Title

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Journal

The Journal of Infectious Diseases, 223(1)

ISSN

0022-1899

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Publication Date

2021-01-04

DOI

10.1093/infdis/jiaa555

Peer reviewed

The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Assessing the Role of Long-Acting Cabotegravir Preexposure Prophylaxis of Human Immunodeficiency Virus: Opportunities and Aspirations

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(See the Major Article by Maloney et al on pages 72–82.)

Keywords. HIV; PrEP; CAB LA; cabotegravir; TDF/FTC; MSM; combination prevention; long-acting.

Human immunodeficiency virus (HIV) has provided critical lessons for all novel infectious diseases. With 40 years of hindsight, it is clear that a combination of prevention efforts is required to prevent onward HIV transmission, in the absence of a vaccine. Such prevention tools include a variety of behavior changes required for risk reduction, the development of treatment as prevention both for the health of the individual and to eliminate onward transmission, and, most recently, the application of antiretroviral agents as preexposure prophylaxis (PrEP) for people at the highest risk for HIV acquisition [1].

The combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) was approved for PrEP by the United States Food and Drug Administration (FDA) in 2012 [2]. A series of studies suggested that for rectal exposures, TDF/FTC provides high levels of protection, even with intermittent usage [3]; vaginal protection appears to require dosing with greater fidelity to achieve and maintain high levels of protection [4]. A combination of tenofovir alafenamide with emtricitabine (TAF/FTC) was approved by the FDA in 2019 as an alternative to TDF/FTC for prevention of HIV for nonvaginal exposures [2, 5]. Despite the potential for high levels of protection from HIV provided by oral tablet–based PrEP, the population-level impact has been limited due to lack of awareness, access, adherence, persistence, and other structural barriers for people at greatest risk.

For these reasons, there has been great interest in developing other ways to deliver PrEP. Long-acting PrEP can reduce some of the limitations of daily oral PrEP. Long-acting PrEP includes antiviral rings, monoclonal broadly neutralizing antibodies, antiviral implants and other slow-release devices, and agents with apparent longer half-lives, including injectable antiviral agents [6]. The development of long-acting injectable formulations of cabotegravir and rilpivirine has led to development of a combination of the latter agents for intermittent administration for treatment of HIV [7], and cabotegravir injections for prevention of HIV [8, 9].

In this issue of *The Journal of Infectious Diseases*, Maloney et al used a mathematical model to compare the population-level benefits of TDF/FTC and long-acting cabotegravir (CAB LA) in prevention of HIV acquisition in men who have sex with men (MSM) in Atlanta, Georgia over 10 years [10]. To populate the model, the authors used results drawn from recent data from the ARTnet study of 4904 MSM, reporting on 16 198 sexual partnerships. These results accounted for duration, concurrency, and other attributes of sexual partnerships [11]. Maloney et al assumed that 15% of PrEP-eligible MSM would use PrEP at baseline. Replacement of 50% of TDF/FTC with CAB LA was predicted to reduce HIV incidence by 4.3%. However, if PrEP use doubled, 50% increased usage of CAB LA might lead to a 17.3% reduction in HIV incidence. The benefits of CAB LA included increased "coverage" of at-risk sex acts and additional protection from infection after discontinuation of CAB LA, ascribed to its very long half-life [8].

This is one of several modeling exercises comparing daily oral and long-acting PrEP for MSM [12] and women [13, 14]. These reports used somewhat different mathematical approaches and have made different assumptions. Not surprisingly,

Received 26 August 2020; editorial decision 26 August 2020; accepted 1 September 2020; published online September 3, 2020.

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The Journal of Infectious Diseases® 2021;223:1–3

DOI: 10.1093/infdis/jiaa555

however, the models predict that the greater the number of at-risk people who choose to use PrEP, and the larger the number who choose the long-acting formulation of PrEP, the greater the prevention benefit.

Some of these models [10, 14] are based on broad estimates of the efficacy of CAB LA. Maloney et al assumed 99% protection from CAB LA, and they explored differences in half-life, which would affect the duration of protection, providing a measure of "forgiveness" to delayed injection dosing [10]. But the results of detailed studies of the pharmacology of CAB LA in men and women [8, 9] and a large phase 3 trial [15] have clarified these assumptions. Extrapolating from nonhuman primate data, CAB LA can be expected to provide high levels of protection for at least 8 weeks after injection [8], and in the human phase 2 clinical trials, individuals born male had a mean apparent terminal half-life of 45.3 days [9].

Most recently, CAB LA was directly compared to TDF/FTC in 4570 MSM and transgender women in the United States, South America, Asia, and Africa [15]. The incidence of HIV was 1.22 per 100 person-years in participants receiving TDF/FTC and 0.41 per 100 person-years in those receiving CAB LA, leading to the conclusion that CAB LA is superior to TDF/FTC. The basis for the benefit most likely resulted from less than protective levels of adherence to medication in some study participants receiving TDF/FTC. In addition, 13 study participants receiving CAB LA acquired incident HIV, and these cases are being studied in detail. To date, CAB LA has been used with a "lead-in" with oral cabotegravir, which may provide an additional period of vulnerability to infection. In addition, the benefits of long-acting PrEP agents might be compromised by selection of resistant viral variants that emerge during treatment discontinuation as therapeutic levels slowly wane [9, 14].

While the study by Maloney et al focused on MSM, there is substantial interest in CAB LA for high-risk women [13, 16]. Efficacy trials of oral TDF/FTC for HIV prevention against vaginal exposures have been mixed [4], and these divergent results have been ascribed to a combination of low adherence and poor drug penetration into tissues of the female genital tract. A phase 3 study comparing CAB LA to oral TDF/FTC is ongoing in sub-Saharan Africa [16].

Modeling studies of PrEP shine a light on the benefits and limitations of the intervention and on new agents such as CAB LA. But they are perhaps too narrow in their scope. The advantages of cabotegravir extend beyond improved adherence. Novel agents and delivery methods may attract new PrEP users, who find injections simpler and less stigmatizing. Population models cannot examine many special situations for which these agents are particularly attractive. For example, MSM visiting sexually transmitted infection (STI) clinics with syphilis have an extremely elevated risk of acquiring HIV [17], and a same-day injection of an antiviral agent may offer a special advantage. In addition, the deployment of long-acting agents may take advantage of alternative healthcare settings such as pharmacies and minute clinics, increasing access and acceptability.

PrEP modeling does not consider the critical importance of combinations of interventions. Maximal prevention of sexual transmission of HIV involves risk reduction behavior, including but not limited to condom use for STI prevention, STI testing and treatment, detection and treatment of people with infection, and PrEP in those who will benefit the most. Jenness et al [1] have argued that improvements to an integrated HIV prevention and care continuum could avert more than two-thirds of HIV infections expected among MSM in Atlanta over the next decade. HIV screening interventions, including linkage to PrEP, were predicted to provide a major prevention benefit.

The United States has committed to a program called Ending the HIV Epidemic: A Plan for America [1, 18]. Expansion of PrEP is one of the pillars of this plan. It has been estimated that >1 million people are candidates for PrEP, whereas <100 000 people accessed it in 2017 [19]. The model provided by Maloney et al [10] reinforces the idea that novel agents and formulations that attract new populations to combination prevention interventions including PrEP will contribute to the Ending the HIV Epidemic efforts, potentially making aspirational targets within reach.

Notes

Financial support. M. S. C. and R. J. L. were supported by grant (UM1-AI068619, to the HIV Prevention Trials Network (HPTN) from the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health and by the NIAID Division of Intramural Research; by the National Institute of Diabetes and Digestive and Kidney Diseases (5R01DK108424).

Potential conflicts of interest. M. S. C. reports other support from Merck, outside of the submitted work. R. L. reports personal fees and other support from Gilead Sciences, Merck, and Roche, outside of the submitted work.

Both authors have 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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