

Enter TAF and Genvoya

By Tim Horn

Tenofovir alafenamide (TAF), an alternative to the tenofovir disoproxil (TDF) found in several fixed-dose combination (FDC) tablets, was recently approved by the US Food and Drug Administration as a component of Genvoya, an FDC that also contains the integrase inhibitor elvitegravir, the boosting agent cobicistat, and the nucleoside analog emtricitabine. Genvoya has been green-lighted for use for people 12 years of age and older who are either starting HIV treatment for the first time or those wishing to switch their current regimens—provided that they have been on a stable regimen for at least six months, have an undetectable viral load and no history of HIV treatment failure or resistance to any of the drugs in the tablet.

What is TAF?

Both TAF and TDF are prodrugs of tenofovir, which means they must first be converted to the active agent tenofovir before becoming active against HIV. TDF is first converted to tenofovir in the blood, whereas TAF largely undergoes alterations inside lymphocytes and other cells. Compared with TDF, TAF achieves concentrations of tenofovir inside cells that are four to seven times higher at plasma concentrations that are 90% lower.

Low-milligram TAF dosing – either 10 mg or 25 mg, depending on the other drugs used in combination – together with reduced tenofovir circulating in the bloodstream has the potential to reduce bone and kidney toxicities, compared with TDF dosing. The low-milligram dosing also clearly helps with pill size for co-formulations—Genvoya is a bit smaller than its predecessor Stribild. Additionally, using less drug also has the potential to reduce the cost of anticipated generic versions in low-income countries, where the marketing price is more closely related to manufacturing costs.

It would be easier to be excited about the potential advantages of TAF over TDF if the development timeline were not based on extending the initial TDF patent despite safety concerns with TDF. Gilead Sciences presented in test tube and animal data for TAF in 2001, but early clinical trial results in humans were not reported until 2011. That is at least 10 years of accumulated renal and bone toxicity among people living with HIV using TDF while TAF stayed on the shelf.

This coordinated delay means that TAF-inclusive regimens are becoming available just a few years before TDF's patent expiration (December 2017). Using this strategy, Gilead has extended the patent on tenofovir for six years based on the primary patent on TAF – and for longer based on other co-formulations.

Genvoya's Approval

FDA approval of Genvoya was largely based on the results of two phase 3 clinical trials comparing that TAF-inclusive FDC with Stribild in HIV-positive adults starting antiretroviral therapy for the first time. After nearly one year of treatment (48 weeks), 800 of 866 (92%) participants randomized to Genvoya and 784 of 867 (90%) participants receiving Stribild had undetectable HIV levels. It is these results that confirmed TAF was comparable to—“non-inferior” in scientific terms—to TDF.

Both Genvoya and Stribild were well tolerated in the phase 3 clinical trials. Study volunteers receiving Genvoya had significantly smaller decline in estimated glomerular filtration rate (eGFR) and less proteinuria—two markers of kidney toxicity. In fact, a separate study of Genvoya in people with mild-to-moderate kidney insufficiency supported both the efficacy and safety of the drug.

Those receiving Genvoya also experienced small reductions in bone mineral density.

At What Cost?

Though Genvoya is a welcome addition to the HIV treatment toolbox, the development of TAF has been shadowed by a significant concern: that the prices of TAF-inclusive FDCs would exceed the exorbitant costs associated with existing regimens. Enter the Fair Pricing Coalition (FPC), which negotiates drug pricing and access programs with manufacturers in the months prior to a new medication's approval.

A few days following Genvoya's approval, a FPC press release signaled that the coalition of U.S. treatment activists welcomed Gilead's announcement that the price for the new FDC would be identical to the one currently established for Stribild: \$31,362 a year. Though this wholesale acquisition cost (WAC) hardly reverses a trend of exorbitant drug pricing in the United States, the FPC noted that it underscores a growing recognition that HIV treatment expenditures are beyond what the market can reasonably bear.

"Genvoya, the first coformulation to be approved containing TAF, is an important improvement over Stribild containing TDF, particularly for an aging population of people living with HIV at increased risk of kidney problems and bone density loss," says Lynda Dee, Executive Director of AIDS Action Baltimore and a co-chair of the FPC. "Our request to Gilead that Genvoya be priced neutrally with Stribild was heard. We now need to ensure that this welcome addition is priced affordably for all cash-strapped public insurance programs and that future TAF-inclusive coformulations are priced to ensure access for all people living with HIV."

Genvoya's WAC is the price point where many negotiations with payers begin and strident advocacy to further control costs continues. The next step is for negotiations to proceed with public insurance programs that receive discounts and rebates that serve to lower the cost below the WAC price. Most of these programs are in fragile financial shape. According to the FPC, for these programs to consider covering TAF-inclusive regimens, they will require deeply discounted prices, such as those in place for older coformulations containing TDF. According to Dee, the FPC will remain strident in ensuing Gilead negotiates in good faith with public insurance programs.

The FPC is also imploring Gilead to approach its WAC determinations for future TAF-inclusive coformulations, including FTC/TAF (F/TAF) and rilpivirine/FTC/TAF (R/F/TAF)—the company's follow-up products to Truvada and Complera that are likely to be approved by the FDA in April and July, respectively—with caution. Whereas Genvoya contains 10 mg of TAF, R/F/TAF will contain 25 mg TAF and F/TAF will be available as two coformulations: one containing 10 mg TAF for use in regimens containing boosting agents and another containing 25 mg TAF for use in combination with antiretrovirals that don't require boosting, such as ViiV's dolutegravir (Tivicay).

The FPC actually requested that the highest dose of TAF to be used in combination with other antiretrovirals be priced comparably with TDF. A WAC price for either dosing formulation of F/TAF or rilpivirine/F/TAF that is above that for Truvada or Complera, two combination tablets that debuted at high prices and have undergone numerous cost hikes, would be a serious misstep, the coalition argues.

TAF-inclusive coformulations are entering the U.S. marketplace on the brink of a watershed moment in HIV drug pricing history. Whether or not Gilead timed the debut of TAF-inclusive FDCs to extend the company's dominance on the HIV treatment landscape in the U.S., the pending arrival of lower-cost generic TDF and generic-inclusive coformulations—along with the potential for regimens employing fewer drugs to achieve and maintain viral suppression—are important factors with which Gilead must contend. And because the net benefit of TAF over TDF, notably whether it significantly reduces the risk of serious kidney disease or bone fractures (neither phase 3 study was adequately designed to address this important question, particularly when a number of HIV and treatment factors have been linked to an increase risk of these serious health concerns), hasn't been determined, TAF-inclusive regimens may need to be priced competitively with future generic-based drug combinations.

The FPC hopes that the neutral pricing between Gilead's Genvoya and Stribild hopefully signals an end to drug pricing that has spiraled out of control. The coalition adds that it is now time for a downward trend, not only because of shifting dynamics in the marketplace, but because personal and public health benefits to people living with HIV require ready access to safe and effective treatment options, despite limited resources.