Is Gilead’s Entire HIV Enterprise Built on a False Promise?

A new analysis finds that Gilead Sciences’ updated version of its key antiretroviral tenofovir may not actually offer any safety benefits.

May 9, 2018 By Benjamin Ryan

Gilead Sciences, the pharmaceutical giant that has long dominated the HIV treatment market, owes its success to something of a wonder drug: tenofovir. The antiretroviral (ARV), which for nearly two decades has come in a form known as tenofovir disoproxil fumarate, or TDF, is highly effective and well tolerated. However, TDF is associated with kidney and bone toxicities. Seeking to rectify this downside, Gilead recently developed tenofovir alafenamide, or TAF, an updated version of TDF.

By producing new combination ARV tablets that swapped TDF for TAF, Gilead improved the side-effect profile of its therapies, since clinical trials have indicated TAF is associated with improved biomarkers (lab test results) of kidney and bone health compared with TDF.

The swap also put a recently patented ARV into Gilead’s combination tablets just as TDF-inclusive regimens face the loss of patent protection, probably beginning in 2021 with Atripla (efavirenz/tenofovir disoproxil fumarate/emtricitabine). According to intellectual property law, even if only a single medication in such a tablet remains on patent, the entire tablet is protected against generic competition. So migrating from an HIV portfolio based on TDF to one geared around TAF helps buttress Gilead’s finances for years to come.

Here’s the rub that may undermine Gilead’s strategy: The health benefits of TAF over TDF could in fact be something of a mirage.

That was the finding of a group of British researchers who recently conducted an analysis of 11 randomized trials that compared TAF with TDF among 8,111 people who were monitored for a cumulative 10,791 years. These investigators found that TAF was indeed associated with improved kidney and bone toxicities in trials that compared TAF and TDF. But such benefits were largely seen only when the drugs were used with so-called boosting agents, including Norvir (ritonavir) and Tybost (cobicistat), which are used in HIV treatment regimens to boost the body’s levels of ARVs. In comparison trials that did not include boosters, TAF offered only minor safety benefits over TDF.

“Gilead talks about this difference between the drugs, which we don’t think is real,” says the analysis’s lead author, Andrew Hill, MD, of the Department of Pharmacology and Therapeutics at the University of Liverpool in the United Kingdom. “We simply can’t see it. We’ve looked at all the available data. It’s all the clinical trials that exist.”

Tenofovir: a powerhouse in Gilead’s portfolio

TDF, which belongs to the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) class of ARVs, has been the cornerstone of global HIV treatment for most of the modern era of combination ARV treatment for the virus. As recently as a few years ago, an estimated 84 percent of U.S. residents on HIV treatment took TDF as a part of their regimen.

The main somatic side effects of TDF are relatively minor and include nausea, diarrhea and headache. Clinical trials have also found that compared with other NRTIs, TDF is associated with greater kidney toxicities and a drop in the glomerular filtration rate (GRF), a marker of kidney function, as well as a greater decline in bone mineral density.

Approved by the Food and Drug Administration (FDA) for HIV treatment in 2001 under the brand name Viread, TDF would become the backbone of Gilead’s initial run of blockbuster single-tablet combination HIV regimens, including Atripla in 2006, Complera (rilpivirine/tenofovir disoproxil fumarate/emtricitabine) in 2011 and Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) in 2012.

TDF was approved for hepatitis B virus (HBV) treatment in 2008. The drug is also included in the two-drug combo tablet Truvada (tenofovir disoproxil fumarate/emtricitabine), which was approved for use as a component of an HIV treatment regimen in 2004 and for use as pre-exposure prophylaxis (PrEP) against HIV in 2012.

In more recent years, Gilead developed TAF as a potentially safer alternative to TDF. TAF is better at entering cells, so a dose only one tenth that of TDF is required, and it also yields lower concentrations of the drug in plasma, thus lowering the chance of toxicities. A recent series of advanced clinical trials comparing the two drugs found that TAF was associated with lower rates of biomarkers of kidney and bone toxicities compared with TDF.

In November 2015, Gilead released its first combination tablet in which the company replaced TDF with TAF, updating Stribild to produce Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide). The company proceeded to update the remainder of the TDF-containing tablets with TAF-containing versions, except for Atripla, which contains the black-sheep ARV Sustiva (efavirenz), a drug associated with numerous troubling side effects, including nightmares and suicidal behaviors. Complera was updated as Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide) in March 2016, and Truvada was updated as Descovy (emtricitabine/tenofovir alafenamide) in April 2016, though it has not yet been approved for use as PrEP.

Vemlidy (tenofovir alafenamide), a stand-alone version of TAF, was approved for HBV treatment in November 2016.

A Phase III study comparing the effectiveness of Descovy versus Truvada as PrEP that includes 5,400 HIV-negative transgender women and cisgender men who have sex with men at high risk for the virus is under way. The trial is expected to complete its primary phase in February 2019 and to wrap up in September 2020.

In February 2018, Gilead released its first single-tablet regimen based on the integrase inhibitor class of ARVs, Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide), which includes TAF.

Skeptical scientists:

Publishing their findings in the Journal of Virus Eradication, Andrew Hill and his three coauthors analyzed data from nine TAF versus TDF trials that looked at the ARVs' use as HIV treatment and two trials in which the drugs were used among people with HBV. A total of 4,574 of the participants in these trials received Norvir or Tybost as a booster for TAF or TDF; these individuals were monitored for a cumulative 7,198 years. Additionally, 3,537 participants took TAF or TDF without a booster; they were followed for a cumulative 3,594 years.

In the studies that included boosters, those who took TAF, compared with those receiving TDF, had a 2 percent higher rate of full suppression of HIV; however, this finding was of borderline statistical significance, meaning it may have occurred by chance. Also, those on boosted TAF had a 1 percent lower likelihood of discontinuing the drug due to kidney-related adverse health events compared

with those on boosted TDF. (This means that if 100 people were treated with each drug for one year, one extra person would stop TDF for kidney-related health problems compared with those on TAF.) Similarly, the risk of bone fracture and the risk of stopping treatment due to bone-related adverse health events were each 1 percent lower among those receiving boosted TAF compared with those on boosted TDF.

As for the booster-free trials, there were no such differences between those taking TAF versus those on TDF.

When it came to changes in bone mineral density, un-boosted TAF did appear to offer a safety benefit over un-boosted TDF. In the studies that included boosting agents, hip and spine bone mineral density declines were a respective 1.98 percent and 2.11 percent smaller among those taking TAF compared with those on TDF. In the studies that did not include boosters, these differences in bone mineral density declines were narrower, at a 1.48 percent and 1.73 percent smaller decline in the hip and spine, respectively; nevertheless, the differences were still statistically significant.

The existence of such differences in the decline in bone mineral density between those on unboosted TAF versus TDF does not necessarily mean the former drug will prevent bone fractures compared with the latter. (Additionally, such declines developed relatively soon after individuals began treatment and did not progress much going forward.) At this time, “the clinical significant of these differences is unclear,” according to Hill’s paper.

TDF is most commonly used worldwide without a booster. The TDF-inclusive Stribild and its TAF-inclusive counterpart Genvoya are the only single-tablet regimens to include either drug with a booster.

Hill is particularly critical of Gilead for only ever using one standard dose of TDF in all its combination tablets, despite the fact that when the drug is used with Norvir (ritonavir) and Tybost (cobicistat), TDF levels rise by 37 percent and 23 percent with each respective booster. In other words, taking TDF with a booster in effect causes an overdose of the drug, according to Hill.

Gilead “knew that tenofovir concentrations went up when you gave it with a booster, they knew that that could increase toxicity, and they didn’t do anything about it,” Hill says. “They could have lowered the dose. If they’d lowered the dose, how many bone fractures, how many kidney failures, how many Fanconi syndromes [a rare kidney disease] would have been avoided?”

In 2014, Hill and his colleagues urged Gilead to conduct trials of a lower dose of TDF along with a booster to see whether that switch would yield lower bone and kidney toxicities.

“What they’ve done instead,” Hill says of the company, “is ask people to use a new form of tenofovir, which is patented, where they continue to make money, rather than the old form, which is now generic.”

When Gilead combines TAF with a booster, specifically in Genvoya, the company does in fact lower

the dose, from the standard 25 milligrams to 10 mg. This fact, Hill argues, creates a “double standard,” in which Gilead effectively acknowledges boosters’ effect on TAF but denies this effect when it comes to TDF.

Responding to Hill’s paper, Gilead released a statement to POZ in which the company pointed to a recent pooled analysis of some 3,800 people taking Truvada-based regimens, 58 percent of whom switched to Descovy-based regimens. Presented at the 9th International AIDS Society Conference on HIV Science in Paris (IAS 2017) in July 2017, the study found that switching from TDF to TAF was associated with various improvements in kidney and bone biomarkers; and, according to Gilead’s statement, the study “included boosted and unboosted regimens.” (The analysis did not break down such findings about biomarkers according to whether individuals used a booster, however.) The statement then acknowledges, “The long-term clinical significance of these changes are not known.”

Gilead also critiqued Hill’s focus on a lack of difference between taking TAF versus TDF according to what are known as clinical endpoints, specifically bone fracture and stopping treatment for kidney-related reasons. These clinical endpoints, Gilead states, “are rare events that take place over many years of medication, and in populations of various risk. In addition, the meta-analysis is confounded due to combining studies with inherent differences in duration of therapy, patient populations and disease states.”

“Gilead themselves had presentations of their own studies, in long-term follow up, saying that TDF was safe, back in 2008,” Hill says in response. “It is strange that the same company is now saying that their drug unboosted TDF is now associated with clinical adverse events, when previously they assured patients and doctors that it was safe.”

Will switching from TDF to TAF actually prevent bone fractures?Thinkstock

Is TAF worth the money?

A 2016 paper published in Clinical Infectious Diseases included a cost-effectiveness analysis of TAF compared with TDF. Even when the paper's authors presumed the worst about TDF's side-effect profile compared with TAF, they nevertheless concluded that TAF was worth only a maximum premium of about $1,000 annually over TDF.

This sole paper to address the cost-effectiveness of TAF over TDF, however, based its analysis on findings from studies of the drugs when used with boosters. (That was the only data available at the time.) Hill's paper argues that such an analysis exaggerates TAF's benefits and that future economic analyses of this kind should instead rely on data from unboosted TAF versus TDF.

Rochelle P. Walensky, MD, MPH, the chief of infectious disease at Massachusetts General Hospital, which is affiliated with Harvard Medical School, was the lead author of the 2016 paper. Of prescribers' responsibility to consider the cost of HIV treatments, she says, "I am of the belief that we should be able to pay a little bit more for something that's a little bit better."

Once regimens containing generic TDF hit the market, they are likely to be more than just a little bit less expensive than comparable branded TAF-containing regimens.

That said, the pharma company Mylan just received approval for three combination tablets that include TDF and are comparable to existing Gilead tablets, but which are priced at about a 40 percent discount. Symfi (efavirenz 600 mg/lamivudine/tenofovir disoproxil fumarate) and Symfi Lo (efavirenz 400 mg/lamivudine/tenofovir disoproxil fumarate) are each comparable to Atripla. (Symfi contains the same dose of Sustiva, or efavirenz, as Atripla, while Symfi Lo contains a lower dose of that drug.) And Mylan's Cimduo (tenofovir disoproxil fumarate/lamivudine), which is not yet available, is comparable to Truvada, although not approved for use as PrEP. For convoluted reasons, these tablets are not considered generics; nevertheless, they may signal the direction in which the cost of ARVs is headed once full-on generic regimens with TDF start to hit the market.

"When Truvada comes off patent in 2021," says Tim Horn, MS, deputy executive director of HIV and HCV programs at Treatment Action Group, who coauthored the cost-effectiveness analysis with Walensky, "I think we can fully expect there to be a lot of competition." Consequently, he says, generic versions of the tablet may lead insurers to pressure prescribers to favor the cheaper alternative, whether for use as HIV treatment or PrEP.

By then, the Descovy as PrEP trial will likely have concluded. The findings of Hill's paper raise doubts about whether this huge and highly costly trial will actually reveal any significant safety benefits of that combination tablet over Truvada among HIV-negative individuals.

Gilead may have something of an ace up its sleeve regarding future debates over prescribing branded versus generic HIV regimens, thanks to the fact that the company has not released the new integrase inhibitor included in Biktarvy, bictegravir, as a stand-alone pill. Without stand-alone bictegravir, prescribers will not be able to assemble a comparable regimen including the drug plus multiple generic ARVs. Integrase inhibitors are prized as the new standard bearers of ARV treatment because of their powerful effectiveness in suppressing HIV and because the virus develops resistance to such drugs at a low rate.

On the other hand, because bictegravir is so similar to Tivicay (dolutegravir), Horn projects that insurers may give preferential status to such an available stand-alone integrase inhibitor plus Cimduo or a pair of cheaper generic ARVs.

"Without stand-alone bictegravir," Horn says, "Gilead runs the risk of being shut out of the game."

Walensky says she wouldn't prescribe a TDF-inclusive ARV regimen to an individual with HIV who had comorbidities (additional health problems). But if the cost of such a regimen were lower than for a TAF-inclusive regimen, she would indeed consider prescribing TDF to someone relatively young and healthy.

"We will never be able to drive these drug prices down unless we demonstrate that we're going to have some restraint in who gets the really expensive drugs," Walensky says of her fellow ARV prescribers and her own prescribing practices. "If we don't as a community do that, then pharma can charge us whatever they want because we will pay it."

Editor's note: A previous version of this article incorrectly stated that the price for

Mylan’s Cimduo had not yet been announced.

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