I ANTI-HIV AGENTS

A. TAF is coming

Tenofovir (Viread) belongs to a family of drugs commonly called nukes. Tenofovir is used as part of potent combination anti-HIV therapy (ART) and is sold in the following fixed-dose combinations:

- Truvada – tenofovir + FTC
- Atripla – tenofovir + FTC + efavirenz
- Complera – tenofovir + FTC + rilpivirine
- Stribild – tenofovir + FTC + cobicistat + elvitegravir

These drugs are made by Gilead Sciences.

Old tenofovir (TDF)

The formulation of tenofovir that is currently sold is called TDF (tenofovir disoproxil fumarate). Once it is swallowed and absorbed from the intestines, it moves to the blood and eventually inside cells of the immune system. In the intestines, blood and cells, enzymes process TDF into tenofovir. This final form (tenofovir) is the form of the drug that has antiviral activity.

TDF is not well absorbed from the intestine and does not quickly enter the blood or cells. As a result, a relatively large dose of TDF (300 mg) must be taken by adults who use it as part of ART.
Enter TAF

A new oral formulation of tenofovir has been developed by Gilead Sciences. The new formulation is called TAF (tenofovir alafenamide). In lab experiments with cells of the immune system and TAF, researchers have found that TAF is quickly converted into the antiviral form of the drug, tenofovir. Furthermore, levels of tenofovir concentrate inside cells of the immune system, much more so than when the original formulation, TDF, was used. Also, when TAF is used, levels of tenofovir in the blood are considerably lower than when TDF is used. Likely this is because tenofovir that arises from TAF concentrates inside cells of the immune system.

Experiments with dogs have also found that TAF concentrates inside cells of the immune system and lymph nodes and lymphatic tissues.

The greater accumulation of tenofovir arising from TAF in cells of the immune system means that a much smaller dose of TAF can be used (10 to 25 mg per day) compared to TDF.

The relative concentration of tenofovir derived from TAF within the immune system means that less of this drug is in the blood. This likely has safety implications. For instance, the original formulation of the drug could cause kidney injury in some patients because TDF accumulated in the blood and some kidney cells. Clinical trials with TAF suggest that, so far, TAF is safer than TDF when used as part of ART.

Access

The first TAF-containing medicine, Genvoya, was licensed by the U.S. Food and Drug Administration (FDA) in November 2015 and will likely be licensed by Health Canada late in 2015. This medicine will be a fixed-dose combination (all in one pill) of the following drugs:

- TAF + FTC + cobicistat + elvitegravir

There is currently a similar pill called Stribild that contains TDF and the other medicines listed above.

After Genvoya is licensed in Canada, Gilead then has to negotiate with Canada’s provinces and territories about the price of this pill on their lists of subsidized medicines. These negotiations can take months; therefore, Genvoya is not likely to be on the list of medicines subsidized by the provinces and territories until late in 2016.

At the beginning of this report we listed several drugs that contain TDF. All of these drugs will have TAF-containing formulations developed over the next several years, and the new versions will follow the same negotiating process as Genvoya to gain access to provincial and territorial formularies.

TAF is being tested as a replacement for TDF in several clinical trials. Next we report on two such studies. Other studies featuring TAF will appear in a future issue of TreatmentUpdate.

REFERENCES:


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

As mentioned previously in this issue of TreatmentUpdate, TAF is being tested as an alternative to 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 than (the technical term for this is non-inferior) 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
- beta2-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 beta2-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 that is an alternative to Stribild is 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.

REFERENCES:

C. A study about switching from TDF to TAF

Researchers enrolled HIV-positive participants who were taking regimens containing TDF (tenofovir disoproxil fumarate), the original formulation of tenofovir. All participants had been on their current regimen for at least 96 weeks and had a viral load less than 50 copies/ml during this time. Once in the study, participants were randomly assigned to either receive a regimen containing TAF (tenofovir alafenamide), the new formulation of tenofovir, or to continue with their existing TDF-containing regimen. Researchers presented interim results analysed from 48 weeks of data (the study is planned to continue for 96 weeks). The results suggest that switching to a TAF-based regimen is generally safer than continuing to take TDF-containing regimens, particularly for bone and kidney health.

Study details

Prior to being randomized, participants were on the following regimens, all of which contained TDF:
- Stribild, a fixed-dose combination of TDF + FTC + elvitegravir + cobicistat (459 people)
- TDF + FTC + atazanavir + ritonavir (601 people)
- Atripla, a fixed-dose combination of TDF + FTC + efavirenz (376 people)

Participants were randomized on a 2:1 ratio to receive one of the following regimens:
- TAF + FTC + elvitegravir + cobicistat (959 people)
- continue their existing regimen (477 people)

The average profile of participants upon entering the study was as follows:
- age – 41 years
- 89% men, 11% women
- CD4+ cell count – 670 cells/mm³
- proportion who had less than 200 CD4+ cells – less than 1%
- proportion who had mild to moderate levels of sugar in their urine – 9% (suggestive of kidney dysfunction)

Results

Proportion of participants with a viral load less than 50 copies/ml at week 48:
- TAF-based regimen – 97%
- TDF-based regimen – 93%

The proportion of participants with virological failure was 1% in each of the randomized interventions.

The proportion of participants with no virological data at week 48 was as follows:
- TAF-based regimen – 2%
- TDF-based regimen – 6%

A note about claims of superiority

The overall statistical analysis suggests that a TAF-based regimen is statistically superior to a TDF-based regimen. However, this statistical difference
arose because more participants taking a TDF-based regimen did not have data available for analysis at week 48. This may have occurred because they dropped out of the study or were not able to be found by researchers or there may be other reasons that the data were missing. Furthermore, the regimen that TAF users received contained the integrase inhibitor elvitegravir. Integrase inhibitors are the most potent anti-HIV drugs; they quickly reduce viral load and an integrase inhibitor-based regimen would likely outperform a regimen containing a protease inhibitor (such as atazanavir) or a non-nuke (such as efavirenz). Therefore, the claim of statistical superiority may be technically correct, but it might also arise because of factors likely unrelated to the use of TAF.

Comparing regimens
At week 48, the following proportion of participants had a viral load that was less than 50 copies/ml:

- prior use of Atripla and then switched to a TAF-based regimen – 96%
- prior use of Atripla and continued on that regimen – 90%
- prior use of atazanavir and then switched to a TAF-based regimen – 97%
- prior use of atazanavir and continued on that regimen – 92%
- prior use of Stribild and then switched to a TAF-based regimen – 98%
- prior use of Stribild and continued on that regimen – 97%

Other reasons that participants receiving either TAF or TDF gave for leaving prematurely seemed to be related to anxiety and depression.

General side effects
Here is the distribution of side effects reported by at least 5% of participants, showing marginal differences between the two formulations of tenofovir:

Diarrhea
- TAF users – 10%
- TDF users – 9%

Headache
- TAF users – 7%
- TDF users – 4%

Bone/joint pain
- TAF users – 6%
- TDF users – 5%

Problems falling asleep or staying asleep
- TAF users – 5%
- TDF users – 6%

Back pain
- TAF users – 5%
- TDF users – 5%

Nausea
- TAF users – 5%
- TDF users – 3%

Abnormal lab test results
Moderate to seriously abnormal lab test results occurred in 25% to 30% of participants, depending on the medicines they were taking. As with other studies of TAF, this drug did not appear to cause more abnormal lab test results than TDF.

The most common abnormal blood test results that were moderate to serious in severity were distributed as follows:

Elevations in the enzyme creatine kinase (possibly suggestive of muscle injury)
- TAF users – 10%
- TDF users – 10%

Side effects and complications
Overall, the proportion of participants who left the study prematurely due to side effects was as follows:

- TAF-based regimen – 1%
- TDF-based regimen – 3%

Some of these people left because of kidney-related events, as follows:

- TAF-based regimen – one case each of kidney failure and declining kidney function
- TDF-based regimen – one case of chronic kidney disease and a handful of cases of kidney injury
Elevations in the liver enzyme AST (suggestive of liver injury)
- TAF users – 5%
- TDF users – 7%

Elevations in the liver enzyme ALT (suggestive of liver injury)
- TAF users – 5%
- TDF users – 5%

Less-than-normal levels of neutrophils (these cells are part of the immune system)
- TAF users – 4%
- TDF users – 3%

Less-than-normal levels of phosphate (suggestive of kidney injury)
- TAF users – 2%
- TDF users – 3%

Focus on lipids (cholesterol and triglycerides)
In general, when researchers assessed blood samples that were taken when participants had been fasting, they found that, over time, there were modest elevations in lipid levels among TAF users compared to TDF users. The lipids assessed included the following:

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

However, the ratio of total cholesterol to HDL-C was similar in TAF and TDF users, suggesting that their future risk for cardiovascular disease was more or less the same in people who received TAF or TDF.

The distribution of participants who initiated lipid-lowering therapy during the study was as follows:
- TAF users – 8%
- TDF users – 6%

Comparing changes in bone density
Overall, a statistically significant increase in bone density (2%) occurred among TAF users. In contrast, participants who remained on TDF had their bone density decrease slightly.

Changes in osteoporosis status
Bone thinness can be grouped into two categories—osteopenia, a mild form of decreased bone density, and osteoporosis, a severe form of bone density loss.

Looking at the spine
At the start of the study, osteopenia and osteoporosis were distributed among participants as follows:

TAF-based regimen
- 36% had osteopenia in the spine
- 6% had osteoporosis of the spine

TDF-based regimen
- 35% had osteopenia in the spine
- 7% had osteoporosis of the spine

After 48 weeks, the distribution of these conditions in the spine was as follows:

TAF-based regimen
- 32% had osteopenia
- 5% had osteoporosis

TDF-based regimen
- 37% had osteopenia
- 8% had osteoporosis

Looking at the hips
When researchers assessed bone density in the hips, the distribution of osteopenia and osteoporosis at the start of the study was as follows:

TAF-based regimen
- 31% had osteopenia in the hips
- 0.7% had osteoporosis of the hips

TDF-based regimen
- 32% had osteopenia in the hips
- 1.3% had osteoporosis of the hips

After 48 weeks, the distribution of osteoporosis and osteopenia in the hips was as follows:

TAF-based regimen
- 26% had osteopenia
- 0.7% had osteoporosis

TDF-based regimen
- 32% had osteopenia
- 2.1% had osteoporosis
Kidney injury

Research has found that the original formulation of tenofovir (TDF) can, in some users, cause varying degrees of kidney injury. Therefore, in clinical trials of TDF (and its successor compound, TAF) it is important to conduct detailed and complex assessments of kidney health.

In the present study, in general, participants taking TDF-based regimens were more likely to develop signals of kidney injury than participants on TAF-based regimens.

Researchers assessed certain proteins in the urine as follows:

- protein to creatinine ratio
- albumin to creatinine ratio
- retinol-binding protein to creatinine ratio
- beta₂-microglobulin to creatinine ratio

Note: Some of the tests above, particularly concerning retinol-binding protein and beta₂-microglobulin, are usually only done as part of research, not routine care in the clinic.

While participants were on a TAF-based regimen, levels of the four proteins in the urine fell, suggesting improved kidney health in participants. Another measure of kidney health, eGFR (estimated glomerular filtration rate), improved very modestly in TAF users. In contrast, changes to the urinary proteins among participants on a TDF-based regimen were unfavourable.

Key points

Switching from a TDF-based regimen to a TAF-based regimen appears to be safer for kidney and bones.

TAF appears to be equivalent to TDF when used as part of combination anti-HIV therapy.

REFERENCE:


D. TAF in people with kidney dysfunction

As mentioned previously in this issue of TreatmentUpdate, clinical trials assessing the new formulation of tenofovir (tenofovir alafenamide, or TAF) and sometimes comparing it to the original formulation (tenofovir disoproxil fumarate, or TDF) are ongoing. Studies have found that TAF is as effective as TDF and is very likely safer, particularly for the kidneys and bones. Participants enrolled in these studies had relatively good kidney health.

But will TAF be safe in people with pre-existing kidney dysfunction? To try to answer this question, researchers conducted study 292-0112. In this study, researchers sought participants who had mild-to-moderate kidney dysfunction graded with the use of eGFR (estimated glomerular filtration rate). After screening, researchers recruited 242 HIV-positive participants who had an eGFR between 30 and 69 mL/minute, who were on stable combination anti-HIV therapy (commonly called ART) and who had a viral load less than 50 copies/ml. All participants were switched to a TAF-containing regimen and monitored for 48 weeks. In general, TAF was safe and when this formulation of tenofovir was substituted for TDF, improvements in bone density and kidney health were seen. However, not every participant who switched from TDF to TAF had improvement in kidney injury, particularly in cases of severe injury to these organs.

Study details

All 242 participants were switched from their current regimen to the following regimen:

- TAF + FTC + elvitegravir + cobicistat (this fixed-dose combination pill is called Genvoya)

The average profile of participants when they entered the study was as follows:

- age – 58 years (note that 28% of participants were at least 65 years old)
- 79% men, 21% women
- CD4+ count – 632 cells/mm³
- HIV viral load – less than 50 copies/ml
- 40% had hypertension
- 14% had type 2 diabetes
• eGFR – 56 mL/minute (note that 34% of participants had an eGFR of at least 60 mL/min)
• 33% had mild-to-moderate levels of protein in their urine, suggestive of kidney injury

Overall, 158 participants were taking TDF as part of their regimen and 84 participants were taking other nukes.

Results

In the everyday world outside a clinical trial, when assessing kidney health, doctors usually request lab analyses of blood, and in particular the amount of the waste product creatinine. They can then put the amount of creatinine detected into a formula and get an estimate of the functioning of the kidneys. This is called the estimated glomerular filtration rate (eGFR). Doctors routinely use eGFR because assessing the actual GFR (written as aGFR) would be cumbersome for patients. Note that the eGFR is an estimate and it is useful for routine laboratory analyses requested by doctors.

However, in the present research setting, it was important to find out about the aGFR because eGFR is a calculated value (not a measured one). In the present study, researchers were able to assess the actual GFR. They found that there were no significant changes in the aGFR and only minor ones with eGFR after participants switched to a TAF-based regimen. Overall, this suggests that TAF does not have a major impact on the kidneys’ ability to filter blood.

The researchers also had laboratories analyse participants’ urine and they assessed certain proteins in the urine, as follows:

• protein to creatinine ratio
• albumin to creatinine ratio
• retinol-binding protein to creatinine ratio
• beta₂-microglobulin to creatinine ratio

They found significant reductions in these proteins among TAF users but not TDF users. Overall, this suggests that TAF helped to reduce kidney injury compared to TDF.

A moderate-to-severe degree of kidney injury

Researchers focused on people with high levels of total protein in their urine samples (more than 200 mg/gram,) as this sub-group would likely have a higher level of kidney injury than other participants.

Switching from TDF to TAF

In conducting their analyses, researchers found that among participants who had been on a TDF-containing regimen at the start of the study, 47% had high levels of protein in their urine, suggestive of kidney injury. After switching from TDF to TAF, 48 weeks later the proportion with a high level of protein in their urine was 13%. This difference was statistically significant. It shows that switching from TDF to TAF is associated with significant improvements in kidney health. However, note that this switch does not help everyone who used TDF. Perhaps not everyone’s kidneys recovered after the switch because of the severity of kidney injury, or there may have been other factors that could have affected kidney health that were unrelated to TAF, such as the presence of higher-than-normal blood pressure, type 2 diabetes and so on.

No initial use of TDF but using TAF

Among participants who had not been taking TDF but were instead taking other nukes at the start of the study, 29% had high levels of protein in their urine. After these participants switched their regimens to TAF, 48 weeks later the proportion with a high level of protein in their urine was 22%. This difference was not statistically significant.

These changes confirm that TDF can play a major role in kidney injury and that switching to TAF may greatly reduce the severity of kidney injury in some patients.

A focus on albumin

Another way to assess kidney injury is to measure the levels of a specific protein—albumin—in the urine.
The distribution of elevated albumin levels among participants who entered the study using TDF was as follows:

- at the start of the study – 55% had elevated albumin levels in their urine
- after being on TAF for 48 weeks – 22% had elevated levels of albumin in their urine

This difference in albumin levels was statistically significant. Thus, there may be a role for replacing TDF with TAF in people with kidney injury.

In contrast, among participants who used nukes other than TDF at the start of the study and then exchanged these nukes for TAF, there was little change in elevated albumin levels. Among these participants, the distribution of elevated albumin levels was as follows:

- at the start of the study – 37% had elevated albumin levels in their urine
- after being on TAF for 48 weeks – 34% had elevated levels of albumin in their urine

**Changes in bone mineral density**

The following changes in bone mineral density occurred during the study:

**Spine**
- participants who switched from TDF to TAF – an increase of 2.3%
- participants who switched from another nuke to TAF – an increase of 1%

**Hips**
- participants who switched from TDF to TAF – an increase of 1.5%
- participants who switched from another nuke to TAF – an increase of 0.7%

**Changes in lipids**

As with other studies, participants who switched from TDF to TAF generally had an increase in their fasting lipid levels, including the following:

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

Participants who switched to TAF from a nuke other than TDF had modest decreases in their lipid levels.

**Key points**

Switching from a regimen based on TDF to TAF resulted in improvements in assessments of kidney and bone health.

Participants who were not using a TDF-based regimen who switched to TAF did not have significant changes in assessments of kidney or bone health. However, their lipid levels decreased somewhat.

Overall, the data from the present study suggest that people who are encountering kidney dysfunction while taking a TDF-based regimen can generally expect improvement when they switch to a TAF-based regimen. Note that not every participant who switched to a TAF-based regimen had such an improvement.

**REFERENCE:**


**II HEPATITIS C VIRUS**

**A. Severe liver injury and its impact on the brain**

Hepatitis C virus (HCV) infects the liver. Once the immune system detects HCV-infected liver cells, it tries to destroy those cells and restrict the spread of HCV within the liver. However, in many cases the immune system does not vanquish HCV and this viral infection becomes established or chronic. Despite this initial failure, the immune system continues to attempt to contain the infection. The ongoing struggle between HCV and the immune system causes inflammation within the liver. Due to this ongoing inflammation and infection, healthy liver cells are gradually replaced with useless scar tissue and the liver becomes...
increasingly dysfunctional. Eventually, when scar tissue has encompassed most of the liver, cirrhosis has occurred. This greatly increases the risk for serious complications, including liver failure, liver cancer and death.

Cirrhosis and the brain—a spectrum of symptoms

One complication that occurs in cirrhosis is HE (hepatic encephalopathy). This problem can occur when unfriendly bacteria in the gut produce excessive levels of substances that can cause inflammation in the brain. These substances include ammonia and chemical signals used by brain cells. Since the liver is dysfunctional, toxins produced by bacteria are not removed from the blood and persist in the body.

HE represents a spectrum of issues, from mild to severe. In the early stages there may be sleep disturbances, anxiety, impaired concentration and problems with memory and thinking clearly. As HE grows worse, caregivers and family members notice that, in some cases, affected patients become irritable.

In later stages of HE, there can be changes in personality, persistent confusion, inappropriate behaviour and loss of connection to the present (patients may not know the day, week, month or season).

In the most extreme cases of HE, people can sleep most of the time (and it can be difficult to wake them up), speech becomes slurred and the patient can eventually go into a coma.

Mild forms of HE

In the mild or very early stage of HE—called minimal HE (MHE) or covert HE (CHE)—a person's ability to carry out routine tasks can be affected and their quality of life can be degraded. Furthermore, emerging research suggests that episodes of CHE appear to be linked to a future risk for decreased survival in some people.

Some risk factors

If the cause of CHE is related to underlying HCV infection of the liver, getting treatment for HCV can help resolve CHE. If liver injury and cirrhosis arise because of alcoholism, quitting alcohol can help.

Factors that can trigger an episode of CHE include the following:

- serious infections other than HCV
- intestinal bleeding
- constipation
- less-than-ideal levels of electrolytes (sodium, potassium) in the blood
- too high a dose of a diuretic (a drug that increases urination) – this can inadvertently cause a loss of electrolytes

The difficulty of recognition and diagnosis

Researchers estimate that up to 80% of people with cirrhosis can develop CHE. Yet there is no simple, quick test to help doctors diagnose CHE. In part, this is because CHE's initial effects can be subtle and may require extensive neuropsychological testing to unmask. Such testing is not routinely done and there is no consensus among specialists as to the ideal group of tests to use when assessing CHE. However, someone who may be experiencing CHE should always discuss this condition with their doctor(s). As with many health-related issues, treating a problem in its early stages can often be simpler and may even reverse the condition. Measuring levels of ammonia in the blood has not been found to help predict or diagnose CHE.

After a diagnosis

Once a diagnosis of CHE has been made, there may be several treatment options that can be discussed with your care providers, such as the following:

Non-absorbable sugars

A substance such as lactulose, an artificial form of sugar, is sometimes useful in treating CHE or HE. Lactulose is not absorbed, but once swallowed it goes to the intestine. From there, it helps to pull ammonia and other toxic products produced by bacteria from the blood into the intestine, where they can be released into the stool. Clinical trials have generally found that most people with overt HE (and in some cases, CHE) improve after treatment with lactulose. However, lactulose can have side effects, including nausea, gas, abdominal cramps and diarrhea. Due to these side effects some
patients may not be able to tolerate lactulose over the long-term.

**Antibiotics**
Rifaximin (Zaxine) is an antibiotic that is very poorly absorbed. This poor absorption helps the antibiotic concentrate in the intestines, where it can reduce the growth of unfriendly bacteria, causing their production of toxins to decrease. This antibiotic has generally been well tolerated in clinical trials, although headache may be a side effect. In clinical trials, rifaximin resulted in improvement in CHE and HE. Some doctors prescribe both lactulose and rifaximin for treating CHE and HE. The cost of rifaximin is not covered by all provincial and territorial drug formularies. Ask your doctor or nurse for the latest information about coverage of this drug in your region.

**Probiotics (friendly bacteria)**
There have been small clinical trials of probiotics for HE and CHE. Probiotics can change the balance of bacteria in the intestines, increasing the proportion of friendly bacteria. This can result in decreased levels of ammonia and other substances. However, the ideal mixture and dose of bacteria for treating CHE is not known. Although there are many different combinations of probiotics available over the counter, it is always best to discuss the possible use of these with your doctor. His/her advice and monitoring will be essential in managing CHE and any complications that could possibly occur.

**LOLA (L-ornithine-L-aspartate)**
Two amino acids (L-ornithine and L-aspartate) have been tested in cases of HE and CHE. In theory, these amino acids should activate the body’s mechanisms for breaking down ammonia. Controlled clinical trials with LOLA have produced mixed results. However, researchers noticed that six months after participants had stopped one study of LOLA, only 5% of participants who received LOLA had developed overt HE vs. 38% of participants who received placebo. This finding is intriguing and raises the possibility that LOLA might have some potential benefit. As with any other possible intervention for CHE, your doctor’s advice and approval should always be sought.

**For the future**
More research is needed in the following areas:

- developing simple, quick tests to help unmask CHE
- getting doctors to agree about which tests to use when assessing a person for the presence of CHE
- better treatments or combinations of treatment for CHE
- determining the timing of treatment for CHE
- ways to prevent the development of CHE

**Resources:**

*Understanding Cirrhosis of the Liver: First steps for the newly diagnosed – Canadian Association of Hepatology Nurses (CAHN), CATIE*

**REFERENCES:**

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

CATIE provides information resources to help people living with HIV and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

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For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients’ needs. CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

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A Practical Guide to HIV Drug Treatment
The latest on what is known about the various aspects of treatment, including a description of the virus and the immune system, the stages of HIV disease, the tests used to assess health status, and anti-HIV medications.

A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

The Positive Side magazine
Holistic health information and views written by and for people living with HIV.

Fact Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

Contact CATIE
By e-mail: info@catie.ca
On the Web: www.catie.ca
By telephone: 416.203.7122
1.800.263.1638 (toll-free)
By fax: 416.203.8284
By social media: www.facebook.com/CATIEInfo; www.twitter.com/CATIEInfo
By post: 505-555 Richmond Street W
Box 1104
Toronto, Ontario
M5V 3B1
Canada

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