# The Coinfection Challenge

New treatment options for people living with HIV and hepatitis C

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The first time Jeffrey Mende attempted a cure his hepatitis C virus (HCV), the medications saddled him with such dreadful flu-like symptoms, depression and crippling fatigue, he could hardly function.

“I literally couldn’t make it down to the car without becoming completely exhausted,” recalls the 51-year-old Frazier Park, California, resident. HIV positive since 1987, he says he likely contracted hep C from a contaminated tattoo needle in 2003; a routine test came up positive the following year.

About halfway through what was supposed to be a six-month hep C treatment, Mende told his doctor he’d rather die than feel so sick any longer. They agreed it was best to take him off the drugs and try again once treatments had improved, but hopefully not before the virus led to significant scarring—known as fibrosis—of his still fairly healthy liver.

While Mende’s first treatment attempt was as recent as 2010, dreary HCV therapy experiences such as the one he suffered have today, for the most part, been relegated to the history books. Over the past few years, game-changing new hep C treatments have hit the market. These direct-acting antivirals (DAAs) have reduced typical side effects to much more tolerable levels.

The new drugs have also greatly improved the chances of vanquishing HCV—the cure rate is 95 percent and up for many subgroups of the hep C population—and they have reduced the required treatment time to just eight or 12 weeks for most people with hep C, although others need 16 or 24 weeks.

Mende, who is on disability and works part-time as an Uber and Lyft driver, was enrolled in a clinical trial with a DAA called telaprevir, which was approved by the U.S. Food and Drug Administration (FDA) in 2011 under the brand name Incivek.

While Incivek had shaved down treatment times and raised cure rates compared with previous protocols, the drug still had to be paired with the dreaded mainstay of hep C treatment: weekly injections of interferon (responsible for the worst of the side effects) plus daily ribavirin pills (which can cause anemia). That’s why Mende elected to nix his treatment.

Come the end of 2013, the introduction of Gilead Sciences’ blockbuster Sovaldi (sofosbuvir) allowed for the long-awaited phase-out of interferon to begin. The bad news was that treatment cost a notorious $1,000 a day. A year later, Gilead’s once-a-day single-pill combination tablet Harvoni

(ledipasvir/sofosbuvir) gave many people living with hep C the chance to avoid ribavirin as well.

Even more exciting for the coinfected population, HIV is no longer a barrier to successful hep C treatment. While hep C cure rates with older treatments were lower among those with HIV, the current crop of hep C treatments has erased this deficit.

Over the past winter, Mende went on Harvoni and had a relatively breezy 12 weeks of treatment. Come springtime, he was pronounced cured of HCV.

Mende is fortunate to have his liver still in relatively good shape, with only minimal fibrosis. When compared with monoinfected individuals, people also living with HIV have a greater risk of liver disease progression and other health complications resulting from hep C.

Consequently, the American Association for the Study of Liver Diseases (AASLD) recommends that the estimated one in four HIV-positive Americans who are coinfected with HCV receive a higher priority for hep C treatment.

Hep C may also contribute to other health problems that already occur at higher rates among people living with HIV, such as diabetes, kidney disease and cardiovascular disease.

Daniel Fierer, MD, an associate professor of medicine in infectious diseases at Mount Sinai Hospital in New York City, sees a large coinfected population. He says that until recently many coinfected people were so alienated by the bleakness of hep C therapies that they often dropped out of care for that virus.

The arrival of new treatments has meant re-engaging those individuals and encouraging them to get on the meds. Fierer puts it simply and bluntly: “Get in now; we can do it now!”

According to Fierer, it’s vital that anyone with hep C see an infectious disease physician, liver specialist or gastroenterologist who specializes in the virus to establish the level of damage to the liver. Those who have cirrhosis, the most advanced stage of liver disease, are in the most urgent need of treatment.

Seeking HCV treatment is especially critical for coinfected people, since liver disease is one of the leading causes of hospitalization and death among HIV-positive people. Unfortunately, however, cure rates with currently available treatments can be lower for those with cirrhosis (though new treatments on the horizon may improve their chances).

Successful hep C treatment typically stops further liver scarring and may even reverse it, to an extent. Clearing HCV also lowers, but doesn’t necessarily eliminate, the elevated risk of cirrhosis, liver cancer, liver failure (if someone hasn’t already developed these conditions) and death among people with hep C.

A recent modeling study found that coinfected people who delay treatment until they have advanced fibrosis or cirrhosis are at a much greater risk of dying than those who are treated when they have minimal or no scarring.

Michael Gottlieb, MD, a Los Angeles HIV specialist who is Jeffrey Mende’s physician, says that one reason to consider delaying hep C treatment is if someone just isn’t ready to adhere to such an expensive regimen. Treatment costs may run $100,000 or more, so insurance coverage can be a challenge to secure, even when the physician, as Gottlieb says, “plays the HIV card” with the insurer.

One challenge HIV-coinfected people and their physicians need to negotiate is the potential for interactions between HIV and hep C medications. Some pairings may cause the levels of one of the drugs to drop, potentially jeopardizing the effectiveness of that treatment and leading to drug resistance.

Conversely, drug levels may increase and lead to toxic effects, such as damage to the kidneys in the case of raised levels of the widely prescribed HIV medication Viread (tenofovir), which is included in several combination tablets.

Fierer, for one, tries to avoid switching his patients' HIV regimens to accommodate particular hep C treatments, preferring a treatment for the latter virus that is likely to have fewer interactions with HIV meds.

For example, AbbVie's Viekira Pak (ombitasvir/paritaprevir/ritonavir; dasabuvir), which was approved in late 2014, has a greater number of identified serious potential drug interactions with HIV medications than Harvoni.

"The unintended consequences of switching antiretrovirals cannot be underestimated," Fierer stresses. He points to scenarios such as someone missing a week of HIV treatment because the pharmacy fails to deliver the new regimen on time, or someone getting confused and taking multiple HIV regimens at once. Switching HIV meds may also introduce new side effects or other toxicities.

Meanwhile, Kris Kowdley, MD, director of the Liver Care Network at Swedish Medical Center in Seattle, doesn't see much cause for worry when it comes to finding the right hep C treatments for his coinfected patients.

"It requires an additional step in the HIV-positive patient to make sure that they're on an antiretroviral regimen that will not be a problem," Kowdley says, adding that "some adjustment of the HIV regimen might need to be made." This could mean tinkering with the dose of certain medications, which would require switching to individual pills instead of a single-tablet combination HIV regimen if a person is taking one of those.

In addition, some HCV/HIV drug combinations may simply need close monitoring to make sure they aren't causing any health problems—for example, conducting regular tests of kidney function if someone is taking Viread.

Considering these potential drug-drug interactions, Jacob Langness, PharmD, a clinical pharmacy specialist in HIV and hepatology at the University of Colorado Hospital, says it's important to see a clinician who is experienced in coinfection treatment and is hopefully up to date on the evolving hep C research landscape.

Another good way to ensure your safety is by getting your medications from a pharmacy that regularly fills HIV and HCV prescriptions, which should hopefully have staff who are knowledgeable about potential negative interactions with hep C therapies.

As for Jeffrey Mende, his HIV medications weren't among the few that cause conflicts with Harvoni, so he was able to sail through hep C treatment with no shifts to his HIV regimen and no interactions between medications.

Since getting cured of hep C, he says, “I feel so much more energized. I’m sleeping better.” On the other hand, “My anxiety’s been high. But I think that’s just because we’re buying a house.”

## Hepatitis C Treatment Options

If you’re living with hep C, various factors will influence which treatments will be recommended for you, as well as how long you should take it (8, 12, 16 or 24 weeks), and what your likelihood of a cure will be.

The first factor is which genotype (genetic variant) of the virus you have. About 70 percent of Americans have genotype 1 (which is divided into types 1a and 1b), with the rest largely split between genotypes 2 and 3. Genotypes 4, 5 and 6 are rarer in the United States.

Other variables include whether you have been treated for hep C before and if you have cirrhosis.

The treatment recommendations below are according to the American Association for the Study of Liver Disease (AASLD) guidelines.

### Harvoni (ledipasvir/sofosbuvir)
(Gilead)

This single-tablet, once-a-day treatment is by far the most widely prescribed hep C regimen.

For those with genotype 1, cure rates in clinical trials of Harvoni were between 94 and 99 percent. Eight weeks of the single-tablet regimen are recommended if someone has not been treated before, does not have cirrhosis, and has a viral load below 6 million. Otherwise, people with genotype 1 should take 12 weeks of treatment, and 24 weeks if they have been treated before and have cirrhosis.

Harvoni is not FDA-approved to treat genotype 4, but it may be prescribed off-label for this purpose. In a recent study, 12 weeks of Harvoni cured 93 percent of people with genotype 4, half of whom had cirrhosis.

Harvoni is considered safe to combine with most HIV antiretrovirals.

### Viekira Pak (ombitasvir/paritaprevir/ritonavir; dasabuvir)
(AbbVie)

This regimen, which requires taking multiple pills each day, is an alternative to Harvoni for the treatment of genotypes 1 and 4, although treating the latter genotype is not FDA-approved.

Twelve weeks of treatment are recommended. Individuals with genotype 1a (a subtype of genotype 1) or who have cirrhosis should be treated for 24 weeks. Ribavirin is recommended as an adjunct for those with genotypes 1a and 4 and for those with genotype 1b who have cirrhosis. Cure rates for those with genotype 1 are comparable to Harvoni’s.

People with genotype 4 don’t need to take the dasabuvir component of Viekira Pak. In a recent trial of treatment-naive people with genotype 4 who did not have cirrhosis, 100 percent were cured if they took Viekira Pak (minus dasabuvir) with ribavirin and 91 percent were cured if they did not take ribavirin.

Taking Viekira Pak with HIV meds can be more complicated than with Harvoni. It is not recommended to pair the regimen with Sustiva (efavirenz), Norvir (ritonavir)–boosted Reyataz (atazanavir), Kaletra (lopinavir/ritonavir) or Edurant (rilpivirine).

Sovaldi (sofosbuvir)
(Gilead)
For those with genotype 2, a Sovaldi and ribavirin regimen is recommended for 12 weeks, or 16 weeks if they have cirrhosis. Genotype 2s with little or no fibrosis have a greater than 90 percent chance of a cure. In a recent small trial, treatment-experienced people with cirrhosis had an 87 percent cure rate after 16 weeks of treatment and 100 percent after 24 weeks. If they also took interferon and were treated for 12 weeks, the cure rate was 94 percent.

Genotype 3 is considered the most difficult to treat. Currently, 24 weeks of Sovaldi and ribavirin is the recommended regimen, although this will likely change if daclatasvir is approved. Those being treated for the first time have about a 92 to 94 percent chance of a cure, while those who failed a previous hep C regimen have a success rate in the 80 percent range, and people who have cirrhosis have only about a 60 percent cure rate.

Sovaldi is considered safe to use with most HIV medications.

Olysio (simeprevir)
(Janssen)
Olysio is not approved for use among people with HIV, although it may be prescribed off-label. There are numerous HIV medications that aren't considered a safe pairing with the hep C therapy, although finding a good combination is certainly feasible.

Daclatasvir
(Bristol-Myers Squibb)
Daclatasvir was recently approved for use in combination with Sovaldi to treat genotype 3 of hep C. In a major clinical trial of 12 weeks of the regimen given to people with genotype 3, including those with cirrhosis, 86 percent of those who had been treated before were cured, as were 90 percent of those treated for the first time.

Daclatasvir has minimal identified interactions with HIV medications.

The following is awaiting FDA approval (as of press time):

Grazoprevir/Elbasvir
(Merck)
This fixed-dose combo tablet will likely be approved to treat genotypes 1, 4 and 6 toward the end of 2015. In recent trials, participants with these genotypes had a 92 percent to 100 percent cure rate after 12 weeks of treatment, unless they had cirrhosis, in which case 89 percent were cured (except among those coinfected with HIV who had cirrhosis, in which case 100 percent were cured).

Grazoprevir/elbasvir is not recommended to be taken with Sustiva, Kaletra, or Norvir–boosted Prezista (darunavir) or Reyataz.

Editor's note: This article has been updated.

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