# It’s Time for Tenofovir 2.0

One of the most important drugs in the HIV arsenal is getting a tune-up.

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Tenofovir (Viread), one of the most widely prescribed antiretrovirals (ARVs) and the bedrock of first-line HIV therapy, is getting an upgrade. On November 6, Gilead Sciences, which manufactures the drug, applied to the U.S. Food and Drug Administration (FDA) for approval of a single-pill combination regimen with the same components as Stribild (elvitegravir/cobicistat/tenofovir/emtricitabine), only with a retooled version of tenofovir. The upgraded tenofovir offers various benefits over the traditional take on the nucleoside reverse transcriptase inhibitor (NRTI), and appears poised to make various already highly tolerable HIV regimens even more so.

Tenofovir disoproxil fumarate, abbreviated as TDF, is the full generic name of the current form of the drug. TDF is a component of three out of the four single-pill, once-daily ARV combination tablets on the market today: Atripla (efavirenz/tenofovir/emtricitabine), Complera (rilpivirine/tenofovir/emtricitabine) and Stribild. In addition, TDF makes up half of Truvada (tenofovir/emtricitabine), which in addition to its use as treatment for HIV is approved as pre-exposure prophylaxis (PrEP) to prevent acquisition of the virus among HIV-negative people, as well as for treating hepatitis B virus (HBV).

Tenofovir is vital to the HIV treatment landscape. According to Gilead, approximately 84 percent of HIV-positive Americans who are on treatment take an ARV regimen containing TDF. And among those who are going on ARVs for the first time, 88 percent are prescribed a TDF-inclusive regimen.

The 2.0 version of the drug is known as tenofovir alafenamide fumarate, or TAF. Both TDF and TAF are prodrugs, which means they are converted to their active form within the body. But while TDF is converted outside of immune cells, TAF is converted inside of them. So, in effect, TAF better targets those cells; consequently there is much less left of the medication in the bloodstream to cause toxicities. Because of this concentrated targeting, TAF’s necessary dose is just 10 percent of TDF’s, further improving TAF’s toxicity profile and making the drug easier to combine into single-pill combo regimens, since its volume is diminished. The dose can be lowered even further when TAF is combined with the boosting agent Tybost (cobicistat), which, like Norvir (ritonavir), raises the levels of certain ARVs in the body.

In Gilead’s application to the FDA for approval of the TAF-containing take on Stribild (which, if

approved, would receive a new name, while the old Stribild would stay on the market), the company submitted 48-week data from two Phase III studies, in which the TAF-containing combination tablet proved as effective as TDF-containing Stribild when given to treatment-naive people with HIV. In promising news, that new tablet boasted improved kidney and bone safety.

Recent research into another single-tablet regimen, containing TAF along with Tybost–boosted Prezista (darunavir) and Emtriva (emtricitabine), has also found that the tablet is less toxic than a comparable multi-pill regimen that includes TDF, while boasting the same efficacy.

Those taking TDF are at risk for mild to moderate kidney toxicity. Consequently, recently updated treatment guidelines from the HIV Medicine Association advise that those with reduced kidney function should not take TDF-containing regimens. In addition, the majority of people taking the older version of tenofovir will experience a 1 to 2 percent drop in bone mineral density. However, in most cases, this drop won't lead to a clinically significant result, such as a fracture. So, on the whole, TDF is quite a low-risk drug, which is a primary reason why it is so widely prescribed.

"TAF is exciting because it's going to lessen even those risks," says Tony Mills, MD, an HIV specialist in West Hollywood. He notes that such an improved toxicity profile may reassure primary care physicians, who are often wary of prescribing drugs they believe are akin to chemotherapy agents.

Gilead spokesperson Ryan McKeel notes that an improved toxicity profile for TAF is particularly attractive for an aging HIV population. After all, getting older means an increased risk for low bone mineral density and renal impairment.

TAF may also offer benefits on the drug resistance front. Ongoing research suggests that people whose virus has some resistance to TDF may have success with TAF instead. This is good news considering how heavily dependent the HIV population is on tenofovir. Additionally, should people taking Truvada as PrEP contract HIV and then develop tenofovir resistance, treating them with a TAF-containing regimen may prove effective—thus allaying a major (if potentially overblown) concern about PrEP. However, Tim Horn, HIV project director at Treatment Action Group, speculates that TAF's apparent drug resistance benefits have a limit, and that the drug may not be a viable option for those with extensive NRTI resistance.

In addition to running Phase III trials of the single-tablet regimen containing TAF plus Tybost–boosted Prezista and Emtriva, Gilead is conducting Phase III clinical trials of a TAF-containing version of Truvada. Other research, only in its early stages, is also looking at this new Truvada to see if it would be a good option as PrEP.

The ones who probably aren't too happy about seeing TAF integrated into the HIV arsenal are those who foot the bill. TDF is set to lose its patent in 2018, opening the door for generic production and a likely drop in cost for those new competitors. But Gilead expects that TAF's patent should run through 2025. Because of the nuances of drug patent laws, Gilead can use TAF as a tool to keep drawing profits from the company's aging portfolio of HIV medications; adding

TAF to fixed-dose combination therapies that include ARVs with expiring patents will extend the patent for the entire combination pill. The new version of Stribild will likely stay on patent until 2029. In another slick move, Gilead isn't developing TAF as a standalone drug, which forecloses upon the possibility of ever piecing together generic equivalents of TAF-inclusive combination pills.

According to Horn, it's no secret that Gilead has known about the TAF technology since shortly after the turn of the 21st century.

"Why Gilead decided to sit on it until now, in terms of its clinical development—those reasons certainly are mystifying," Horn says wryly. "That this technology doesn't seem to be making the light of day until TDF is in the twilight of its patent protection most likely isn't a coincidence."

In other words, it stands to reason that Gilead sat on TAF until the timing was right to fight generic competition and protect profits for years to come.

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