Hepatitis C virus (HCV) can be grouped into six major strains, or genotypes, such as genotypes 1, 2, 3, 4, 5 and 6. These can be further divided into sub-types, such as 1a, 1b and so on.

The latest generation of oral combination therapies for HCV—Harvoni and Holkira Pak—mostly target genotype 1 (though they are being tested against other genotypes). Genotype 1 is relatively common in North America and Western Europe. However, due to immigration and travel, other genotypes can be found in people with HCV who are living in high-income countries and regions.

Several pharmaceutical companies are developing regimens that should, at least in theory, be able to treat all genotypes. If such a regimen were in a single pill that could be taken once daily until a cure was achieved it would have the following potential:

- remove the need for laboratory testing for genotypes
- perhaps encourage the planning and implementation of mass treatment campaigns for HCV

The pharmaceutical company Gilead Sciences is developing a fixed-dose combination (all in one pill) of the following anti-HCV drugs:

- sofosbuvir
- velpatasvir (formerly called GS-5816)

Clinical trials with combinations of these drugs have shown impressive antiviral activity in patients infected with different strains of HCV. Furthermore, the combination was generally well tolerated.

In this CATIE News bulletin, we explore the results from phase II studies of combinations of sofosbuvir and velpatasvir given as separate pills to 377 participants. In these studies, participants had HCV infection without any co-infections such as HIV or hepatitis B virus and had not been previously treated. No participant had extensive scarring of the liver (cirrhosis). Study drugs were given for eight or 12 weeks.

Results of a much larger phase III clinical study of sofosbuvir and velpatasvir are in press and will be reviewed in an upcoming CATIE News bulletin.

About the study drugs

Sofosbuvir works by impairing the activity of a critical enzyme called NS5B. HCV-infected cells use this enzyme to make new copies of the virus. Sofosbuvir is already licensed in high-income countries and sold as Sovaldi and in the combination tablet Harvoni (sofosbuvir + ledipasvir).

Velpatasvir works by inhibiting the activity of another key enzyme called NS5A.

When used together, both drugs have potent antiviral activity against a range of HCV genotypes. Researchers call such an effect—against a broad range of HCV—pan-genotypic.

In some cases in the present report, the broad-spectrum antiviral drug ribavirin was also used.

Study details
Doctors and nurses at 48 clinics across the U.S. recruited 377 participants infected with HCV genotypes 1 through 6.

The average profile of participants was as follows:

- age – late 40s to mid 50s
- 58% men, 42% women
- most participants had an HCV viral load between 6 and 7 logs

Gilead divided the study into parts A and B. In part A, some participants with genotypes 1 through 6 were randomly assigned to take the following drugs for 12 consecutive weeks:

- sofosbuvir, 400 mg once daily
- velpatasvir, 25 or 100 mg once daily

In part B, the remaining participants were assigned to take the following drugs for eight consecutive weeks:

- sofosbuvir, 400 mg once daily
- velpatasvir, 25 or 100 mg once daily

OR

- sofosbuvir, 400 mg once daily
- velpatasvir, 25 or 100 mg once daily
- ribavirin, 1,000 to 1,200 mg daily (taken in two divided doses)

**Cure assessment**

Blood samples were taken during and after treatment. A person with an undetectable viral load 12 weeks after the cessation of therapy was considered cured. This time point is written as SVR\textsubscript{12} (sustained virological response).

The viral load test used in this study could not accurately count HCV if it was less than 25 IU/mL. This level of 25 IU/mL is known as the lower limit of quantification (LLOQ) and is commonly called “undetectable.”

**Results**

Overall, 89\% (337) of 377 participants achieved an SVR\textsubscript{12}; that is, HCV was undetectable in their blood 12 weeks after the cessation of therapy. This figure of 89\% is an average figure and it masks perhaps more effective subgroup results where as many as 100\% of participants (28 of 28) who were given sofosbuvir + velpatasvir (100 mg/day) for 12 weeks were cured. Of the participants who were given sofosbuvir + velpatasvir (25 mg/day), 96\% were cured.

In general, a 12-week course of treatment was more effective than eight weeks of treatment.

Among the participants who had an SVR\textsubscript{12}, 324 returned to their clinic for another test 24 weeks after the cessation of therapy. Bear in mind that not everyone returned because the clinic staff was unable to track them, perhaps because they moved or for other reasons. Of these 324 people, more than 99\% were cured. That is, more than 99\% had an SVR\textsubscript{24} as their HCV viral load continued to be undetectable.

**Why not 100\% SVR\textsubscript{24}?**

The exception to this trend of SVR\textsubscript{24} occurred in one participant—a 29-year-old woman infected with genotype 1a. Her pre-treatment HCV viral load was 6.8 log but became undetectable after the fourth week of therapy—sofosbuvir + velpatasvir 25 mg taken for 12 weeks. This combination continued to suppress HCV and she achieved an SVR\textsubscript{12}. However, 24 weeks after the cessation of therapy, blood tests revealed that her viral load was detectable. Stunned by this unexpected finding, technicians analysed samples of her blood taken before treatment and when it later became detectable. Specifically, they assessed the genes of HCV found before and after treatment. Their analysis,
according to the study authors, strongly suggested that “a new HCV infection had occurred rather than a reemergence of the pretreatment viral population.” In other words, she became infected with a new strain of HCV after she had been cured.

**Results—Part A (12-week regimens)**

**Genotype 1 infection**
- sofosbuvir + velpatasvir (25 mg): 96% (26 of 27 people) achieved SVR\textsubscript{12}
- sofosbuvir + velpatasvir (100 mg): 100% (28 of 28 people) achieved SVR\textsubscript{12}

**Genotype 3 infection**
- sofosbuvir + velpatasvir (25 mg): 96% (25 of 27 people) achieved SVR\textsubscript{12}
- sofosbuvir + velpatasvir (100 mg): 93% (25 of 27 people) achieved SVR\textsubscript{12}

**Genotypes 2, 4, 5 or 6**
- sofosbuvir + velpatasvir 25 mg: 96% (22 of 23 people) achieved SVR\textsubscript{12}
- sofosbuvir + velpatasvir 100 mg: 95% (21 of 22 people) achieved SVR\textsubscript{12}

**Results—Part B (eight-week regimens)**

**Genotype 1**
- sofosbuvir + velpatasvir (25 mg): 85% (26 of 30 people) achieved SVR\textsubscript{12}
- sofosbuvir + velpatasvir (25 mg) + ribavirin: 83% (25 of 30 people) achieved SVR\textsubscript{12}
- sofosbuvir + velpatasvir (100 mg): 90% (26 of 29 people) achieved SVR\textsubscript{12}
- sofosbuvir + velpatasvir (100 mg) + ribavirin: 81% (25 of 31 people) achieved SVR\textsubscript{12}

**Genotype 2**
- sofosbuvir + velpatasvir (25 mg): 77% (20 of 26 people) achieved SVR\textsubscript{12}
- sofosbuvir + velpatasvir (25 mg) + ribavirin: 88% (22 of 25 people) achieved SVR\textsubscript{12}
- sofosbuvir + velpatasvir (100 mg): 88% (23 of 26 people) achieved SVR\textsubscript{12}
- sofosbuvir + velpatasvir (100 mg) + ribavirin: 88% (23 of 26 people) achieved SVR\textsubscript{12}

**Safety**

Overall, almost 70% of participants reported at least one possible side effect. Common side effects included the following:
- tiredness or lack of energy – 21%
- headache – 20%
- nausea – 12%

There were no differences in the type or frequency of side effects with different doses of velpatasvir.

Participants who took ribavirin-containing regimens were more likely to report the following side effects: tiredness/lack of energy, difficulty falling asleep and rash. Such side effects have been seen in previous clinical trials of ribavirin-containing regimens.

**Individual cases**

Here are accounts of two people and their outcomes that required investigation.

**Case 1**
One participant, a 19-year-old woman with genotype 1, was taking sofosbuvir and velpatasvir (25 mg). On her sixth day of therapy she developed the following:

- abdominal pain of mild intensity
- pounding or racing heart beats (palpitations) of mild intensity
- dizziness of moderate intensity

An investigator determined that these symptoms were related to the study drugs and instructed her to stop taking them the following day. Her symptoms resolved within 48 hours of treatment cessation.

**Case 2**

A 36-year-old man with genotype 2 and a history of what the research team called “pre-existing psychiatric disease” (details were not released) committed suicide after completing 12 weeks of sofosbuvir + velpatasvir (25 mg). Investigators judged that the study drugs did not trigger his death.

**Bear in mind**

1. Although the overall number of people in this study is large (377), because there were many subgroups for the different regimens and genotypes, the results should be considered very promising but preliminary. Furthermore, due to these small subgroups, it was not possible to produce meaningful statistical analysis. Statistically robust results will be discussed in upcoming CATIE News bulletins where we review the results from phase III clinical trials of the combination of sofosbuvir and velpatasvir.
2. The best results were generally seen with 100 mg of velpatasvir and when therapy lasted for 12 rather than eight weeks.
3. The study was conducted in the U.S. and, as a result, enrolled relatively few participants with genotypes 4, 5 or 6.
4. No patients who had previously attempted HCV treatment or who had severe scarring of the liver (cirrhosis) were enrolled.

**For the future**

Gilead Sciences plans to submit a dossier including data from phase III clinical trials of sofosbuvir + velpatasvir to the U.S. Food and Drug Administration (FDA) seeking licensure of this combination. Similar submissions are planned for Canada and the European Union. Therefore, it is likely that sometime in 2016 a fixed-dose combination (one pill) of sofosbuvir and velpatasvir (100 mg) will become available in Canada, the U.S. and the European Union.

**Resources**

Harvoni (ledipasvir + sofosbuvir) – CATIE fact sheet

Holkira Pak (dasabuvir + ombitasvir/paritaprevir/ritonavir) – CATIE fact sheet

CATIE’s hepatitis C information

---Sean R. Hosein

**REFERENCES:**

Decision 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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