The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Next-Generation Preexposure Prophylaxis: Choices For Effective HIV Prevention

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(See the Major Article by Markowitz et al., on pages 1398-406.)

Evidence supporting the use of antiretroviral medications to prevent new human immunodeficiency virus (HIV) infections—as both treatment to eliminate infectiousness and prophylaxis to block acquisition—has revolutionized thinking about HIV prevention. Indeed, HIV treatment and preexposure prophylaxis (PrEP) are now core components of US and global efforts to end the HIV epidemic [1]. Oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was the first PrEP agent [2, 3], and its key regulatory and normative agency milestones have included Food and Drug Administration approval in 2012, Centers for Disease Control and Prevention and World Health Organization guidelines in 2014 and 2015, and drug regulatory approval and national guidelines currently in >40 countries worldwide [4]. PrEP with TDF/FTC pills is now standard of care for HIV prevention, and wide-scale implementation is underway globally.

TDF/FTC clinical trials found that individuals who had high-level adherence, as measured by drug levels in blood samples, were protected from HIV [5, 6]. Unsurprisingly, those who did not adhere well to oral TDF/FTC treatment were not protected. Implementation studies have subsequently shown the same virtual elimination of HIV risk in the women and men who take TDF/FTC, but critical gaps at the population level, with lack of access, stigma, and inability to or lack of interest in taking a daily pill, mean that many persons who could benefit from PrEP are not. Thus, while substantial reductions in new HIV infections have been realized in settings where PrEP has been implemented with high coverage [7], there is still far to go to achieve PrEP's full prevention potential at scale.

One medication option for PrEP is not enough. Just like PrEP, HIV treatment's clinical and prevention benefits are directly tied to adherence. Antiretroviral treatment has evolved markedly in the 3 decades since zidovudine was first approved, toward regimens that are easier to take and fit better into people's lives: initial regimens comprised multiple pills taken multiple times daily, subsequent regimens involved multiple pills taken once daily followed by single-tablet regimens, and recent regimens include injectable therapy administered at multiple-week intervals [8]. For PrEP, alternative options to a daily oral pill are needed to provide options that fit into people's diverse life experiences and preferences. Such next-generation PrEP candidates would ideally improve on TDF/FTC, with characteristics like less frequent or nonoral dosing, a better ability to be taken privately, and even greater forgiveness to less-than-perfect adherence.

In this issue of *The Journal of Infectious Diseases*, Markowitz et al report data from a rhesus simian/human immunodeficiency virus (SHIV) intrarectal challenge model by which they assessed the potential PrEP efficacy of oral MK-8591, a long-acting nucleoside reverse transcriptase–translocation inhibitor. MK-8591 is highly potent against HIV replication; its potency is approximately 10–1000-fold greater than that of existing antiretrovirals [9]. The results presented by Markowitz et al showed robust efficacy for protection against SHIV infection at weekly dosing of 1.3 and 0.43 mg/kg, which would translate into doses of <250 μg in humans, providing important evidence to advance MK-8591 into further clinical investigation. Notably, pharmacokinetic work predicts that MK-8591 could be dosed not only weekly, as tested in the current study, but instead monthly, maintaining concentrations that are estimated to provide HIV protection. A once-monthly pill would, of course, be a substantially different product than daily TDF/FTC treatment; in addition, the high potency of MK-8591 could make it attractive to formulate into long-acting injections or implants. Thus, the work by Markowitz et al is an important step toward a possible new PrEP option. MK-8591 already has some early human data [10], the next step toward eventual evaluation for safety and efficacy as PrEP in large-scale trials.

For all prevention interventions, including PrEP, users regularly weigh side effects, efficacy, life burden, and other factors when making choices. For another preventive action, contraception, multiple options exist, in a variety of forms, including several types of

Received 17 May 2019; editorial decision 17 May 2019; accepted 20 May 2019; published online June 7, 2019.

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The Journal of Infectious Diseases® 2020;221:1387–9

DOI: 10.1093/infdis/jiz273

pills, injectable and implantable systemic medications, intrauterine devices that delivery little or no drug systemically, and options that can be called on for use only at the time of sex or, like, emergency contraception, even after sex. In the contraceptive field, there is broad appreciation that expanding options results in more individuals achieving effective prevention of unintended pregnancy [11]. Thus, for PrEP, having more options on the table will not necessarily mean that treatment for oral TDF/FTC users will be shifted to the next available thing but that, instead, and better, more options will allow more people to use PrEP and be protected from HIV.

User preferences will vary, across individuals and populations, and if multiple PrEP options can be developed, the result will be increased reach, coverage, and impact. Since a highly effective and safe daily pill option exists for TDF/FTC therapy, there is particular enthusiasm for developing longer-acting delivery approaches for PrEP, such as pills of high potency and long half-life, depot injectables, and vaginal rings or subdermal implants that slowly release medication, as well as on-demand products that people can use when needed. Recent studies of hypothetical prevention choices among adolescent girls and young women in Africa found that each different PrEP option appealed as a first choice to an important fraction of individuals [12]; thus, work will need to be done to determine how to facilitate decision-making once multiple options are available.

Seven years have passed since the Food and Drug Administration approved oral TDF/FTC treatment for PrEP, and a handful of new PrEP products appear to be on the horizon. For women, a flexible silicone intravaginal ring that slowly releases the antiretroviral nonnucleoside reverse transcriptase inhibitor dapivirine was recently demonstrated to provide HIV protection on the order of approximately 30% [13, 14], with protection potentially ≥50% with better use. Now undergoing regulatory review, the monthly dapivirine vaginal ring could provide women, particularly those in settings where the HIV burden is high, with a longer-acting prevention option that is safe, reversible, and discreet. An updated version of TDF/FTC—daily oral tenofovir alafenamide (TAF) plus FTC—recently demonstrated a level of HIV protection comparable to that of TDF/FTC therapy [15], with a smaller pill, biomarkers that might suggest even better long-term safety, and some pharmacologic properties that could be more forgiving to missed doses. Two clinical trials (HPTN 083 and 084) are currently underway to evaluate the safety and efficacy of cabotegravir, an HIV integrase inhibitor formulated as a long-acting injectable (CAB-LA), with results eagerly expected in a few years [16]. If CAB-LA treatment is safe and comparably efficacious to TDF/FTC therapy, it will provide an exciting new prevention option, but some individuals may have challenges with an intramuscular injection, some may have personal preferences about systemic medications, some may desire for reversibility (ie, to start and stop PrEP, as seems to be modestly common in TDF/FTC users [17] and is often the case for contraceptive users), and some may not like whatever potential side effects CAB-LA may have. Thus, none of these alone will be the best PrEP option for all potential users. All PrEP medications have some amount of pharmacokinetic "tail"—a period when the drug is still present in the body but unlikely to still be highly effective for prevention (although still potentially able to drive HIV resistance); longer-acting formulations in general have longer tails, with clinical and virologic consequences still to be determined. Other novel PrEP approaches, including implants, microarray patches, rapidly-acting vaginal and rectal inserts, rectal enemas, and other topical options, are in early phase studies [18], suggesting that we have only seen the beginning PrEP options.

We all want options so we can make the choice that best fits us. That sentiment is true in many aspects of our lives—in the consumer products we purchase, the work we choose to do, the entertainment that rounds out our lives, and the healthcare decisions that we make. HIV prevention is no different. We are at an exciting time for HIV prevention—oral TDF/FTC proved to the world that highly effective and safe PrEP was possible. Next-generation products will expand options in the not-too-distant future so that people can make the choices that will increase PrEP's prevention impact.

Notes

Financial support. This work was supported by the National Institutes of Health (grants P30AI027757, R01MH095507, and K99MH118134).

Potential conflicts of interest. Both authors: No reported conflicts.

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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