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From *TreatmentUpdate 191*

Quad (Stribild) — Safety and effectiveness issues in depth

The FDA reviewed health-related information collected from 1,408 HIV-positive people who participated in two pivotal clinical trials.

In a trial called GS-US-236-0102 (we shorten this to trial '102), researchers compared the following regimens in a randomized, placebo-controlled design:

- Quad
- Atripla (a fixed-dose tablet containing efavirenz, tenofovir and FTC)

In trial GS-US-236-0103 (shortened to trial '103), researchers compared the following regimens also in a randomized, placebo-controlled design:

- Quad
- atazanavir (Reyataz) + ritonavir (Norvir) + tenofovir + FTC

As both studies were of a similar design, the FDA reviewers often pooled or combined the data from these studies when conducting their analysis.

In total, 1,408 participants were recruited and distributed as follows:

- Quad – 701 participants
- Atripla – 352 participants
- atazanavir-based regimen – 355 participants

In summary, the FDA found that the Quad is an effective therapy for HIV infection. The agency also found that the safety profile was "generally acceptable." The reviewers noted that a small but "disproportionate number of renal adverse events leading to [premature discontinuation from the studies] occurred in Quad [users] compared to [participants receiving other study regimens]."

Study details

So far, we do not have many details about participants. However, we do know that 90% were men and 10% were women. The average age was 38 years and prior to these studies participants had not previously taken treatment.

Gilead submitted data collected after participants had been in the studies for 48 weeks.

Results

The main goal of the studies was to assess the proportion of participants whose viral load was less than 50 copies/ml at the 48th week. This result was distributed as follows:

Trial '102

- Quad – 88% of participants had a viral load below the 50-copy/ml mark at week 48
- Atripla – 84% of participants had a viral load below the 50-copy/ml mark at week 48

Trial '103

- Quad – 90% of participants had a viral load below the 50-copy mark at week 48
- atazanavir-based regimen – 87% of participants had a viral load below the 50-copy mark at week 48

Based on the statistics underpinning the study's design, these results suggest that the Quad is roughly equivalent (the technical term is "non-inferior") in potency to Atripla.

There were **no** major differences in efficacy when sub-group analyses were done examining gender, race, region, viral load at the start of the study, CD4+ counts and so on. However, only about 10% of participants were women. This gender imbalance will have other implications, which will be discussed at the end of this report on the Quad.

At week 48, increases in CD4+ cell counts, compared to their values at the start of the study, were not significantly different among all regimens in the study as the following shows:

Study '102

- Quad – 239 more CD4+ cells
- Atripla – 206 more CD4+ cells

Study '103

- Quad – 207 more CD4+ cells
- atazanavir-based regimen – 211 more CD4+ cells

Focus on elvitegravir

This drug works in a similar way to the integrase inhibitor raltegravir (Isentress)—by interfering with an enzyme called integrase. This interference by elvitegravir or raltegravir helps to block HIV's ability to take over a cell and turn it into a mini virus factory.

In laboratory experiments with cells, elvitegravir was tested against HIV collected from different regions of the world. This drug is active against different strains, or clades, of HIV, including clades A, B, C, D, E, F, G and O.

Strains of HIV that have become resistant to elvitegravir are also likely to be resistant to raltegravir (and vice versa).

Focus on cobicistat

The purpose of cobicistat is to boost the level of elvitegravir. Cobicistat does this by interfering with enzymes found in the intestine and liver—places where elvitegravir is processed or broken down. These enzymes are called CYP3A4 and CYP2D6. By reducing the activity of these enzymes, cobicistat helps to delay the breakdown of elvitegravir, and so the concentration of elvitegravir in the blood remains elevated for about a day. This allows for once-daily dosing of the Quad.

Drugs such as cobicistat that are used to boost and maintain the level of other drugs in the body are called pharmacokinetic (PK) enhancers or boosters. An example of a commonly used PK booster is the protease inhibitor ritonavir.

When ritonavir was first introduced in the mid-1990s it was meant to be taken at a dose of 600 mg twice daily as part of potent combination anti-HIV therapy, commonly called ART or HAART. However, researchers in Ottawa quickly found that lower doses of ritonavir could be used to boost the level of other protease inhibitors. This made ritonavir more tolerable and resulted in greater efficacy. Today ritonavir is most commonly used at a dose of 100 or 200 mg once daily to boost these other protease inhibitors:

- atazanavir
- darunavir (Prezista)
- lopinavir (in Kaletra)

The FDA notes that cobicistat has a similar shape or structure (a "structural analogue") to ritonavir. In theory, cobicistat is not supposed to have anti-HIV activity. In lab experiments with cells and HIV, Gilead scientists could not detect anti-HIV activity from cobicistat.

Yet in analysing a limited number of blood samples from participants who took the Quad and whose regimen failed, Gilead made a surprising finding: 9 out of 14 people had HIV that had mutations in its protease gene. This would have been expected had they taken a protease inhibitor before. Moreover, in 3 of the 9 participants, the mutations in

the protease gene allowed HIV to resist some protease inhibitors.

This finding is very surprising because prior to the study all participants who received the Quad had not previously been exposed to protease inhibitors or any other ART. Also, cobicistat is not supposed to have antiviral activity. The FDA is not certain why these resistance mutations occurred or what it may mean. The agency states that "this issue will require careful follow up."

Interaction issues

As cobicistat is similar in shape and activity to the PK booster ritonavir, it should be expected that, like ritonavir, it will affect the body's processing of many drugs. This means that there is much potential for drug-drug interactions potentially enhancing existing drug side effects, causing new ones or altering the effectiveness of elvitegravir or another drug.

Due to this potential, the FDA recommends that Quad users do not take the antibiotic rifabutin (Mycobutin).

Cobicistat has a complex interaction with oral female contraceptives (commonly called "the Pill") and the FDA is studying how to advise doctors who wish to prescribe both the Quad and the Pill.

The full range of cobicistat-related drug interactions is not known and studies are underway or planned with opiate substitution therapies such as methadone and buprenorphine as well as the anti-HCV (hepatitis C virus) agents boceprevir (Victrelis) and telaprevir (Incevik).

Safety issues—Deaths

There were six deaths in the studies, as follows:

- Quad – 1 person
- Atripla – 2 people
- atazanavir-based regimen – 3 people

Causes of death were as follows:

- suicide – 2 people; one was taking Atripla and one was taking the Quad. According to the FDA, the latter person had a history of "major depression, bipolar disorder, insomnia and amphetamine abuse." His depression was stable when he entered the study.
- cancer (metastatic carcinoma) – 1 person
- overwhelming bacterial infection – 1 person
- life-threatening pneumonia – 1 person
- cardiac arrest due to "an overdose of recreational drugs" – 1 person

Researchers decided that none of these deaths were due to the study medications.

Overview of side effects

All drugs can cause side effects and the proportion of people who left the study prematurely because of side effects was similarly distributed, as follows:

- Quad – 4% of participants
- Atripla – 5% of participant
- Atazanavir-based regimen – 5% of participants

The side effects generally responsible for premature departure from the study were as follows:

- diarrhea
- nausea
- fatigue
- fever
- increased levels of the waste product creatinine in the blood

- kidney failure

The last two adverse effects occurred in 5 people, all of whom were taking the Quad.

Here is the distribution of adverse effects that occurred in 3% or more of Quad users. For comparison, the occurrence of the same adverse effect in the other regimens is shown:

Diarrhea

- Quad – 22%
- Atripla – 19%
- atazanavir-based regimen – 27%

Nausea

- Quad – 20%
- Atripla – 14%
- atazanavir-based regimen – 19%

Farting

- Quad – 4%
- Atripla – 1%
- atazanavir-based regimen – 8%

Abnormal dreams

- Quad – 9%
- Atripla – 27%
- atazanavir-based regimen – 4%

Difficulty falling asleep

- Quad – 8%
- Atripla – 14%
- atazanavir-based regimen – 5%

Depression

- Quad – 8%
- Atripla – 11%
- atazanavir-based regimen – 7%

Dizziness

- Quad – 6%
- Atripla – 24%
- atazanavir-based regimen – 12%

Headache

- Quad – 15%
- Atripla – 10%
- atazanavir-based regimen – 12%

Adverse events affecting muscles and/or bones were more common among Quad users, as follows:

- Quad – 21%

- Atripla – 16%
- atazanavir-based regimen – 16%

According to the FDA, most of these side effects were “mild or moderate in severity.”

However, the following events that occurred among Quad users were of severe intensity:

- back pain (2 people)
- bone pain (1 person)
- joint pain (1 person)

There was one very serious case of muscle weakness and muscle breakdown, also in a Quad user. Two other Quad users left the study prematurely because of painful limbs and muscle breakdown.

Bone health

According to the FDA, “In previous clinical trials, tenofovir has been associated with bone toxicity, including decreases in bone mineral density.” The occurrence of thinner-than-normal bones (osteopenia) and severely thin bones (osteoporosis) was as follows:

- Quad – 1.3%
- Atripla – 0%
- atazanavir-based regimen – 2.2%

Overall, the proportion of participants with broken bones was less than 1% and distributed as follows:

- Quad – 0.4%
- Atripla – 0.9%
- atazanavir-based regimen – 0.9%

Most of the fractures were mild or moderate in severity.

Study technicians also performed low-dose X-ray scans (called DEXA) of bones to assess their density in a subset of participants:

- Quad – 54 participants
- atazanavir-based regimen – 66 participants

Overall, small decreases in bone density in the spine and hip occurred. This has happened in other clinical trials and appears to be relatively common in the first year or two of ART. After this time, bone density tends to stabilize.

Heart health

The heart has four chambers that help to pump blood. The coordination of heartbeats, and therefore pumping, is controlled by the heart’s electrical system. A tiny wave of electricity is released from its electrical system, causing its chambers to beat and blood to pump. This electrical activity can be assessed by a cardiogram.

According to heart specialists at the FDA who reviewed the data on the Quad, it is possible that cobicistat may affect some of the heart’s electrical activity, particularly in the following populations:

- elderly people
- people who have pre-existing problems with their heart’s electrical system
- people who are receiving drugs such as verapamil (used to treat high blood pressure, heart pain and irregular heartbeats)

However, subsequent and separate cardiovascular investigations by Gilead have not found disturbances in the heart’s electrical system caused by cobicistat or the Quad.

Ritonavir tends to alter lipid levels (cholesterol and triglyceride) in the blood. However, in comparing the Quad to Atripla, researchers found that cholesterol abnormalities were generally greater among users of Atripla.

Kidney health and cobicistat

The kidneys filter blood, removing wastes, which are put into urine, and reabsorbing useful substances and putting them back into blood. The ability of the kidneys to filter the waste product creatinine appears to be impaired in cobicistat users. It is not yet clear to the FDA if this is due to potential damage caused by cobicistat or if it is a harmless change in kidney function brought about by exposure to cobicistat, as argued by Gilead. It may be that the estimated GFR (eGFR) suggests that creatinine levels are elevated but actual GFR assessments have not found such elevations. This apparent discrepancy between estimated and actual GFR may account for the apparently conflicting assessments of creatinine.

The kidneys are more than just filters. These bean-shaped organs help convert vitamin D into its active form, help regulate blood pressure and produce a hormone called EPO that regulates the production of red blood cells. Dysfunctional kidneys can have a broad impact on a person's health.

Fanconi syndrome—Background

The Quad contains tenofovir and, according to the FDA, reports over the past decade have found that tenofovir has been linked to the appearance or worsening of kidney health in some users. In some cases, an extreme form of kidney damage called Fanconi syndrome has appeared. In this syndrome, vital substances filtered from the blood by the kidneys are sent to the urine rather than back into the blood supply. This problem occurs because tubes (called tubules) in the kidneys that are used to filter substances accumulate tenofovir at concentrations much greater than found in the blood. These tubes are rich in cellular power plants called mitochondria. Research suggests that the high concentration of tenofovir in these tubes damages mitochondria. When mitochondria are damaged they do not produce enough energy for cells, and so the affected cell becomes dysfunctional and can die. Affected tubules can no longer properly filter substances so vital nutrients get lost into urine. The particular form of damage associated with tenofovir is called proximal tubular dysfunction.

Symptoms of Fanconi syndrome can include the following:

- bone pain
- fatigue
- excessive urination

Analysis of urine samples from people with Fanconi syndrome can find the following nutrients:

- amino acids
- sugar (glucose)
- minerals such as magnesium, phosphorus and sodium

Factors that can greatly increase the risk of developing Fanconi syndrome include the following:

- older age
- less-than-ideal body weight
- co-morbidities such as diabetes, higher-than-normal blood pressure and co-infection with hepatitis C virus
- the use of other medicines that can injure the kidneys

Adverse events that affected the kidneys were more common among people who used the Quad compared to other regimens. These were distributed as follows:

- Quad – 8%
- Atripla – 7%
- atazanavir-based regimen – 5%

According to the FDA, 8 people taking the Quad had to stop because of severe kidney dysfunction, as follows:

- kidney failure – 3 people
- Fanconi syndrome – 1 person
- increased creatinine levels in the blood – 4 people

One person taking an atazanavir-based regimen developed severe kidney damage.

According to the FDA's analysis, 4 participants receiving the Quad developed proximal tubular dysfunction and had to leave the study (none taking the other regimens). All 4 participants were from the U.S. and ranged in age between 20 and 60 years.

Two of the 4 participants, one age 56 and the other 60, had a past medical history of higher-than-normal blood pressure and were receiving medicines for this condition. Tests done before they began to use the Quad suggested that they had mild kidney dysfunction. Once they started taking the Quad, they developed serious kidney dysfunction leading to kidney failure within one or two months.

Prior to their departure from the study, all 4 men had glucose and/or protein detected in their urine samples.

The FDA noted that 4 additional Quad users and 1 person taking the atazanavir-based regimen also developed serious kidney problems and had to leave the study. None of these five participants had proximal tubular dysfunction, according to the FDA.

Gilead Sciences provided the FDA with interim safety data from an ongoing study (GS-US-216-0114) in which the following regimens were being compared:

- atazanavir + cobicistat + tenofovir + FTC
- atazanavir + ritonavir + tenofovir + FTC

In examining the data from this study, the FDA identified 5 cases of proximal tubular dysfunction among cobicistat users and 2 cases in the group receiving ritonavir.

Participants who developed this problem did not have higher-than-normal blood pressure and were not receiving other drugs known to cause kidney dysfunction. One of the participants who received cobicistat had a history of type 2 diabetes, which could have predisposed him to developing kidney dysfunction.

Based on all the data from trials of cobicistat and past trials of tenofovir and Truvada, the FDA concluded that "the frequency of probable proximal tubulopathy leading to study drug discontinuation [in phase III clinical trials where participants received cobicistat] was greater than might be expected solely due to tenofovir." Moreover, the FDA also noted that pivotal clinical trials of rilpivirine (Edurant, and in Complera) also used Truvada but "no discontinuations of study drug due to Fanconi syndrome [or any other serious renal adverse effects] were reported. "

Steps to safety

Gilead has proposed that the following steps be taken by doctors who prescribe or are considering prescribing the Quad:

- request laboratory assessment of creatinine levels in the blood and urine so that the rate at which creatinine leaves the body (called creatinine clearance) is known before prescribing the Quad
- do not prescribe the Quad if the creatinine clearance is less than 70 ml/minute
- while on treatment with the Quad, if a patient's creatinine clearance falls below 50 ml/min, they should discontinue taking the Quad
- perform "routine monitoring" of creatinine clearance and other assessments of kidney health, such as eGFR (estimated glomerular filtration rate) and phosphorus levels in the blood of people with kidney dysfunction or who are at risk for kidney dysfunction
- avoid prescribing the Quad to patients who need to take drugs that cause kidney dysfunction or who have recently used such drugs

Gender imbalance

As previously mentioned, women comprised about 10% of the volunteers in the studies used to seek licensure of the Quad. This small proportion of women limited the ability of the FDA to detect signals of toxicity particular to women.

In conclusion

The review by the FDA shows that after one year of use, the Quad is generally effective and safe. There are issues concerning signals of kidney safety, however, serious issues of kidney dysfunction and damage were uncommon.

— Sean R. Hosein

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