TAF vs. TDF (original tenofovir)—improvements in safety

As mentioned previously in this issue of *TreatmentUpdate*, TAF is being tested as a replacement for TDF—the original formulation of tenofovir. In this report we provide details about two pivotal trials of TAF-based regimens. Note that since the trials are identical in design, the data are pooled, or combined.

In two double-blind clinical trials, researchers randomly assigned 1,733 HIV-positive participants to receive one of the following regimens, taken once daily:

- TAF (tenofovir alafenamide) 10 mg + elvitegravir 150 mg + cobicistat 150 mg + FTC 200 mg (866 people)
- TDF (tenofovir disoproxil fumarate) 300 mg + elvitegravir 150 mg + cobicistat 150 mg + FTC 200 mg (867 people)

Prior to the study none of the participants had taken potent combination anti-HIV therapy (commonly called ART).

Analysis after 48 weeks found that the virological effectiveness of the TAF-based regimen was no worse (the technical term for this is non-inferior) than the TDF-based regimen. Increases in CD4+ cell counts were broadly similar between regimens. Furthermore, TAF users had, on average, fewer signals of kidney injury compared to TDF users and decreases in bone mineral density were generally milder. Long-term studies are needed to assess if these favourable changes with TAF persist.

**Study details**

Researchers recruited participants from the following regions and countries:

- North America
- Europe
- Australia
- Thailand
- Japan
- Latin America

The average profile of participants upon entering the study was as follows (note that percentages are rounded so the total may not equal 100%):

- age – 34 years
- 85% men, 15% women
- eGFR (estimated glomerular filtration rate; one way of assessing kidney health) – 115 mL/minute

**HIV disease status:**

- CD4+ count – 405 cells/mm³
- HIV viral load – 38,000 copies/ml
- proportion of participants with a viral load greater than 100,000 copies/ml – 23%
- symptom-free – 91%
- some symptoms present – 5%
- AIDS – 4%

**HIV risk factor:**

- condomless heterosexual sex – 25%
• condomless sex between men – 74%
• injecting street drugs – 1%

All study regimens were taken with food.

Results

After 48 weeks the proportion of participants whose viral load was less than 50 copies/ml was as follows:

- TAF-based regimen – 92%
- TDF-based regimen – 90%

Using a viral load assay with a lower limit of quantification (that could accurately count down to as low as 20 copies/ml), the proportion of participants in each regimen with an undetectable viral load was as follows:

- TAF-based regimen – 84%
- TDF-based regimen – 84%

This suggests that both formulations of tenofovir are roughly equivalent.

Among participants who entered the study with a viral load in the blood greater than 100,000 copies/ml, the proportion with a viral load less than 50 copies/ml at week 48 was as follows:

- TAF-based regimen – 87%
- TDF-based regimen – 89%

The TAF-based regimen was modestly more effective in women and in people with a baseline viral load of less than 100,000 copies/ml. However, the number of women in this study was relatively small (260 women out of 1,733 participants, making up 15% of all participants) and this clinical trial is not the definitive study of TAF in HIV-positive women.

A note on CD4+ cell counts

Most clinical trials of modern ART calculate a median change in CD4+ count to smooth large changes that might occur when participants begin a study with very high or very low CD4+ counts. However, in the two studies reported here, Gilead scientists appeared to have done something unusual—they reported the average change in CD4+ counts. Furthermore, they assert that the change in average CD4+ cell counts favours the TAF-based regimen. This is particularly odd since many other important changes in nearly all other major lab tests were reported as median values. This suggests the possibility that the median changes in CD4+ counts were not statistically different between the two study regimens. We cannot be certain about this, as Gilead has not reported the median changes in CD4+ cell counts. However, we urge our readers to treat any claims of a TAF-based regimen somehow resulting in a superior CD4+ count in these studies with caution. At any rate, it is likely that the increases in CD4+ cell counts between the regimens were broadly similar—in the range of about 200 more CD4+ cells/mm$^3$ at week 48.

Virological failure

Researchers defined virological failure in one of the following ways:

- having a viral load of 50 copies/ml or greater
- having a viral load of 50 copies/ml or greater after it had previously been less than 50 copies/ml
- viral load had increased by 1 log from its lowest-ever level

Participants who fulfilled one of these criteria underwent further viral load testing.

Cases of virological failure were distributed as follows:

- TAF-based regimen – seven participants
- TDF-based regimen – five participants
Analysis of their HIV found that all participants had developed resistance to FTC (and 3TC).

Eight participants developed HIV that was resistant to the integrase inhibitor elvitegravir, distributed as follows:

- TAF-based regimen – five participants
- TDF-based regimen – three participants

In all eight of the above cases, lab tests found that HIV was still susceptible to another integrase inhibitor, dolutegravir (Tivicay and in Triumeq). This meant that should these people and their doctors choose to do so, they could use dolutegravir in a future treatment regimen.

**Side effects**

According to the researchers, the study drugs were “well tolerated” and most side effects were graded as having mild or moderate intensity. There were no new side effects associated with use of TAF. Common side effects reported with both regimens were similarly distributed and included the following:

- diarrhea – 18%
- nausea – 16%
- headache – 14%
- fatigue – 8%
- vomiting – 7%
- dizziness – 4%

Deaths in the study were distributed as follows:

- TAF-based regimen – two deaths occurred; one from alcohol poisoning and another from stroke
- TDF-based regimen – three deaths occurred; in one case a participant’s heart stopped beating, in another there was an overdose with multiple drugs, and in the third case the flow of blood to the heart was blocked

Investigation revealed that these deaths were not caused by the study medicines.

**Focus on the kidneys**

The old formulation of tenofovir, TDF, was known to cause kidney injury in some participants. In the present studies, no participants who took TAF quit because of kidney-related injury. In contrast, four participants who took TDF quit the study because of kidney injury that either resulted in reduced functioning of these vital organs or because of inflammation.

A common way of assessing kidney health is with a blood test for levels of a protein called creatinine, which is then used to calculate the eGFR (estimated glomerular filtration rate). Decreased eGFR over time suggests ongoing kidney dysfunction or injury. In general, decreases in eGFR among users of a TAF-based regimen were very mild.

Using sophisticated analyses of proteins in the urine, researchers found that levels of these proteins were decreased in a subset of TAF users and increased in a subset of TDF users. This pattern suggested that a TAF-based regimen is relatively safer for the kidneys than a TDF-based regimen.

The proteins assessed were as follows:

- urinary protein to creatinine ratio
- urinary albumin to creatinine ratio
- beta\textsubscript{2}-microglobulin

Another protein in the urine that was assessed was retinol-binding protein. Levels of this protein were mildly elevated in TAF users compared to being significantly elevated among some TDF users. This suggests that use of a TDF-based regimen is associated with a degree of kidney inflammation and that TAF is generally safe.

Bear in mind that urinary assessments of beta\textsubscript{2}-microglobulin and retinol-binding proteins are not routinely done in most clinics. Rather, they are largely research-based tools.
Changes in bone mineral density

In general, HIV-positive people are at risk for decreased bone mineral density, perhaps because of the inflammation caused by chronic infection with this virus and perhaps other reasons. For more about risk factors for thin bones, see Reduced bone density and HIV in TreatmentUpdate 189.

Overall, in the present studies, all participants developed thinner bones. Other clinical trials have found that people who initiate ART do experience thinning bones; however, bone density then stabilizes between two and four years after ART initiation.

On average, participants taking a TAF-based regimen lost about 2% of bone density in their spine compared to a loss of 3% among participants who used a TDF-based regimen.

Users of a TAF-based regimen lost about 1% of the bone density in their hips compared to a loss of 3% among TDF users.

These differences in the loss of bone density between regimens were statistically significant.

Although eight cases of bone fractures occurred (one in a person taking a TAF-based regimen and the other seven in those taking a TDF-based regimen), these fractures were not related to the study drugs. Rather, they occurred because of violence or accidents.

Impact on fatty substances in the blood (lipids)

Researchers found that increases in the levels of lipids (cholesterol and triglycerides) occurred in tests of blood samples taken when participants were fasting.

Participants taking TAF-based regimens were more likely to have increases in the following:

- total cholesterol
- bad cholesterol (LDL-C)
- good cholesterol (HDL-C)
- triglycerides

Overall, these changes would seem to be unfavourable. However, when looking at the ratio of total cholesterol to HDL-C, participants who took TAF-containing regimens had identical results to participants who took a TDF-containing regimen. This finding suggests that the risk for cardiovascular disease (heart attack, stroke) was the same regardless of which form of tenofovir the participants used.

Slightly more people taking a TAF-based regimen (4%) had to start lipid-lowering therapy than people who took a TDF-based regimen (3%). This difference was not statistically significant.

Key points

A regimen based on TAF or TDF seems to be roughly equivalent in effectiveness.

A TAF-based regimen has a reduced potential for causing kidney injury and thinning bones than a TDF-based regimen.

The present studies had low proportions of women.

Long-term studies of TAF-containing regimens are needed, both in treatment-experienced people and in those who are initiating ART with such a regimen. This will better help doctors and patients understand the safety of TAF.

Beginning in 2016, Gilead Sciences will begin the process of gradually introducing TAF as an alternative to TDF in its fixed-dose formulations. As mentioned earlier in this issue of TreatmentUpdate, the first new TAF-containing regimen is an alternative to Stribild called Genvoya.

In cases where a pharmacological booster (such as ritonavir or cobicistat) is used in a regimen, the dose of TAF recommended by the manufacturer is likely to be 10 mg per day. In cases where no pharmacological booster is
used, the daily dose likely to be recommended is 25 mg per day.

—Sean R. Hosein

REFERENCES:


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