HHS Public Access

Author manuscript

Ann Intern Med. Author manuscript; available in PMC 2020 August 18.

Published in final edited form as:

Ann Intern Med. 2020 February 18; 172(4): 281–282. doi:10.7326/M19-3337.

Tenofovir Alafenamide for HIV Preexposure Prophylaxis — What Can We DISCOVER About Its True Value?

Douglas S. Krakower, MD[1,2,3], **Demetre C. Daskalakis, MD**[4], **Judith Feinberg, MD**[5], **Julia L. Marcus, PhD**[2,3]

[1]Beth Israel Deaconess Medical Center, Boston, MA, USA

[2]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

[3]The Fenway Institute, Boston, MA, USA

[4]New York City Department of Health and Mental Hygiene, New York, NY, USA

[5]West Virginia University, Morgantown, WV, USA

Abstract

This is the prepublication, author-produced version of a manuscript accepted for publication in *Annals of Internal Medicine*. This version does not include post-acceptance editing and formatting. The American College of Physicians, the publisher of *Annals of Internal Medicine*, is not responsible for the content or presentation of the author-produced accepted version of the manuscript or any version that a third party derives from it. Readers who wish to access the definitive published version of this manuscript and any ancillary material related to this manuscript (e.g., correspondence, corrections, editorials, linked articles) should go to Annals.org or to the print issue in which the article appears. Those who cite this manuscript should cite the published version, as it is the official version of record.

In early 2019, the U.S. government launched the Ending the HIV Epidemic initiative, which aims to reduce HIV incidence by 90% before 2030. Daily preexposure prophylaxis (PrEP) with a single pill containing tenofovir disoproxil fumarate with emtricitabine (TDF/FTC) virtually eliminates sexual HIV transmission, and scale-up of PrEP is a critical component of the federal initiative. Before TDF/FTC was used for PrEP, it was a cornerstone of HIV treatment, but it has been largely replaced by tenofovir alafenamide with emtricitabine (TAF/FTC), a newer regimen that was equally effective but perceived to be safer. As we embark on a national effort to scale up PrEP, should we also abandon TDF/FTC in favor of TAF/FTC for HIV prevention?

Correspondence: Douglas S. Krakower, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, 110 Francis St., Boston, MA 02215 (dkrakowe@bidmc.harvard.edu).

Mailing Addresses for Authors

Douglas S. Krakower, MD; Beth Israel Deaconess Medical Center, 110 Francis St, Boston, MA 02215

Demetre C. Daskalakis, MD; New York City Department of Health and Mental Hygiene, 42-09 28th St, New York, NY 11101

Judith Feinberg, MD; West Virginia University, 930 Chestnut Ridge R, Morgantown, WV 26505

Julia L. Marcus, PhD; Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Dr, Ste 401, Boston, MA 02215

Until recently, when people thought of PrEP, they thought of TDF/FTC's brand name in the U.S., Truvada®. However, in October 2019, the U.S. Food and Drug Administration approved TAF/FTC (Descovy®) for PrEP. Gilead Sciences, which manufactures both TDF/FTC and TAF/FTC, has claimed that TAF/FTC is safer (1), and even that it is more effective (2), than TDF/FTC for PrEP. If TAF/FTC were indeed safer and more effective than TDF/FTC, there would be broad implications for patients, clinicians, and payers, as hundreds of thousands of people using TDF/FTC PrEP would presumably switch to TAF/FTC, and people initiating PrEP – as many as 1 million Americans at full scale – would use the newer formulation. There are also major financial implications for Gilead. Generic TDF/FTC will become available in 2020, whereas Gilead has exclusive rights to manufacture TAF/FTC until 2022 and is pursuing a patent extension until 2025. Thus, having TAF/FTC as the preferred PrEP option would extend their market dominance for years to come.

So, what does the evidence tell us about these two PrEP options?

There are robust data on the efficacy of TDF/FTC PrEP for populations impacted by HIV, including men who have sex with men (MSM), transgender women, people who inject drugs, and heterosexuals whose partners are living with HIV. The data are so compelling that the U.S. Preventive Services Task Force issued a grade A recommendation for this regimen in 2019. In contrast, the only efficacy data for TAF/FTC are from a single randomized trial, DISCOVER, that demonstrated that TAF/FTC was non-inferior compared with TDF/FTC as once-daily PrEP (1). Importantly, DISCOVER enrolled only MSM and a very small number of transgender women; thus, Food and Drug Administration approval for TAF/FTC as PrEP excluded those at risk from "receptive vaginal sex" and its efficacy remains unknown for other priority populations, including people who inject drugs (3). No HIV prevention drug should, in the future, be allowed to undergo Food and Drug Administration review without data addressing *all* key populations at risk for HIV.

Is TAF/FTC more effective than TDF/FTC for PrEP? Pharmacokinetic data suggest that TAF rapidly achieves higher and more sustained drug levels than TDF in the peripheral blood mononuclear cells targeted by HIV (2). However, TAF achieves lower concentrations in the genital and rectal mucosa (4), and there is no consensus on pharmacokinetic correlates of protection for PrEP. More importantly, TAF/FTC did not meet criteria for superior efficacy compared with TDF/FTC. Thus, while patients and clinicians can view daily TAF/FTC and TDF/FTC as equally efficacious for MSM and possibly transgender women, it would be a clinical leap of faith to use TAF/FTC instead of TDF/FTC in other populations.

TAF's faster achievement of drug level could theoretically be favorable for event-driven PrEP (i.e., short courses of pericoital PrEP), where HIV exposure occurs soon after pill ingestion. But event-driven TDF/FTC PrEP is over 90% effective for MSM – the only population in which event-driven PrEP has been studied – so there is little room for improvement. In the absence of efficacy data for event-driven TAF/FTC, and without recommendations for event-driven TDF/FTC PrEP from the Centers for Disease Control and Prevention, prescribing event-driven TAF/FTC would be far afield of current guidelines.

Is TAF/FTC safer than TDF/FTC for PrEP? When used as part of multidrug regimens for HIV treatment, TDF can cause renal or bone adverse events (5, 6), while TAF is associated with weight gain and changes in lipid parameters (7), although serious harms are rare. However, when used as PrEP, a decade's worth of research has demonstrated the excellent safety of TDF/FTC. A systematic review of TDF/FTC or TDF alone when used as PrEP by thousands of trial participants found no differences in renal or bone harms compared with placebo or no treatment (8). It is also reassuring that over 200,000 people have been prescribed TDF/FTC PrEP in the U.S. with no published reports of serious toxicities.

In DISCOVER, there were incremental differences in safety parameters for TAF/FTC and TDF/FTC, with some favoring TAF/FTC and others favoring TDF/FTC (Table). TDF/FTC was associated with decreases in renal glomerular function biomarkers and bone mineral density, whereas TAF/FTC was linked to weight gain and dyslipidemia (4, 9). However, these statistically significant changes in biomarkers were not clinically relevant. Almost no participants in either group stopped using PrEP because of adverse events. The preponderance of evidence suggests that both PrEP formulations are as safe as other commonly used preventive medications, such as oral contraceptives or statins, whose small risks of harm are vastly outweighed by their benefits.

From a societal perspective, the implications of supplanting TDF/FTC with TAF/FTC for PrEP would be substantial and potentially detrimental. TDF/FTC and TAF/FTC are currently priced the same, but the availability of generic TDF/FTC after 2020 will herald discounts over time. In Australia, for example, generic TDF/FTC costs $8 USD per month, compared with the current average wholesale price of $2,110 per month for brand-name TDF/FTC in the U.S. Even if generic TDF/FTC is only moderately discounted, TAF/FTC is unlikely to be cost-effective. Because cost is a major barrier to PrEP use in the U.S., generics could improve access. But if patients and clinicians perceive TDF/FTC to be a less appealing PrEP option, generics could become stigmatized, further exacerbating inequities in PrEP uptake.

Questions about the value of TAF/FTC were raised when it was newly introduced for HIV treatment. Despite evidence that TAF/FTC would not be cost-effective compared with generic TDF/FTC (10), the newer regimen quickly and irrevocably displaced TDF/FTC for HIV treatment in the U.S. A similar shift for PrEP – especially for populations in which TAF/FTC is untested – would be premature, costly, and counterproductive for population impact. Unless we want the past to be prologue, stakeholders – including patients, clinicians, payers, and those who issue clinical guidelines – need to be forward-thinking about what is considered first-line for PrEP. Given the available clinical evidence and public health context, when people think of PrEP, they should still think of TDF/FTC.

References

1. Hare CB, Coll J, Ruane P, Molina JM, Mayer KH, Jessen H, et al. The phase 3 DISCOVER study: daily F/TAF or F/TDF for HIV preexposure prophylaxis. Conference on Retroviruses and Opportunistic Infections Seattle, WA; March 4-7, 2019.
2. Spinner CD, Brunetta J, Shalit P, Prins M, Cespedes M, Brainard D, et al. DISCOVER study for HIV pre-exposure prophylaxis (PrEP): F/TAF has a more rapid onset and longer sustained duration

of HIV protection compared with F/TDF. >IAS Conference on HIV Science Mexico City, Mexico; July 21-24, 2019.

3. Goldstein RH, Walensky RP. Where Were the Women? Gender Parity in Clinical Trials. N Engl J Med. 2019 10 30 [Epub ahead of print]
4. U.S. Food and Drug Administration. FDA Briefing Information for the August 7, 2019 Meeting of the Antimicrobial Drugs Advisory Committee. https://www.fda.gov/media/129607/download. Accessed on October 8 2019.
5. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS. 2010;24(11):1667–78. [PubMed: 20523203]
6. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA. 2004;292(2):191–201. [PubMed: 15249568]
7. Venter WDF, Moorhouse M, Sokhela S, Fairlie L, Mashabane N, Masenya M, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med. 2019;381(9):803–15. [PubMed: 31339677]
8. Pilkington V, Hill A, Hughes S, Nwokolo N, Pozniak A. How safe is TDF/FTC as PrEP? A systematic review and meta-analysis of the risk of adverse events in 13 randomised trials of PrEP. J Virus Erad. 2018;4(4):215–24. [PubMed: 30515300]
9. U.S. Food and Drug Administration. Gilead Sciences Briefing Information for the August 7, 2019 Meeting of the Antimicrobial Drugs Advisory Committee. https://www.fda.gov/media/129609/download. Accessed on October 8 2019.
10. Walensky RP, Horn TH, Paltiel AD. The Epi-TAF for Tenofovir Disoproxil Fumarate? Clin Infect Dis. 2016;62(7):915–8. [PubMed: 26658300]

Table.

Effectiveness, safety, and cost of TDF/FTC and TAF/FTC for HIV preexposure prophylaxis

	TDF/FTC	TAF/FTC
Effectiveness *		
MSM and transgender women	~99%	~99%
Heterosexual women and men	~99%	Unknown
People who inject drugs	74-84%	Unknown
Changes in safety parameters at 48 weeks(4, 9)		
Estimated glomerular filtration rate, mean (mL/min)	−2.0	+2.0
Hip bone mineral density, mean (%)	−1.0	+0.2
Fasting low-density lipoprotein, median (mg/dL)	−6.5	+1.0
Body weight, mean (kg)	0	+1.1
Cost		
Average wholesale price per month	$2,110	$2,110
Generic version available	2020	2022 to 2025

TDF/FTC, tenofovir disoproxil fumarate with emtricitabine; TAF/FTC, tenofovir alafenamide with emtricitabine.

* Effectiveness estimates for TDF/FTC are from the Centers for Disease Control and Prevention (https://www.cdc.gov/hiv/risk/estimates/preventionstrategies.html).