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EDITORIAL COMMENTARY

Novel Approaches for Development of Human Immunodeficiency Virus Preexposure Prophylaxis Agents

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(See the Brief Report by Mullick and Murray, on pages 214–7.)

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The US Centers for Disease Control and Prevention estimate that there are >1 100 000 people living with human immunodeficiency virus (HIV) in the United States [1]. In 2017, 38 739 people with a new diagnosis of HIV infection were reported [2], a number that has not changed substantially in recent years despite considerable attention to HIV prevention.

Improved strategies for HIV prevention are needed. Accordingly, the use of preexposure prophylaxis (PrEP) to prevent HIV infection has captured considerable attention. Clinical trials in men who have sex with men (MSM) with the combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC, sold as Truvada by Gilead) demonstrated the ability of this combination to prevent HIV acquisition [3–5]. This drug combination was approved for HIV prevention in the United States in 2012. The protective benefit of TDF/FTC PrEP persists even in the face of "classical" sexually transmitted disease (STD) infections including gonorrhea and syphilis [3–6], STDs that are extremely common in sexually active populations and can increase the risk of HIV acquisition [7]. Indeed, syphilis infection can serve as a harbinger for future HIV acquisition. Pathela et al reported that an MSM in New York City with syphilis had a 1 in 20 chance of acquiring HIV in the next 12 months [8], results that have led to a recommendation of TDF/FTC PrEP in at least some people with incident STD infections [9].

Randomized clinical trials demonstrating reduction in HIV infections support widespread usage of TDF/FTC [3–5], and randomized clinical trials with the endpoint of prevention of HIV infection continue to be the best approach to determine the efficacy of new HIV prevention tools. Such trials compare new agent(s) or strategies to a standard of care including prevention tools with proven benefit. For example, one ongoing trial is comparing a new injectable PrEP drug, long-acting cabotegravir, to oral TDF/FTC to prevent HIV acquisition in MSM (NCT02720094). Parenthetically, while TDF/FTC clearly prevents HIV infection, difficulty of daily adherence to a pill means that interpretations of this kind of comparison are complicated by pill usage (and real-world "effectiveness") as well as true differences in biologic efficacy.

But suppose a future approved antiviral agent prevents HIV infection almost perfectly. Under these conditions, how can efficacy of other new drugs or strategies be demonstrated? In this issue of *The Journal of Infectious Diseases*, Mullick and Murray [10] offer a provocative approach to future evaluation of new PrEP agents through the use of incident rectal gonorrhea infections as a surrogate for exposure to HIV [10]. The authors reviewed 8 articles in which HIV incidence was noted in MSM who also had anal gonorrhea infection at some time during the period of observation. The authors found a close correlation between detection of rectal gonorrhea infection and incident HIV infection, and used the data to generate a model to predict the probability of HIV acquisition for a given rate of rectal gonorrhea.

This approach raises the issue of a surrogate for measurement of protection from HIV infection. In vaccine development, we try to determine immune defenses required for HIV prevention that can then serve as a surrogate to identify promising candidates for further vaccine development [11]. For better understanding of TDF/FTC, Anderson et al reported that an intracellular tenofovir diphosphate concentration of 16 fmol/million blood mononuclear cells was associated with a 90% reduction of HIV acquisition in MSM using TDF/FTC PrEP [12]. In the current article, Mullick and Murray use rectal gonorrhea infection as a surrogate for exposure to HIV, rather than as a surrogate for the preventive efficacy of a new agent. The authors argue that in trials of a new PrEP agent, rectal gonorrhea detected in the absence of HIV infection could be taken to mean that prevention of HIV infection had actually occurred.

The authors acknowledge a series of problems with this approach. The 8 articles

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reviewed (among 2485 considered) had limitations: Data were collected over a long period of time, and the numbers of actual cases of gonorrhea and HIV were often quite small. While absence of incident HIV infections could mean that PrEP agents prevented HIV, alternative explanations of such results are possible. Gonococcal infections might be found in communities where HIV is still uncommon and, in these communities, exposure to gonorrhea cannot serve to predict HIV risk. Accordingly, 2 unstated requirements for this approach are essential: that gonorrhea and HIV are persistently co-circulating infections in the risk populations considered, and that gonococcal infection does not undermine the protective benefit of TDF/FTC [3–6]. In addition, in communities where HIV is common, a substantial fraction of HIV-infected people are likely to be receiving antiviral treatment, rendering them no longer contagious [13] and confounding interpretation of the benefit of PrEP. Indeed, the detection and treatment of all people with HIV is the cornerstone of HIV prevention worldwide, and as more people are treated, HIV incidence has fallen in many communities [14]. The need to aggressively and independently prevent and treat gonorrhea and HIV infections might be expected to compromise the approach proposed.

Where do we go from here? First, STDs have long been used as markers for HIV risk behaviors [15] and as an inclusion criterion for many HIV prevention trials. The data provided by Mullick and Murray [10] reiterate this relationship. The authors recognize that STDs other than gonorrhea are also common in at-risk populations (and were also measured in most of the articles cited) and could be used to develop a more complex view of potential HIV exposure. The authors note that a prospective estimate of the proportion of treated HIV-infected people in a community would strengthen the validity of the approach, a point that emphasizes the importance of HIV testing and the HIV treatment continuum. Perhaps most importantly, the article shines a light on the urgent need for novel study designs and approaches to assess new HIV prevention agents and strategies [16, 17]; creative ideas should be seriously considered.

Notes

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References

1. Centers for Disease Control and Prevention. HIV surveillance report, 2017. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Accessed 2 January 2019.
2. Centers for Disease Control and Prevention. Diagnoses of HIV infection in the United States and dependent areas, 2017. https://www.cdc.gov/hiv/statistics/overview/ataglance.html. Accessed 2 January 2019.
3. Grant RM, Lama JR, Anderson PL, et al; iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med **2010**; 363:2587–99.
4. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet **2016**; 387:53–60.
5. Molina JM, Capitant C, Spire B, et al; ANRS IPERGAY Study Group. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med **2015**; 373:2237–46.
6. Volk JE, Marcus JL, Phengrasamy T, et al. No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. Clin Infect Dis **2015**; 61:1601–3.
7. Carlson JM, Schaefer M, Monaco DC, et al. HIV transmission. Selection bias at the heterosexual HIV-1 transmission bottleneck. Science **2014**; 345:1254031.
8. Pathela P, Braunstein SL, Blank S, Shepard C, Schillinger JA. The high risk of an HIV diagnosis following a diagnosis of syphilis: a population-level analysis of New York City men. Clin Infect Dis **2015**; 61:281–7.
9. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the US: 2017 clinical practice guideline. Atlanta, GA: Department of Health and Human Services, **2018**. https://www.cdc.gov/hiv/guidelines/preventing.html. Accessed 2 January 2019.
10. Mullick C, Murray J. Correlations between human immunodeficiency virus (HIV) infection and rectal gonorrhea incidence in men who have sex with men: implications for future HIV pre-exposure prophylaxis trials. J Infect Dis **2020**; 221:214–7.
11. Haynes BF, Gilbert PB, McElrath MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med **2012**; 366:1275–86.

12. Anderson PL, Glidden DV, Liu A, et al; iPrEx Study Team. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med **2012**; 4:151ra125.
13. Cohen MS, Chen YQ, McCauley M, et al; HPTN 052 Study Team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med **2011**; 365:493–505.
14. Justman JE, Mugurungi O, El-Sadr WM. HIV population surveys—bringing precision to the global response. N Engl J Med **2018**; 378:1859–61.
15. Wasserheit JN. Epidemiological synergy. Interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. Sex Transm Dis **1992**; 19:61–77.
16. Cutrell A, Donnell D, Dunn DT, et al. HIV prevention trial design in an era of effective pre-exposure prophylaxis. HIV Clin Trials **2017**; 18:177–88.
17. Dunn DT, Glidden DV, Stirrup OT, McCormack S. The averted infections ratio: a novel measure of effectiveness of experimental HIV pre-exposure prophylaxis agents. Lancet HIV **2018**; 5:e329–34.