 3% per year. The FDA-approved prescription drug label in the United States notes that high-risk characteristics include involvement in a social network in which the HIV infection prevalence is high, limited use of condoms, a history of sexually transmitted infections, exchange of sex for commodities, incarceration, drug and alcohol use, and sex partners of unknown HIV status. While these definitions are helpful for resource allocation and geographic PrEP prioritization, providers need simple questions that can define those patients who would benefit from PrEP and then need to use those in a way that achieves prevention impact.

In this issue of *The Journal of Infectious Diseases* [13], Jenness et al present a mathematical model that assesses the CDC’s recommended criteria for PrEP use in US men who have sex with men (MSM): essentially, recent receptive or insertive anal sex, without a condom, with a partner of unknown HIV status (within or outside of a monogamous relationship) or anal sex, regardless of condom use, in an ongoing relationship with a known HIV-positive partner. The model was parameterized with sexual behavior data from US populations, realistic PrEP adherence was included based on data from recent demonstration studies, and sensitivity analyses explored a range of coverage, adherence, and time windows for behaviors. The authors found that, with 40% coverage among those meeting

at-risk criteria and 62% adhering to PrEP, one third of new infections in the United States could be prevented over the next 10 years.

In the Jenness et al model, the greatest contributor to new infections averted was coverage: as more at-risk men receive PrEP, the impact of PrEP increases. Simple behavioral criteria, such as those defined by the CDC, were designed to facilitate PrEP prescribing and, if followed, could result in substantial impact. However, the number of persons prescribed PrEP in most locales remains low from a coverage perspective, and, thus, its impact to date on the HIV epidemic, in the United States and globally, is substantially smaller than it could be. Challenges to increasing the numbers of at-risk persons who are receiving PrEP include barriers to access (to whom should PrEP be prescribed, where can it be received, and who will pay for it) and slow diffusion of awareness in priority populations. However, substantial increases in awareness have been documented, often through social media and homegrown public health campaigns. Some barriers to access (such as prescription coverage) have not been as formidable in all cases as initially expected, and public and private healthcare models for PrEP delivery have been described [10, 14, 15]. Notably, the CDC criteria are broad, which will help achieve appropriate coverage of the target population. Alternatives that limit access to PrEP to those at only the absolute highest risk might surprisingly limit its impact. For example, although the Jenness et al model did not assess recent sexually transmitted infection

Received and accepted 24 May 2016.

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**The Journal of Infectious Diseases**®

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as a criterion for PrEP, other analyses have shown that, since most new infections occur in men without a recent sexually transmitted infection, restricting PrEP access to only those with the highest risk would have individual benefit but limited impact on the total epidemic [16]. Importantly, broad inclusiveness for consideration for PrEP does not mean that PrEP should be universal—the CDC estimates that one quarter of MSM, a fifth of injection drug users, and <0.5% of heterosexuals in the United States meet the defined criteria for consideration of offering PrEP as a prevention choice [17].

It remains to be seen whether the levels of coverage, adherence, and impact modeled by Jenness et al can be achieved at scale. However, PrEP studies from the United States, the United Kingdom, Canada, France, and other high-income countries are showing that those who seek out PrEP have substantial HIV risk and adhere well, resulting in near elimination of HIV acquisition [3, 4, 10, 18]. In other words, those who are starting PrEP are very much appropriate candidates for this intervention. These populations have included a racially and educationally diverse population of men who have had appreciable rates of substance abuse, income insecurity, depression, and other potential challenges to PrEP use; nevertheless, they achieved substantial benefit from PrEP. Men taking PrEP report decreased anxiety, increased communication and trust, greater self-efficacy, and improved sexual pleasure and intimacy—benefits that are not part of the FDA-approved label for PrEP but certainly reinforce how PrEP is wanted and valued [19].

For infectious diseases professionals, PrEP makes us think differently. It is composed of antiretroviral medications, but it is not antiretroviral treatment. Treatment is uniformly needed and lifelong, but PrEP is an option for those at risk and for periods in their life when other prevention options may not be enough. Adherence to treatment must be sustained for life, without breaks; PrEP adherence needs only correspond to periods of risk, and moreover

the daily dosing schedule can yield a high level of protection even among people who, on occasion, have missed a dose [20]. Importantly, PrEP use is not necessary throughout life but should be expected to stop when behavioral risks have diminished or other prevention strategies are used consistently. Finally, PrEP availability pushes us to become comfortable talking regularly with patients about behavioral risk, and it expands the scope of prescribers to those in primary care and frontline public health roles, who have not often prescribed antiretrovirals. Sadly, some evidence has shown how we, as prescribers, may create barriers to PrEP, including by telegraphing judgment and discomfort in talking about sexual and other risks [21]. In many ways, PrEP is analogous to contraception—it is a primary care intervention, with small but important medical risks, that operates in a sexual context and that sometimes has imperfect adherence but nonetheless has tremendous public health impact [22].

Looking ahead, PrEP delivery is likely to evolve in the United States and globally, as experience and comfort are gained. Strategies to simplify delivery might include same-day initiation, less frequent follow-up visits, pragmatic criteria that might reduce the frequency of clinical safety monitoring, simplified HIV and sexually transmitted pathogen testing and pick-up of refills, and task shifting to expand the scope of PrEP providers. Similar approaches have simplified delivery of antiretroviral therapy, both in the United States and in resource-limited settings, resulting in important cost savings without sacrificing good care. As with contraception, streamlined delivery of PrEP results in the greatest numbers with access and the greatest resulting impact [23].

Stable and even increasing HIV infection incidence in some groups in the era of high treatment access in high-income settings shows that business as usual for HIV prevention is not enough to radically reduce new HIV infections [24]. Every provider, public health professional, patient, and advocate who has seen the devastation

wrought by HIV in the last 3 decades wants to see far fewer men and women presenting for care with a new diagnosis of HIV infection. PrEP can be a part of that outcome, especially if pragmatic approaches are sought that aim to achieve the coverage necessary to gain population impact at scale.

## Notes

**Financial support.** This work was supported by the National Institute of Mental Health, National Institutes of Health (grant R01 MH095587).

**Potential conflict of interest.** J. M. B. has led studies of preexposure prophylaxis in which study medication was donated by Gilead Sciences. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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