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

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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 believed to be equally effective but 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?

Until recently, when people thought of PrEP, they thought of TDF–FTC's brand name in the United States, Truvada. However, in October 2019, the U.S. Food and Drug Administration approved TAF–FTC (Descovy) for PrEP. Gilead Sciences, which manufactures both Truvada and Descovy, has claimed that TAF–FTC is safer (1) and more effective (2) than TDF–FTC for PrEP. If TAF–FTC were indeed safer and more effective, there would be broad implications for patients, clinicians, and payers because hundreds of thousands of persons who use TDF–FTC PrEP would presumably switch to TAF–FTC, and those initiating PrEP—more than 1 million Americans at full scale—would use the newer formulation. This also has 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 Gilead's market dominance for years to come.

So, what does the evidence tell us about these 2 PrEP options?

Robust data show the efficacy of TDF–FTC PrEP for populations affected by HIV, including men who have sex with men (MSM), transgender women, persons 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 showed that TAF–FTC was noninferior to TDF–FTC as once-daily PrEP (1). Of note, 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 persons who inject drugs (3). In the future, no HIV prevention drug should 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 important, TAF–FTC did not meet criteria for superior efficacy compared with TDF–FTC. Thus, although patients and clinicians can consider daily TAF–FTC and TDF–FTC to be 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.

The faster achievement of drug levels by TAF could theoretically be favorable for event-driven PrEP (that is, short courses of pericoital PrEP), where HIV exposure occurs soon after pill ingestion. But event-driven PrEP with TDF–FTC is more than 90% effective for MSM—the only population in which event-driven PrEP has been studied—leaving 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), whereas TAF is associated with weight gain and changes in lipid parameters (7), although serious harms are rare. However, a decade's worth of research has demonstrated the excellent safety of TDF–FTC used as PrEP. A systematic review of TDF–FTC or TDF alone 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 more than 200 000 U.S. patients have been prescribed TDF–FTC PrEP and no serious toxicities have been reported.

DISCOVER found incremental differences in safety variables between the 2 drugs. Some favored TAF–FTC and others 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 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 and statins,

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Table. Effectiveness, Safety, and Cost of TDF–FTC and TAF–FTC for HIV PrEP

Variable	TDF-FTC	TAF-FTC
Effectiveness, %*		
MSM and transgender women	~99	~99
Heterosexual women and men	~99	Unknown
Persons who inject drugs	74 to 84	Unknown
Changes in safety parameters at 48 wk (4, 9)		
Mean estimated glomerular filtration rate, *mL/min/1.73 m²*	−2.0	+2.0
Mean hip bone mineral density, *%*	−1.0	+0.2
Median fasting low-density lipoprotein cholesterol		
mmol/L	−0.17	+0.03
mg/dL	−6.5	+1.0
Mean body weight, *kg*	0	+1.1
Cost		
Average wholesale price per month, *$*	2110	2110
Year in which generic version will be available	2020	2022 to 2025

MSM = men who have sex with men; PrEP = preexposure prophylaxis; 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 (www.cdc.gov/hiv/risk/estimates/preventionstrategies.html).

whose small risks for 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. The 2 drugs 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 (U.S. dollars) per month, compared with the current average wholesale price of $2110 per month for brand-name TDF–FTC in the United States. 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 United States, generic drugs could improve access. But if patients and clinicians perceive TDF–FTC as a less appealing PrEP option, generic drugs 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 United States. 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 PrEP. Given the available clinical evidence and public health context, when people think of PrEP, they should still think of TDF–FTC.

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