I ANTI-HIV AGENTS

A. The approaching Quad

Gilead Sciences has developed a single tablet for HIV treatment that contains all of the following drugs:

- elvitegravir – a new integrase inhibitor
- cobicistat – a new drug whose purpose is to raise the concentration of elvitegravir in the blood
- tenofovir – a nuke that is widely used and sold under the brand name Viread and also found in Truvada, Atripla and Complera
- FTC – another nuke that is widely used and also found in Truvada, Atripla and Complera

The co-formulation of these four drugs—elvitegravir, cobicistat, tenofovir and FTC—has been nicknamed the Quad. This new co-formulation is meant to be taken as a once-daily regimen for the treatment of HIV infection by people who have not previously been treated.

Most drug companies first seek approval for the sale of their medicines in the United States. That country’s drug regulatory agency, the Food and Drug Administration (FDA), is expected to license the Quad by the end of this summer. Regulatory agencies in Canada, Australia and the European Union are also reviewing data on the Quad. Health Canada is expected to license the Quad in the autumn of 2012.

The FDA has compiled an analysis of the data submitted for the licensure of the Quad. In this issue of TreatmentUpdate we make use of that FDA analysis to bring to our readers in-depth information about the Quad’s effectiveness, with a particular focus on its safety. This latter point is particularly important because the Quad is not just...
another once-daily regimen in a pill; it contains two new medicines—elvitegravir and cobicistat—that will be used by HIV-positive people for many years. Moreover, Gilead is collaborating with other drug companies to co-formulate cobicistat with other anti-HIV drugs, such as the protease inhibitor atazanavir (Reyataz). Therefore, it is critical to be aware of the risks and benefits of the new drugs contained in the Quad.

B. Quad — 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 (Incivek).

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 participants
- 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%

**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.

REFERENCES:

II ANTI-HCV AGENTS

A. Prevention and treatment for hepatitis C virus (HCV)

In high-income countries such as Canada, Australia and the U.S. and in regions such as Western Europe, hepatitis C virus (HCV) can be spread in the following ways:

- by sharing equipment for substance use (such as needles, straws and rolled-up currency bills)
- by having unprotected anal sex (particularly among men who have sex with men)
- by sharing sex toys
- by being exposed to unsterilized equipment used for tattooing and body piercing

In previous decades, HCV could also be spread through blood transfusions or receipt of blood products such as clotting factors. However, in high-income countries today the blood supply is very safe.

As there is no vaccine available to provide protection from HCV, prevention efforts are critical.

Treatment options expand

In the past decade, treatment for HCV infection has been a combination of these two drugs:

- a long-lasting form of interferon-alpha called pegylated interferon-alpha (peginterferon), taken once weekly
- a broad-spectrum anti-HCV drug called ribavirin, taken twice daily

Treatment with these drugs lasted for between 24 and 48 weeks, depending on what strain of HCV a person was infected with and other factors.

In high-income countries today, regulatory agencies have licensed two new drugs for HCV treatment:

- boceprevir (Victrelis)
- telaprevir (Incivik)

Each drug is meant to be taken in addition to peginterferon and ribavirin. Both boceprevir and telaprevir have to be taken three times daily (every eight hours). This triple therapy is effective at curing HCV infection in some people.
Telaprevir

This drug is prescribed at a dose of 750 mg three times daily (every eight hours) and is generally used as part of triple therapy, along with peginterferon and ribavirin, for 12 consecutive weeks. After this time, depending on how HCV responds to therapy and a person’s treatment history, telaprevir is taken for an additional 12 or 36 weeks, also with peginterferon and ribavirin.

Boceprevir

This drug is prescribed at a dose of 800 mg three times daily (every eight hours) in combination with peg-interferon and ribavirin. All patients first receive a four-week lead-in period with dual therapy with peginterferon and ribavirin, followed by the addition of boceprevir. Depending on how a person’s HCV responds to triple therapy, boceprevir-based therapy can last for between 28 and 48 weeks.

All drugs have side effects and those associated with these two new therapies are discussed in Treatment Update 183. To summarize, the main side effects are as follows:

- peginterferon – problems with sleep, anxiety, fatigue and depression
- ribavirin – anemia, fatigue
- boceprevir – anemia, altered sense of taste
- telaprevir – skin problems (rash, itchiness), anemia

Both boceprevir and telaprevir appear to enhance ribavirin-associated anemia.

Although therapy with either boceprevir or telaprevir can be very effective, the four therapies currently licensed for HCV infection are not ideal because of their frequent dosing, side effects and, in some cases, complex drug interactions. Also, boceprevir and telaprevir are licensed for the treatment of one strain of HCV—genotype 1. There are many HCV genotypes (from 1 to 6) and subtypes within these (such as genotype 1a and 1b and so on), so new therapies are needed to treat these other strains.

In this issue of Treatment Update we explore data concerning boceprevir and telaprevir as well as some of the other HCV drugs in development.

B. HCV treatment in the real world

In phase III clinical trials of boceprevir and telaprevir, participants were in general good health, with mostly mild-to-moderate levels of liver damage from chronic HCV infection. Only a relatively small proportion of participants had severe liver damage—cirrhosis.

In the real world outside a clinical trial, some people with HCV infection will likely be more seriously ill than those in a clinical trial and therefore in urgent need of HCV treatment. However, because such patients are not in good health, it is possible that they may experience more adverse effects from therapy. French researchers with that country’s premier HIV and HCV research agency, ANRS (Agence nationale de recherches sur le sida et les hépatites virales), collected health-related data from telaprevir and boceprevir compassionate use programs. Such programs were instituted prior to the licensure of both drugs by the French regulatory agency Afsaps. This analysis of compassionate use data was called the Cupic study.

Focus on telaprevir

Researchers analysed data collected from 455 participants in 55 clinics across France. Participants began triple therapy between February 2011 and April 2012.

Among the 296 participants who received telaprevir, the average profile prior to entering Cupic was as follows:

- 68% men, 32% women
- age – 57 years
- all had HCV genotype 1 infection (60% had genotype 1b)
- HCV viral load – 3.2 million IU/ml
- when previously treated with peg-interferon and ribavirin, they only partially responded or relapsed

Preliminary safety results

Researchers presented results from the first 16 weeks of therapy. Note that participants received triple therapy with telaprevir for 12 weeks followed by 36 weeks of dual therapy with peginterferon and ribavirin.
About 50% of telaprevir users experienced serious adverse events during the study and 15% of telaprevir users had to leave the study prematurely because of this.

About 2% of telaprevir users died, mostly from the following causes:

- severe bacterial infections
- pneumonia
- internal bleeding
- neurological complications
- lung cancer

Other complications (not causing death) were distributed as follows:

- severe infections – 9%
- severe rash – 8%
- severe weakness – 5%
- complications from deteriorating liver function – 4%

Blood test results

- severe or life-threatening anemia occurred in 10% of telaprevir users
- 57% of telaprevir users had to take the bone marrow stimulant EPO (erythropoietin)
- 15% of telaprevir users needed blood transfusions
- 12% of telaprevir users had their level of blood platelets (needed for clotting) fall to very low levels, placing them at heightened risk for bleeding

Triple therapy with telaprevir was very effective at suppressing HCV levels, even in those who were very ill and had a history of a poor response/relapse to peginterferon and ribavirin. By the 4th week of therapy in Cupic, 51% of telaprevir users had undetectable HCV levels in their blood. Moreover by the 16th week of the study, 71% had undetectable HCV levels. This finding shows that even very ill people can benefit from triple therapy. Long-term monitoring is continuing to assess rates of cure and relapse from triple therapy.

Focus on boceprevir

Researchers analysed data collected from 455 participants in 55 clinics across France. Participants began triple therapy between February 2011 and April 2012. The average profile of the 159 participants who received boceprevir was as follows:

- men 68%, women 32%
- age – 57 years
- all had HCV genotype 1 infection (60% had genotype 1b)
- HCV viral load – 3.2 million IU/ml
- when previously treated with peginterferon and ribavirin, they only partially responded or relapsed

Preliminary safety results

Researchers presented results from the first 16 weeks of therapy. Note that participants who received boceprevir were first given four weeks of dual therapy with peginterferon-alpha and ribavirin, followed by 40 weeks of triple therapy.

Serious adverse events occurred among 38% of boceprevir users and about 7% of boceprevir users had to leave the study prematurely because of these side effects.

About 1% of boceprevir users died, mostly from the following complications:

- lung infections
- severe bacterial infections

Other complications (not causing death) were distributed as follows:

- severe infections – 3%
- severe weakness – 6%
- no cases of severe rash occurred, though one participant developed very itchy skin
- complications of worsening liver function – 4%

Blood test results

- severe anemia occurred among 10% of boceprevir users
- 66% of boceprevir users required the bone marrow stimulant EPO
- 11% of boceprevir users required blood transfusions

Triple therapy with boceprevir was effective at suppressing HCV levels, even in those who were very ill and who had a history of a poor response or relapse to peginterferon and ribavirin. By the 8th week of therapy in Cupic, 37% of boceprevir users had undetectable HCV levels in their blood. By the 16th week of the study, 61% had undetectable HCV levels.
French researchers recommend that patients with cirrhosis be treated with triple therapy “cautiously.” Moreover, they added that such patients need careful monitoring because of the possibility of developing anemia.

REFERENCE:

C. Considering HIV and HCV drug interactions

Boceprevir and telaprevir interact with some drugs used for HIV treatment (and vice versa). Most drug-drug interaction studies have been conducted using healthy HCV- and HIV-negative volunteers. Based on results from these studies, pharmacologists and regulatory authorities in the U.S. and Europe have made recommendations about which drugs should not be used together.

Some infectious disease experts disagree with the recommendations about drug-drug interactions because they have found that in clinical trials with HIV-positive people who were taking ART and boceprevir or telaprevir, adequate antiviral responses against both HCV and HIV were seen.

Why the differences?

There are several possible reasons why experiments with HIV-negative volunteers yielded one set of results and clinical trials with HIV-positive people a different set of results, as follows:

- Many drugs are broken down by the liver and co-infected people tend to have a greater degree of liver dysfunction than HCV-negative people and so drug levels tend to be greater among co-infected people compared to healthy volunteers. Therefore, a decrease of 30% to 50% in drug levels in some co-infected people may not have a clinically meaningful impact.
- Peginterferon is a standard part of triple HCV therapy and this may have provided additional anti-HIV activity that compensated for reduced levels of anti-HIV drugs.

As with many studies of co-infection so far, the number of participants in these studies was too small to draw meaningful conclusions. Fortunately, this situation is being addressed by the U.S. AIDS Clinical Trials Group (ACTG) and in France by the ANRS. Both organizations are recruiting co-infected volunteers to further study the complex drug-drug interactions that can occur when drugs for HIV and HCV are taken by the same person.

REFERENCE
Burger DM. Interactions between antiretrovirals and direct acting antivirals. In: Program and abstracts of the 8th International Workshop on HIV and Hepatitis Co-infection, 30 May–1 June 2012, Madrid, Spain.

D. HIV and telaprevir drug interactions

Phase III clinical trials tend to enroll carefully selected patients who have few or mild-to-moderate pre-existing health conditions. In practice, once a drug is licensed, a wide variety of patients, some of whom may have multiple health conditions, may receive a new drug. One such pre-existing condition is HIV co-infection. As HIV-positive people will most likely be taking potent combination anti-HIV therapy (commonly called ART or HAART), it is essential to study potential interactions between drugs used for HIV and drugs used for HCV.

World-renowned pharmacologist David Burger, PhD, has assembled and reviewed recently presented data on many potential interactions that could occur between different drugs. Here is a summary of his findings.

Telaprevir—Impact on HIV protease inhibitors

In experiments used to assess interactions between drugs, here are the main findings:

- atazanavir – levels decreased by 17% when used with telaprevir
- lopinavir-ritonavir (in Kaletra) – levels were unchanged when used with telaprevir
- darunavir-ritonavir – levels of darunavir fell by 40% when used with telaprevir
- fosamprenavir-ritonavir – levels fell by 47% when used with telaprevir

Dr. Burger suggests that neither darunavir-ritonavir nor fosamprenavir-ritonavir be used with telaprevir.
Note that the above only lists the effects on specific HIV medicines. The impact of these and other drugs on telaprevir will be discussed later.

**Telaprevir—Impact on raltegravir**

Overall, concentrations of the integrase inhibitor raltegravir (Isentress) in the blood rose by 31% when used with telaprevir. Dr. Burger says that a dose adjustment of raltegravir may not be necessary in telaprevir users.

**Telaprevir—Impact on some non-nukes**

Etravirine is a non-nuke sold under the brand name Intelence. Telaprevir decreased etravirine levels in the blood by 6%, a small change.

Rilpivirine is another non-nuke sold under the brand name Edurant and found in Complera. Telaprevir raised rilpivirine levels in the blood by nearly 80%. This could result in dangerous side effects so the combination should not be used.

Efavirenz significantly reduces the concentration of telaprevir in the blood. Professor Burger suggested that efavirenz may be used but the dose of telaprevir should be increased to 1,125 mg every eight hours.

**Effect of HIV protease inhibitors on telaprevir**

In experiments on people, the following changes occurred:

- lopinavir-ritonavir (in Kaletra) reduced telaprevir levels by 54%
- atazanavir-ritonavir reduced telaprevir levels by 20%
- darunavir-ritonavir reduced telaprevir levels by 35%
- fosamprenavir-ritonavir reduced telaprevir levels by 32%

Dr. Burger notes that atazanavir-ritonavir is probably the only combination from this group that is safe to use with telaprevir.

Raltegravir raised telaprevir levels by 7%—a difference that is not significant.

Etravirine reduced telaprevir levels by 18%. When the dose of telaprevir was doubled to 1,500 mg every eight hours, unexpectedly telaprevir levels fell by 20%. This is an example of how unexpected and complex drug-drug interactions can be and why they need to be studied.

Rilpivirine caused telaprevir levels to fall by 8%.

**Telaprevir drug interaction summary**

Dr. Burger recommended that the following courses of action be taken by doctors who are contemplating prescribing telaprevir to people who are co-infected with HIV and HCV:

- etravirine can be used
- efavirenz may be used but the dose of telaprevir should be increased to 1,125 mg every eight hours
- rilpivirine may be used only with much caution
- raltegravir may be used
- atazanavir-ritonavir may be used
- tenofovir may be used

He recommended that the following drugs not be taken by telaprevir users:

- darunavir-ritonavir
- fosamprenavir-ritonavir
- lopinavir-ritonavir

These recommendations are very broad. Each person will likely be taking several other drugs to treat complications of HCV (or HIV infection), therefore much more information about drug interactions is needed. Until the results of large clinical trials conducted by the ACTG and ANRS are completed and consensus has emerged about which drugs to use, we urge physicians who are contemplating prescribing these or other therapies to seek guidance from regulatory authorities, consult the necessary product monographs or speak with other experts, particularly pharmacologists and other specialists who are experienced in treating co-infected patients.

**REFERENCE:**

Burger DM. Interactions between antiretrovirals and direct acting antivirals. In: Program and abstracts of the 8th International Workshop on HIV and Hepatitis Co-infection, 30 May–1 June 2012, Madrid, Spain.
E. HIV and boceprevir
drug interactions

Phase III clinical trials tend to enroll carefully selected patients who have few or mild-to-moderate pre-existing health conditions. In practice, once a drug is licensed, a wide variety of patients, some of whom may have multiple health conditions, may receive a new drug. One such pre-existing condition is HIV co-infection. As HIV-positive people will most likely be taking potent combination anti-HIV therapy (commonly called ART or HAART), it is essential to study potential interactions between drugs used for HIV and drugs used for HCV.

World-renowned pharmacologist David Burger, PhD, has assembled and reviewed data on many potential interactions that could occur between different drugs. Here is a summary of recent research that he presented.

Boceprevir—Impact on HIV protease inhibitors

In experiments used to assess interactions between drugs, here are the main findings:

- levels of atazanavir-ritonavir fell by 35% when used with boceprevir
- levels of lopinavir-ritonavir (in Kaletra) fell by 34% when used with boceprevir
- levels of darunavir-ritonavir fell by 44% when used with boceprevir

These changes are so great that Dr. Burger notes that boceprevir should not be used with these HIV drugs.

Raltegravir
Levels of this drug increased by 1% when used with boceprevir.

Non-nuke interactions
Boceprevir reduced etravirine levels by 23%. Efavirenz reduced boceprevir levels by 19%—these should not be used together.

Effect of HIV drugs on boceprevir
In experiments on people, the following changes occurred:

- atazanavir-ritonavir reduced boceprevir levels by 5%
- lopinavir-ritonavir reduced boceprevir levels by 34%
- darunavir-ritonavir reduced boceprevir levels by 32%
- Efavirenz reduced boceprevir levels by 10%.

Boceprevir drug interaction summary

Dr. Burger recommended that the following courses of action be taken by doctors who are contemplating prescribing boceprevir to people who are co-infected with HIV and HCV:

- tenofovir increases boceprevir levels by 8%—these drugs may be used together
- etravirine may be used with boceprevir
- raltegravir may be used with boceprevir

The following drugs should not be used with boceprevir:

- atazanavir-ritonavir
- lopinavir-ritonavir
- darunavir-ritonavir
- efavirenz reduces boceprevir levels by 19%—these should not be used together

Each person will likely be taking several other drugs to treat complications of HCV (or HIV infection), therefore much more information about drug interactions is needed. Until the results of large clinical trials conducted by the ACTG and ANRS are completed and consensus has emerged about which drugs to use, we urge physicians who are contemplating prescribing these or other therapies to seek guidance from regulatory authorities, consult the necessary product monographs or speak with other experts, particularly pharmacologists and other specialists who are experienced in treating co-infected patients.

REFERENCE:

Burger DM. Interactions between antiretrovirals and direct acting antivirals. In: Program and abstracts of the 8th International Workshop on HIV and Hepatitis Co-infection, 30 May–1 June 2012, Madrid, Spain.

F. France—Studying end-stage liver disease

If left untreated, HCV infection causes healthy liver tissue to be replaced with scar tissue in a process called fibrosis. Eventually, as fibrosis spreads, the liver becomes increasingly dysfunctional and the health of the body is affected
as this vital organ withers. At that point, end-stage liver disease (ESLD) sets in as complications such as serious bacterial infections, internal bleeding, severe fatigue, neurocognitive problems and, in some cases, liver cancer occurs.

Researchers in France have been monitoring the health of 310 participants co-infected with HIV and HCV who had extensive liver damage (cirrhosis). They found that participants who were most likely to develop serious complications of ESLD had the following factors:

- elevated levels of alpha-fetoprotein in their blood
- lower CD4+ cell counts—an average of 275 cells compared to people who had higher counts (395 cells)
- more likely to rent their housing rather than own; this may reflect poorer socioeconomic conditions

After five years of monitoring, about 16% of participants had developed ESLD.

Between 2006 and 2011, selected causes of death in the group were distributed as follows:

- HCV-related, including liver cancer – 43%
- non-AIDS-related cancer – 14%
- AIDS – 10%
- cardiovascular disease – 8%
- non-AIDS-related infections – 8%
- lung problems – 4%
- overdose and suicide – 5%

Even among a subset of participants who were able to clear HCV because of treatment, the risk of developing liver cancer remained, perhaps because of extensive liver damage (cirrhosis).

Bear in mind that this study was observational; it was not a randomized, controlled clinical trial, and its conclusions may therefore be inadvertently biased. But the study shows the need for HCV-positive people to access therapy for this infection much earlier in the course of their illness before extensive liver damage occurs.

REFERENCE:
Salmon D, Pambrun E, Winnock M, et al. Incidence of end stage liver disease (ESLD) in HIV/HCV infected patients in France ‘HEPAVIR ANRS C013’. In: Program and abstracts of the 8th International Workshop on HIV and Hepatitis Co-infection, 30 May–1 June 2012, Madrid, Spain. Abstract 0_02A.

G. Selected HCV drugs in development

HCV has proteins that are essential in order for infected liver cells to make new copies of this virus. Newer HCV drugs are being developed that interfere with the HCV proteins NS3/4A; such drugs are called protease inhibitors. The drugs boceprevir and telaprevir are examples of currently licensed protease inhibitors for HCV treatment.

Drugs that interfere with another protein called NS5B are called polymerase inhibitors. There are two groups of these drugs—nucleoside and non-nucleoside (non-nuke) inhibitors. In general, nucleosides that attack NS5B tend to have greater anti-HCV activity against several HCV genotypes. HCV exposed to nukes is less likely to develop resistance than when treated with non-nukes.

There are many drugs in development for HCV treatment. Below are a few.

**Simeprevir (TMC435)**
This drug impairs the activity of the HCV proteins NS3/4A and is classed as a protease inhibitor. It has at least similar anti-HCV activity as boceprevir or telaprevir when used as part of combination therapy. Simeprevir is taken at a dose of 150 mg once daily. Common side effects include nausea, fatigue and flu-like symptoms. A phase III trial of simeprevir is underway. More information on simeprevir appears later in this issue of TreatmentUpdate.

**Asunaprevir (BMS-650032)**
This protease inhibitor interferes with the HCV protein NS3. It is taken twice daily and has been tested with another anti-HCV agent called daclatasvir. In such cases, dual therapy has cured some cases of HCV infection. More information about this drug appears later in this issue of TreatmentUpdate.

**BI 201335**
This drug is a protease inhibitor and attacks the HCV NS3 protein. BI 201335 is given once daily and is currently in phase III clinical trials where it is being taken in combination with peginterferon-alpha and ribavirin. In phase II clinical trials, cure rates with BI 201335-based therapy ranged between 73% and 87%. Side effects associated with this drug include temporary yellowing of the skin, rash, dry skin and sensitivity to sunlight. Also reported were nausea, vomiting and diarrhea.
Daclatasvir (BMS-790052)
This drug attacks the HCV protein NS5A. A combination of daclatasvir and asunaprevir, with or without peginterferon and ribavirin, has been tested in participants who had previously not responded to dual therapy with peginterferon-alpha and ribavirin. Quadruple therapy resulted in curing 90% of participants after 24 weeks. Double therapy with daclatasvir and asunaprevir resulted in a cure rate of 36%, suggesting that a subset of patients can be successfully treated with an interferon-free regimen.

GS-7977
This is a nucleoside NS5B polymerase inhibitor (formerly called PSI-7977). Preliminary clinical trials have found that GS-7977 has powerful anti-HCV activity against genotype 1 strains. When GS-7977 was used together with peginterferon-alpha and ribavirin in HCV genotype 1 volunteers who had never previously received therapy, large decreases in HCV viral load occurred in as little as three days. When GS-7977 is used as part of triple therapy with interferon and ribavirin it appears to be effective against genotypes 2 and 3. Side effects associated with GS-7977 are not yet clear. Many clinical trials with this drug are planned or underway, some of which do not include using interferon. The best combinations of drugs to use with GS-7977 are not yet clear.

ABT-072
This drug is a non-nucleoside inhibitor of the HCV NS5B polymerase and has potent activity against the virus. Details about the use of this drug appear later in this issue of Treatment Update.

VCH-222
This drug is a non-nucleoside inhibitor with NS5B and has activity against HCV genotypes 1a and 1b. Side effects can include fatigue, mild nausea and diarrhea. A clinical trial of VCH-222 and telaprevir and ribavirin is planned.

REFERENCES:
4. Sulkowski M. Interferon-free HCV treatment regimens. In: Program and abstracts of the 8th International Workshop on HIV and Hepatitis Co-infection, 30 May–1 June 2012, Madrid, Spain. Abstract 0_02A.

H. A novel triple combination—ABT-450 + ABT-072 and ABT-333
ABT-450 is an HCV protease inhibitor that attacks the HCV protein NS3/4A. This drug must be taken with ritonavir to ensure that levels of ABT-450 remain elevated.

ABT-072 and ABT-333 are non-nucleoside inhibitors (non-nukes) that attack the HCV enzyme NS5B.

In the clinical trial we are about to report on, these three drugs were tested in combination with ribavirin in volunteers who were infected with HCV genotype 1. All participants had either never been previously treated (treatment naive) or, if they had, when they previously received interferon and ribavirin their HCV did not adequately respond to this therapy.

Participants were divided into the following groups and received ribavirin in doses of 1,000 to 1,200 mg daily:

Group 1 (treatment naive)
- 11 participants: ABT-450 + ritonavir (150 mg + 100 mg) once daily + ABT-072 (400 mg) once daily + ribavirin

Group 2 (treatment naive)
- 19 participants: ABT-450 + ritonavir (250 mg + 100 mg) once daily + ABT-333 (400 mg) twice daily + ribavirin

Group 3 (treatment naive)
- 14 participants: ABT-450 + ritonavir (150 mg + 100 mg) once daily + ABT-333 (400 mg) twice daily + ribavirin

Group 4 (previous non-responders)
- 17 participants: ABT-450 + ritonavir (150 mg + 100 mg) once daily + ABT-333 (400 mg) twice daily + ribavirin

Experimental treatment was given for 12 consecutive weeks, followed by a period of observation (still ongoing). No participants had
severe liver damage or co-infection with HBV or HIV. Their average profile upon entering the study was as follows:

- 72% men, 28% women
- age – 55 years
- HCV genotypes 1a or 1b present
- HCV viral load greater than 800,000 IU/ml

**Results**

The proportion of participants whose viral load was suppressed after 12 weeks was as follows:

- **Group 1**: 91%
- **Group 2**: 95%
- **Group 3**: 93%
- **Group 4**: 47%

Two participants were able to suppress HCV but then their virus levels resurged.

No deaths or life-threatening complications occurred.

There were isolated cases of elevated liver enzymes (ALT and AST) in the blood but these were symptom-free and the elevations fell after the end of the study.

**Side effects**

Overall, four people developed severe adverse reactions, as follows:

- elevated bilirubin (this may be due to ABT-450)
- fatigue
- pain
- vomiting

None of these adverse reactions were so severe that participants had to leave the study or temporarily stop taking the drugs.

Rash was uncommon and generally mild when it did occur.

Common side effects were as follows:

- fatigue
- nausea
- headache

Overall, 91% of participants who did not previously receive anti-HCV therapy have had their HCV remain undetectable, while about 47% of previous non-responders were able to achieve an undetectable level of HCV after 12 weeks of therapy.

Both doses of ABT-450 (250 and 150 mg) showed similar efficacy.

Clinical trials with the three ABT drugs are continuing. Researchers plan to assess drug-drug interactions with these and commonly used anti-HIV drugs.

**REFERENCE:**

Cohen D, Poordad F, Lawitz E, et al. 12-week interferon-free regimen of ABT-450/r+ABT-333+ribavirin achieved SVR12 in more than 90% of treatment-naïve HCV genotype-1-infected subjects and 47% of previous non-responders. In: Program and abstracts of the 8th International Workshop on HIV and Hepatitis Co-infection, 30 May–1 June 2012, Madrid, Spain.

**I. The debut of simeprevir (TMC435)**

TMC435 is a once-daily NS3/4A HCV protease inhibitor that is taken orally. It is effective against HCV genotype 1 and shows preliminary efficacy against other strains or genotypes of HCV.

A phase II study was conducted to assess preliminary safety and efficacy using volunteers who had previously been treated with interferon + ribavirin and who did not respond to this therapy.

Researchers randomly assigned four groups of participants to receive the following drugs in a double-blind manner:

- **Group 1**: TMC435 + peginterferon + ribavirin for 12 weeks, followed by peginterferon + ribavirin + placebo for 36 weeks
- **Group 2**: TMC435 + peginterferon + ribavirin for 24 weeks, followed by peginterferon + ribavirin + placebo for 24 weeks
- **Group 3**: TMC435 + peginterferon + ribavirin for 48 weeks
- **Group 4**: peginterferon + ribavirin + placebo for 48 weeks

At the end of each treatment period (48 weeks), participants were monitored for an additional 24 weeks.

In groups 1, 2 and 3, half of the participants received TMC435 at a dose of 100 mg daily and the other half received this drug at a dose of 150 mg daily.
The average profile of participants upon entering the study was as follows:

- 68% male, 32% women
- age – 50 years
- weight – 80 kg
- 41% had HCV genotype 1a
- more than 80% had an HCV viral load of 800,000 IU/ml or greater

**Treatment history**

The effect of previous HCV therapy (peginterferon + ribavirin) on participants in this study was as follows:

- 40% relapsed
- 35% had a partial response
- 25% had no significant decrease in their HCV viral load

**Results**

The final analysis from this study relied on data collected from 462 participants. Proportions of participants in each group who were cured were as follows:

- Group 1: 67%
- Group 2: 72%
- Group 3: 80%
- Group 4: 23%

In general, the longer the time on simeprevir, the greater the chances of recovery from HCV infection. Participants who received simeprevir at the higher dose (150 mg once daily) also had better responses to therapy. Response to therapy was good among those who had previously relapsed (85%), prior partial responders (75%) and even prior null responders (51%).

HCV genotype did not significantly affect response to therapy.

Cure rates among participants who had cirrhosis varied between 31% and 81%.

**Focus on virology**

Rates of virologic failure were generally low but increased among participants who had unfavourable treatment histories.

- Viral breakthrough was more common among participants in the simeprevir 100 mg group (13%) than in the 150 mg group (9%).
- After achieving an undetectable viral load, viral relapse was more common among participants taking the simeprevir 100 mg dose (11%) than among those taking the 150 mg dose (9%).

At the time of viral breakthrough, 98% of participants with this problem had detectable HCV resistance. Emerging mutations were as follows:

- genotype 1a – usually R155K alone or in combination
- genotype 1b – usually D168V

These mutations conferred significantly reduced susceptibility to simeprevir.

Common side effects seen in all groups included the following:

- headache
- fatigue
- flu-like illness
- rash

Rash was more common among participants who received simeprevir as follows:

- simeprevir 100 mg once daily – 23% developed rash
- simeprevir 150 mg once daily – 30% developed rash
- placebo – 18% developed rash

Changes in red blood cell levels were similar among all groups.

The 150-mg dose of simeprevir has been selected for phase III clinical trials.

**REFERENCES:**


J. Simeprevir—Cleared from sun sensitivity

Some medicines can make the skin more sensitive to sunlight. This occurs when sunlight (which has ultraviolet, or UV, light) interacts with small concentrations of medicines that are in the skin. Some medicines, such as antibiotics, antidepressants, anti-seizure drugs and anti-hypertensives, as well as some herbs, such as St. John’s wort (and its extracts, hypericin and hyperforin), have this effect.

In general, two patterns of skin sensitivity can occur when the skin is exposed to UV light, as follows:

- immediate burning, redness and temporary swelling within two to six hours of sun exposure
- delayed sunburn with redness and tenderness within 24 hours of exposure

Laboratory experiments suggested that TMC435 (simeprevir) had the potential to be a photosensitizing agent. To explore the potential for this problem, researchers recruited otherwise-healthy volunteers and then randomly assigned them to receive one of the following interventions for nine days:

- simeprevir 150 mg once daily
- ciprofloxacin (Cipro) 500 mg twice daily
- placebo

Cipro was chosen because it is a mild sun sensitizer.

Artificial UV light similar to mid-summer sunlight was given to participants to simulate sun exposure just before and immediately after they stopped taking the study drugs.

Researchers recruited 36 participants (all were White), 33 men and 3 women, and assigned 12 people to receive each intervention.

Results

Eleven volunteers developed mild, moderate or severe photosensitivity; three of these were taking placebo. Three cases of mild photosensitivity occurred among simeprevir users.

No statistically significant differences in the intensity of skin reactions among the different interventions were noted.

K. Simeprevir and different strains of HCV

Like many viruses, there is more than one type or strain of HCV. These strains are called genotypes and are broadly distributed as follows:

- genotype 1 – found throughout the world and common in North American and Western Europe
- genotype 2 – found in North America, Europe, Japan (subtypes 2a and 2b), northern Italy (subtype 2c) and West Africa
- genotype 3 – found throughout the world, particularly in the Indian subcontinent
- genotype 4 – common in Egypt, the Middle East, sub-Saharan Africa and increasingly in Europe
- genotype 5 – found in Southern Africa, Spain, France, Belgium and Syria
- genotype 6 – found in South East Asia

The currently licensed new drugs for HCV treatment—boceprevir and telaprevir—are designed primarily for the treatment of genotype 1 HCV infection. However, telaprevir likely also has some activity against genotype 2. The standard treatment for many of these other strains of HCV is a combination of peginterferon and ribavirin.

TMC435 (simeprevir) has activity against a broad range of strains of HCV in lab experiments, so researchers recently explored its activity in participants who were infected with genotypes 2 through 6.

Simeprevir, at a dose of 200 mg once daily, was given as monotherapy for the first week of the study in order to assess if it had anti-HCV activity against the different genotypes of HCV. After this period, participants received peginterferon and

REFERENCE:
Ribavirin for up to 37 days. Thirty-seven participants were recruited from clinics in Belgium, Germany and Thailand. Eleven percent of participants had cirrhosis (severe liver damage).

Results

Most participants had a significant decline in their HCV viral load when they were taking simeprevir. This decline in HCV viral load was greatest in participants with genotypes 4 and 6 (a decrease of 3 to 4 logs), followed by genotype 2 (a decrease of 2 to 3 logs) and genotype 5 (a decrease of 2 logs).

Genotype 3 did not respond significantly to simeprevir.

In many cases, HCV viral load became undetectable when participants used dual therapy with peginterferon and ribavirin. Switching to dual therapy with peginterferon and ribavirin did not continue to suppress genotype 4 HCV levels.

While most participants reported side effects—flu-like symptoms—the researchers stated that simeprevir was well tolerated and most side effects were of mild-to-moderate intensity.

The present study shows that simeprevir can have significant antiviral activity against some strains or genotypes of HCV. It provides a foundation for designing a study to assess the long-term results of therapy for these other genotypes, particularly genotypes 4, 5, 6 and some subtypes of genotype 2.

Other new anti-HCV drugs also need to be assessed for their activity against multiple subtypes of HCV.

REFERENCE:

L. Daclatasvir and asunaprevir—A potent interferon-free regimen

HCV-positive people whose HCV levels have not sufficiently responded to therapy are often referred to as “null responders” by researchers. Some of these people may show much better responses when retreated with triple therapy that includes boceprevir or telaprevir.
Analysis of blood samples revealed that in almost all cases of virologic failure, the concentration of study drug was less than ideal. Moreover, most cases of virologic failure were associated with a mutation called Y93H, found in NS5A.

**Side effects**

Serious adverse effects occurred in five patients, mainly high fever.

Three participants left the study prematurely due to elevated bilirubin and elevated liver enzymes.

Study drugs did not cause changes to heart rhythms.

No one died during the study.

Common side effects in 27% or more of participants were as follows:

- headache
- runny nose and/or sore throat
- increased levels of the liver enzyme ALT

Some participants developed mild diarrhea while five others reported constipation.

In summary, the combination of asunaprevir and daclatasvir is very potent and likely better tolerated than regimens that include interferon. Further clinical trials are planned or underway with these two new promising anti-HCV agents.

**REFERENCE:**

Suzuki F, Ikeda K, Toyota J, et al. Dual oral therapy with the NS5A inhibitor Daclatasvir (BMS-790052) and NS3 protease inhibitor asunaprevir (BMS-650032) in HCV genotype 1b-infected null responders or ineligible/intolerant to peginterferon/ribavirin. In: Program and abstracts of the 47th annual meeting of the European Association for the Study of the Liver, 18-22 April 2012, Barcelona, Spain.

**M. Daclatasvir and GS-7977**

Daclatasvir was the first oral HCV NS5A inhibitor to be developed. GS-7977 is a nuke with activity against NS5B. Both drugs have powerful anti-HCV activity when used separately. In study AI444-040, researchers in the U.S. studied different combinations of both drugs in a randomized clinical trial with HCV-positive people infected with the following genotypes:

- genotype 1a, 1b, 2, and 3

Researchers recruited participants and assigned them to the following six groups:

**Group A**
- 15 participants with genotypes 1a and 1b: all received GS-7977 monotherapy for seven days after which daclatasvir was added; dual therapy continued for 23 weeks

**Group B**
- 16 participants with genotypes 2 and 3: all received GS-7977 monotherapy for seven days after which daclatasvir 60 mg once daily was added; dual therapy continued for 23 weeks

**Group C**
- 14 participants with genotypes 1a and 1b: all received immediate dual therapy with daclatasvir and GS-7977, both for 24 weeks

**Group D**
- 14 participants with genotypes 2 and 3: all received immediate dual therapy with daclatasvir and GS-7977, both for 24 weeks

**Group E**
- 15 participants with genotypes 1a and 1b: all received triple therapy with daclatasvir, GS-7977 and ribavirin (dosed between 1,000 and 1,200 mg/day), all for 24 weeks

**Group F**
- 14 participants with genotypes 2 and 3: all received triple therapy with daclatasvir, GS-7977 and ribavirin at 800 mg/day, all for 24 weeks

All participants were monitored for an additional 24 weeks once they stopped experimental therapy.

The average profile of participants upon entering the study was as follows:

- age – 53 years
- 50% men, 50% women
- HCV viral load – 4 million IU/ml
Results

The decline in HCV levels was faster among participants who received combination therapy immediately rather than delaying combination therapy. Viral suppression was similar in groups C, D, E and F.

Adding ribavirin did not accelerate the decline of HCV viral load.

After four weeks of experimental therapy, 100% of genotype 1 participants had undetectable levels of HCV. The equivalent figure for genotype 2 and 3 participants was 91%.

Two participants stopped returning to the study clinic for unknown reason(s). Their last blood samples at weeks 12 and 24 respectively were undetectable.

One participant had his HCV levels rise after first suppressing them.

Another participant (in group B) had his HCV levels rise but doctors enhanced his therapy with interferon + ribavirin and his viral load returned to suppressed levels.

Safety

No deaths occurred.

Two participants left the study because of adverse events: one case of stroke (group C) and one case of fibromyalgia (group F). Researchers considered both incidents to be unrelated to the study.

Serious adverse events occurred in 10 patients, but only three cases were judged to be related to the study medicines and all occurred when patients accidentally took extra doses of daclatasvir or GS-7977.

Adverse events in the study that were not related to the experimental treatments were as follows:

- anxiety – 2 participants
- fracture – 1 participant
- lung pain – 1 participant
- intestinal inflammation – 1 participant
- kidney failure – 1 participant

No cases of severely elevated liver enzymes occurred.

The most common laboratory abnormality was anemia and this occurred in participants who received ribavirin.

In summary, the all-oral regimen of two new drugs without ribavirin cured 100% of genotype 1 participants and at least 90% of genotype 2 and 3 participants.

These very promising findings require confirmation in a larger study.

REFERENCE:

Sulkowski M, Gardiner D, Lawitz E, et al. Potent viral suppression with the all oral combination of daclatasvir (NS5A inhibitor) and GS-7977 (nucleotide NS5B inhibitor), +/- ribavirin, in treatment-naïve patients with chronic HCV genotype 1, 2 or 3. In: Program and abstracts of the 47th annual meeting of the European Association for the Study of the Liver, 18-22 April 2012, Barcelona, Spain.
Disclaimer

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

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© CATIE, Vol. 24, No. 5
July 2012

ISSN 1181-7186 (print)
ISSN 1927-8918 (online)
CATIE Ordering Centre Catalogue Number ATI-60199E
(Aussi disponible en français, ATI-60199F)

Production of this newsletter has been made possible through a financial contribution from the Public Health Agency of Canada.