Clinical Infectious Diseases Advance Access published August 13, 2015

If PrEP decreases HIV transmission, what is impeding its uptake?

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Over the past decade there have been ten efficacy trials evaluating the use of oral or topical Tenofovir-based regimens to prevent HIV transmission in at risk populations, including young African heterosexuals, men and transgender women who have sex with men, as well as Thai injecting drug users [1-10]. Seven of these ten studies demonstrated the efficacy of antiretroviral pre-exposure prophylaxis (PrEP), and in three studies where HIV incidence in the intervention arm did not differ from the control condition, the major reason for the lack of efficacy was medication non-adherence [7, 8, 11]. The weight of the evidence from these PrEP studies has led to US FDA approval of for the use of oral Tenofovir co-formulated with Emtricitabine (TDF/FTC) for anti-HIV PrEP [12]. Demonstration projects are underway in several parts of the world, so that it is likely that TDF/FTC for PrEP will soon be approved for use in several countries Latin America, Africa, Asia, and Europe [13]. Of particular note is that the three focusing on men who have sex with men (MSM) had highly successful results, including the PROUD study in the United Kingdom, in which MSM who attended genito-urinary medicine clinics were randomized to receive PrEP immediately, or be put on a waiting list and be offered PrEP after a year. HIV incidence was so high in the waiting list group (7.8% annually), and PrEP was so effective (86% decrease in HIV acquisition), that the study had to stop early, after about 10% of projected enrollment had accrued. These findings are particularly important, given that the rate of new HIV infections continue to increase dramatically among MSM domestically and globally.

Despite the demonstrated efficacy of PrEP, and the approval by regulatory bodies in the US, uptake has not been rapid. In recent years, the concept of a continuum of HIV care has been a helpful heuristic for the assessment of the effectiveness of virological suppression at a population level [14]. In the current issue of *Clinical Infectious Diseases*, Kelley et al have reviewed some of the sources of attenuation in the Atlanta HIV prevention continuum (i.e. barriers to PrEP provision for high-risk MSM) [15]. Their data suggest that only about 15% of MSM who would be appropriate candidates for PrEP would likely access

the medication. Part of the problem is that PrEP awareness remains low, albeit having increased somewhat over the past few years [16, 17]. Social disenfranchisement plays a role, i.e. MSM who are poorer or less educated appear to be less informed about PrEP [18]. Medical mistrust remains entrenched for some Black persons because of earlier adverse experiences with clinical research (e.g. the Tuskegee experiment) leading to tuning out new information [19]. Media campaigns by some "PrEP denialists" may have created confusion for some who might benefit from PrEP [20].

In addition to lack of awareness and misinformation that may be leading to reticence to utilize PrEP, another major barrier is posed by medication and health services costs (more than $12,000 annually for those without insurance). The current *CID* study highlights this challenge in the current health reform environment. Because Atlanta is a "blue" city in a "red" state, its government has not embraced the Affordable Care Act, leaving many who might benefit from PrEP to be either uninsured or underinsured. Since 20 US states have not expanded Medicaid, access to PrEP may be challenging for some living in urban areas of high HIV prevalence, such as Miami, Dallas, Houston, and New Orleans. Awareness and use of PrEP and post-exposure prophylaxis appear to be lower among MSM who live in states with more stigmatizing environments [21]. Although the TDF/FTC manufacturer, Gilead Sciences has a drug assistance program [22], many individuals may fall in between the cracks by having incomes that are too high, and/or by having insurance plans with onerous co-payments.

Since PrEP is a biomedical intervention, accessing it requires either an informed consumer, or a busy clinician taking the time to determine whether a patient might benefit from PrEP. Primary providers generally do not routinely ask about sexual orientation or behavior [23, 24], so many opportunities to initiate PrEP may be missed. Moreover, patients may be uncomfortable to request PrEP, since they may anticipate moralistic conversations if they disclose their sexual orientation [25] and preference for condomless sex. There is no consensus among clinicians about who should provide PrEP. Some would

argue that primary care providers are ideal, since sexual health promotion should be an intimate part of primary care, but many feel they are not equipped to discuss the nuances of sexual behavior [26] and are not familiar with prescribing antiretroviral medication [27]. Conversely, infectious disease specialists who might only provide primary care for people living with HIV may not be comfortable in managing people who are otherwise healthy who request prophylaxis because of behavioral risks. Some attempts to address clinician time constraints include the development of algorithms using a limited number of specified questions to generate a risk score to determine whether a patient might be an appropriate candidate for PrEP [28]. The use of electronic technologies whereby patients can self-report their behavioral risks, either at home or in waiting rooms, could also save time for clinicians to routinely determine whether a patient's recent behavioral patterns might merit a PrEP discussion.

Despite all these impediments, the use of PrEP by MSM appears to be increasing in some quarters. In San Francisco, it is estimated that more than 10% of at risk HIV-infected MSM have used PrEP, but behavioral surveys suggest that many more could benefit [29]. At Fenway Health, a Boston Community Health Center with a specialization in sexual and gender minority health, PrEP prescriptions have increased in recent years, with more than 500 being started in the past year [30]. What San Francisco and Boston share in common is an environment that has supported civil equality for sexual and gender minorities, early implementation of health reform, and access to culturally-tailored behavioral health programs. It would be unfortunate if the uptake of PrEP was limited to a few "blue islands," when it is clear that individuals who might benefit from PrEP may be found in diverse geographic settings. Some of the impediments to wider PrEP use, such as increasing the health literacy of at risk people and enhancing provider education, should be readily overcome by using new technological tools to disseminate information. However, the findings from Atlanta study suggest that the challenges posed by unsupportive health insurance environments may become one of the major impediments remaining for PrEP to be scaled up at a sufficient level to radically decrease the number new HIV infections across the

United States. Availability of an evidence-based, effective HIV prevention intervention should not be dictated by geography, so advocacy to ensure equal access will be essential if the use of antiretroviral PrEP is to have a major impact on HIV incidence.

Funding

This work was supported by the National Institutes of Mental Health at the National Institutes of Health [K23 MH098795 to D.S.K.] and in part by the Harvard University Center for AIDS Research (CFAR), an NIH funded program [P30 AI060354], which is supported by the following NIH Co-Funding and Participating Institutes and Centers: NIAID, NCI, NICHD, NHLBI, NIDA, NIMH, NIA, NIDDK, NIGMS, FIC, and OAR. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Potential Conflicts of Interest

K.H.M. has conducted research with unrestricted project support from Gilead Sciences and Merck.

D.S. K. has conducted research with unrestricted project support from Gilead Sciences and Bristol Myers Squibb.

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