HEPATITIS C TREATMENT AND PREGNANCY

Of all the stories I hear, the most agonizing are those of mothers who have passed hepatitis C virus (HCV) to their children. Although the risk is relatively low that an HCV-positive woman will pass the virus to her baby (6 percent\(^1\)), it is tortuously high to those who carry the burden. This risk is substantially greater if the mother is co-infected with HIV (approximately 11 percent\(^2\) and perhaps much higher).

This adds up to 4000\(^3\) new hepatitis C cases in the U.S. every year. These 4000 hepatitis C infections are preventable, especially with the recent approvals of new HCV medications. Tragically, this preventable infection isn’t being prevented. Women of childbearing age are having problems getting the new hepatitis C drugs. If you want to know what the problem is, keep reading.

THE “OLD” DAYS OF HEPATITIS C TREATMENT

In the olden days (before 2014), hepatitis C treatment relied on peginterferon and ribavirin. Treatment was long, and these two drugs have many side effects, making them difficult to take. Ribavirin had an additional issue in that it could cause miscarriages and birth defects. This risk was so serious that the Food and Drug Administration (FDA) classified it in the Pregnancy Category X, and required ribavirin manufacturers to put this warning on the label:

Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin.

This meant that women had to make a difficult choice. Should they postpone having

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a baby for at least 72 weeks (48 weeks for the treatment plus the 6 months after)? Or, do they skip treatment, take a chance on pregnancy, and hope the odds will be in their favor that they do not pass HCV to the baby. If you were older, treating first might mean foregoing pregnancy altogether. Having babies first meant postponing treatment for many years since breastfeeding is not recommended while taking ribavirin. Also, the medication side effects are so intense that it is often suggested that women wait until their children are at least a few years old. I was such a wreck during my first treatment that I waited until my daughter was in college before I tried it again.

The “New” Days of Hepatitis C Treatment

Everything changed October 2014. The FDA approved Harvoni for genotype 1 patients. It was labeled Pregnancy Category B, which means, “Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.”

In short, Harvoni could be used during pregnancy, but only if the potential benefit justified the potential risk to the fetus. There was the added benefit of shorter treatment of 8 to 12 weeks, so if a woman delayed pregnancy, she did not have to wait long. Also, the safety of breastfeeding was not determined, so nursing might or might not be dangerous.

Two months after Harvoni was approved, Viekira Pak was approved. Viekira Pak is used with or without ribavirin. Viekira is also Pregnancy Category B, so noncirrhotic genotype 1b patients who use this drug combination without ribavirin may consider the possibility of pregnancy or breastfeeding during HCV treatment.

Sovaldi is in Pregnancy category B, but it is used with ribavirin or Olysio. Olysio is Pregnancy Category C, which states, “Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.” Olysio and Sovaldi would be a riskier proposition, but the risk is not as clearly dangerous as it is with ribavirin.

Now That We Can Easily Cure Hepatitis C, What’s the Problem?

The solution seems so simple: treat everyone who wants to be treated. However, the price of HCV treatment is so steep that many insurance companies and state Medicaid programs are denying treatment to patients unless they have advanced liver disease. Women who are pre-menopausal tend to have the least amount of fibrosis. This is because nature has a way of protecting women while they are fertile by giving them a hardier immune system. That benefit stops about the time we turn fifty, leaving us with graying hair and a deteriorating liver. (But, don’t mess with us because we are tough!)

So, if you are a young woman, it is unlikely that you fit the criteria for priority treatment. Although AASLD and IDSA assigned a higher priority to HCV-infected women of childbearing potential wishing to get pregnant, it looks like they were added in as an afterthought.
Women of childbearing potential are at the bottom of AASLD/IDSA’s list, preceded by men who have high-risk sexual practices with other men, active injection drug users, incarcerated persons, and those on long-term hemodialysis. However, except for the dialysis patients, the above groups are also routinely denied HCV treatment.

Lack of access to HCV treatment is immoral, but particularly so for fertile women. Treating women of childbearing age is both curative and preventive. I don’t see how insurers can live with themselves knowing that they can prevent 4000 babies from being born HCV-positive, or justify the anxiety caused to women when HCV treatment is denied.

**Women and Injection Drug Use**

The sad fact is that a large percentage of young women who acquire HCV did so via injection drug use (IDU). Since women are more likely to clear HCV spontaneously than men are, one would think that women who inject drugs are less likely to have hepatitis C than men. However, that is not the case.

A recent study found that female IDUs were significantly more likely to become infected with HCV than men were, most likely because of high-risk injecting behaviors. Women were significantly less likely to inject alone. Other risky injection practices included: injecting heroin/opioids, borrowing used syringes, reuse of a cooker previously used by another injector, injecting every day, pooling money with others to buy drugs, and having a steady IDU sex partner.

**What Women Need to Know about Current HCV Treatments**

If you are prescribed HCV treatment, and you are a woman who can still get pregnant, here is what you need to discuss with your medical provider:

- Are you or could you be pregnant?
- Which HCV treatment is recommended for you?
- Assuming you do not intend to get pregnant during your treatment, which birth control methods will you use?
- If prescribed Viekira Pak, be aware that ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches or contraceptive vaginal rings are contraindicated. To protect yourself against unplanned pregnancy, use progestin only or non-hormonal contraception. You may restart ethinyl estradiol-containing medications two weeks after finishing Viekira Pak.

**Final Words**

If you are a mother who has transmitted hepatitis C to her baby, please take these words to heart: **Forgive yourself. Your child needs a strong mother, one who faces the truth, and is a role model for living bravely with hepatitis C.**

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**Additional Resources**


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At last year’s CROI conference, I wrote about a 6-week study of sofosbuvir, ledipasvir, and GS-9451. This combination was tested against sofosbuvir/ledipasvir alone for 12 weeks and sofosbuvir/ledipasvir plus GS-9669 for 6 weeks. The drugs were combined into one-pill, taken once-daily. There were 20 patients in each arm.

The bottom line is that all 20 patients (100%) achieved a cure in the triple combination of sofosbuvir/ledipasvir and GS-9669 with 6 weeks of treatment. The most common side effects were headache, fatigue and diarrhea.

Comments: This study is a small study and there is currently no information that it has yet entered into phase 3 studies. But given the high cure rates and low side effects hopefully it will be entered into clinical trials with this combination or perhaps Gilead is researching another inhibitor to include.


Exclusivity Deals

Ever since AbbVie’s VIEKIRA PAK’s approval there have been intense negotiations between insurance companies/pharmacies and AbbVie and Gilead to determine who will be the exclusive distributors of the pharmaceutical HCV medications. These deals will help to drive down the costs of the drugs, and this will hopefully translate into more patients having access to HCV medications. The real downside is that the decision as to which medication a patient should be prescribed is now being made by someone other than a patient and medical provider. This is very bad news for patients (see “Predictors” article). The information below is from our blog as of the date that we have put together our newsletter. If you have been denied treatment in the past, you may want to check the list below (or our Blog) to find out if you would now qualify for insurance coverage. The agreements are on-going so keep checking back.

- **AbbVie**: Express Scripts, AIDS Drug Assistance Programs (ADAPs)
- **Gilead**: Aetna, Humana, Anthem, CVS
- **Both—AbbVie/Gilead**: Prime Therapeutics

Merck

In January, Merck announced that it has expanded its hepatitis C generic licensing agreements to include the investigational NS5A inhibitor GS-5816, which is being evaluated in Phase 3 clinical studies as part of a single tablet regimen that combines the compound and sofosbuvir for the treatment of all six genotypes of hepatitis C. If approved by regulatory authorities, the sofosbuvir/GS-5816 regimen would become the first pan-genotypic, all-oral single tablet regimen for HCV. A pan-genotypic therapeutic option is particularly important for developing countries, where genotype testing is often unreliable or not readily available.

In this respect, the development of a two-drug single pill (grazoprevir/elbasvir) will be accelerated. Merck hopes to apply for marketing approval in the first half of 2015. The combination is currently in phase 3 studies. Phase 2 studies of the two drug combination with and without ribavirin in multiple arm studies of monoinfected and HIV/HCV coinfected patient populations with and without cirrhosis resulted in cure rates from 90 to 100%. The most common side effects were fatigue, headache and general weakness.

Gilead

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1. **Fatigue** or feeling tired is the most common symptom of hepatitis C. It is also the most common extrahepatic (occurring outside of the liver) condition of hepatitis C. It is also one of the most common side effects of HCV therapy. It can range from mild to moderate to so severe that it can affect almost every area of life.

2. **Causes:** Fatigue can be caused by many factors besides hepatitis C. Be sure to talk with your medical provider before jumping to a conclusion that the cause is hepatitis C. Other factors that could be causing fatigue could be other extrahepatic manifestations of hepatitis C (thyroid problems, anemia, HCV treatment, depression, sleep problems, poor diet, lack of exercise, medications, alcohol use and so on).

3. **Self-help strategies:** After you have ruled out any other causes with your medical providers, there are many strategies to help improve your energy levels. We have an excellent *Guide to Understanding and Managing Fatigue* that can walk you through many self-help tips such as information on improving sleep, nutrition, exercise, meditation, complementary medicines and much more.

4. **HCV Treatment:** Severe fatigue is one of the extrahepatic manifestations that can qualify someone for treatment. Curing hepatitis C can also cure fatigue, though fatigue can worsen temporarily during treatment. Be sure to talk with your medical provider about the fatigue you are experiencing and other symptoms. Make sure to document all symptoms in your medical records. For some people, it is hard to complain or even talk about their symptoms. It is critical, however, to make sure that you document your complaints. Medical records are important for treatment and disability records.

5. **Support:** One way to fight fatigue is to join a support group (either on-line or in-person) and talk with others who are experiencing fatigue. Try to remember to take care of yourself and to practice self-care tips to keep you well and healthy.
In the past, there were many factors that predicted successful treatment outcome. Today, that list is much longer and is somewhat dependent on the particular HCV inhibitor used to treat hepatitis C.

This article is about the negative predictors of treatment response—genotype, subtype, cirrhosis, prior treatment response and viral load.

**Genotype:**

The most dramatic current negative predictor of treatment response is genotype 3. The current standard of care for treating HCV genotype 3, a combination of sofosbuvir (Sovaldi) plus ribavirin for 24 weeks, has an overall cure rate of 93%. Among those in the group who had never been treated (treatment naïve), the cure rate was 93% for those without cirrhosis compared to 92% for those with cirrhosis. Among treatment experienced patients in this test group, the cure rate was 85% for those without cirrhosis compared to only 60% for those with cirrhosis. Future treatments are needed for people with genotype 3 that have higher cure rates with shorter treatment durations, and which work in cirrhotic patients who have not responded to prior treatment.

**Subtype:**

Subtype has long been known to affect treatment outcome. In regards to genotype 1, subtype 1a is generally harder to treat. If we look at VIEKIRA PAK to treat HCV genotype 1a without cirrhosis, adding ribavirin is indicated. There is no recommendation to add ribavirin to VIEKIRA PAK for treatment of genotype 1b without cirrhosis.

**Cirrhosis:**

People with cirrhosis have always been harder to cure than those without it, although now it is not as difficult as in the past. The recommended treatment duration for genotype 1a patients with cirrhosis is 24 weeks with VIEKIRA PAK plus ribavirin. There is a note that 12 weeks can be considered for some patients based on prior treatment history.

**Treatment-Experienced:**

Patients without cirrhosis can be treated with HARVONI for 12 weeks. Treatment experienced (but not cured) patients with cirrhosis can be harder to cure, so 24 weeks treatment with HARVONI is recommended.

**HCV RNA or Viral Load:**

In the Full Prescribing Information for HARVONI for genotype 1, there is a footnote about the recommended treatment duration saying that “HARVONI for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.” This consideration is based on the ION-3 study of 123 patients with baseline viral loads under 6 million IU/mL who were treated for eight weeks. The cure rates were 97% (119 of 123 patients). This is only true with HARVONI. The viral load thresholds need to be studied in all of the newer therapies.

Even now, matching a person’s characteristics to the specifics of the HCV drugs can help cure most people. The future of hepatitis C treatment holds the promise that, when matched with all of a patient’s characteristics, new medicines or combinations of medications will be able to treat and cure everyone with HCV.

Source: Hepatology January 2015; Volume 61, Issue 1, pages 88–97

Reports show high rates of HCV reinfection among injecting drug users with history of HCV, along with reports of sexually transmitted HCV infection and reinfection in HIV-infected men who have sex with men. This research investigated viral quasispecies dynamics in patients who failed HCV treatment to determine whether treatment failure was associated with reinfection or reemergence of preexisting infection. Previous studies interpreted the evidence as reinfection; this study identified the subjects as having preexisting resistant HCV variants.

The Bottom Line: Resistant HCV strains are more likely the reason for failure to achieve a sustained virological response (SVR) in these study subjects. This could be the result of superinfection or a limitation on the ability to test these HCV strains.

Editorial Comment: Few words cause as much fear in me as “superinfection.” What this study did not discuss is whether the lack of SVR could be connected to immune factors in this study group.


Source: Journal of Viral Hepatitis December 2014; Volume 21, Issue 12, pages 938–943

The purpose of this cross-sectional study was to see if chronic hepatitis C virus (HCV) infection was associated with low muscle mass among adults.

Among 18,513 adults in the U.S., people with chronic HCV had a higher prevalence of low muscle mass compared to uninfected persons (13.8% vs. 6.7%). Even HCV+ persons without significant liver fibrosis had lower muscle mass.

The Bottom Line: Chronic HCV infection is associated with low muscle mass, even in the absence of advanced liver disease.

Editorial Comment: Few muscle mass is a risk factor for osteoporosis. This study strengthens the argument that we should treat people with chronic HCV, regardless of fibrosis stage.


Source: Journal of Clinical Gastroenterology published ahead-of-print October 8, 2014

Hepatitis C is one of many conditions that can cause cirrhosis, a severe scarring of the liver. This study assessed the prevalence of cirrhosis in the US, and defined some of the characteristics of this potentially deadly condition.

The prevalence of cirrhosis is higher in the U.S. than previously estimated (633,323 now versus previously estimated 400,000 adults). The researchers believe that the prevalence is even higher since this research relied on data from the NHANES survey, which did not collect data from people who were in the military, prison,
hospitalized, homeless, or institutionalized.

Alcohol abuse, diabetes and hepatitis C were contributing factors for the majority of those with cirrhosis. Non-Hispanic blacks and Mexican Americans, those living below the poverty level, and those with less than a 12th grade education had the highest prevalence of cirrhosis. Nearly 70% of those who have cirrhosis may not know they have it.

The Bottom Line: The prevalence of cirrhosis is significantly higher than previously thought.

Editorial Comment: The most common factors associated with cirrhosis are preventable – hepatitis C, diabetes, and alcohol abuse. Hepatitis C is curable; a public health program that identifies and cures this virus may reduce the burden of cirrhosis.


Source: Journal of Viral Hepatitis published ahead-of-print December 15, 2014

Hepatitis C is rarely studied in children, and little is known about the cognitive effects of hepatitis C in young patients. This Egyptian study compared cognitive function in 35 HCV-positive children to 35 HCV-negative children. Compared to HCV-negative children, the children with HCV had reduced function in the areas of vocabulary, comprehension, memory, abstract visual reasoning test, quantitative reasoning test, and intelligence quotients.

The Bottom Line: Children with chronic HCV in its early stages showed signs of cognitive impairment, particularly with memory. There appeared to be a correlation between cognitive function and immune response as measured by the production of cytokines.

Editorial Comment: This study is particularly heart breaking. Children are often the last to be studied, and the last to be treated. We tend to be afraid to treat children, understandably concerned that we may injure them. This study represents the tip of the iceberg, telling us how little we know about HCV in children.


Source: Journal of Viral Hepatitis January 2015; Volume 22, Issue 1, pages 18–24

This longitudinal research assessed the relationship between chronic hepatitis C virus (HCV) infection and survival rates. There were 675 subjects (nearly 80% male), enrolled in two detoxification units, with a median follow-up of three years.

The Bottom Line: The mortality rate was high for those with alcohol-related liver disease, regardless of HCV-status; more than 11% died (78 subjects). Risk of death was increased among younger HCV-positive participants compared to those who were HCV-negative. HCV/HIV co-infection was associated with increased risk of death.

Editorial Comment: This study speaks for itself. I can only add that if alcohol is a problem for you, please get help.
• HCSP Factsheet HCV and Women: Pregnancy, Childbirth and Breastfeeding
   www.hcvadvocate.org/hepatitis/factsheets_pdf/Wm_pregnancy.pdf
• Ribavirin Pregnancy Registry www.ribavirinpregnancyregistry.com

ENDNOTES
1 Centers for Disease Control and Prevention www.cdc.gov
4 Recommendations for Testing, Managing, and Treating Hepatitis C - American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) www.hcvguidelines.org
6 Higher Risk of Incident Hepatitis C Virus among Young Women who Inject Drugs Compared with Young Men in Association with Sexual Relationships: A Prospective Analysis from the UFO Study Cohort by Tracy D, et al. BMJ Open May 29, 2014
Get Tested. Get Treated. Get Cured.