There are also other reasons to be treated besides the goal of eradicating the hepatitis C virus. There is a growing body of evidence that suggests that treatment will help reduce liver inflammation, may reverse liver damage (scarring), slow down disease progression and improve symptoms and quality of life. All of these factors are important reasons to seek HCV medical treatment.

Another important step when considering treatment is to review the data on treatment response of the currently Food and Drug Administration (FDA) approved HCV medicines and to partner with a medical provider to make the best possible treatment choice. Part of this process is analyzing the data based on genotype and viral load.

Note: The predictors of treatment response listed below have varying degrees of affect on treatment response. The addition of an HCV inhibitor in some respects will overcome some of the negative predictive factors. Interferon-free therapies that include a combination of HCV inhibitors will greatly reduce negative predictors of treatment response.
Predictors of Treatment Response

Subtype
People with HCV genotype 1 subtype a (1a) respond more favorably than people with 1b. HCV inhibitors that target specific subtypes are in clinical development.

HCV RNA or Viral Load
Viral load is an important determinant of treatment response. The lower the HCV RNA (viral load) the better the chance of eradicating the hepatitis C virus.

- **Low viral load:** under 800,000 IU/mL
- **High viral load:** over 800,000 IU/mL

Some recent studies have suggested that the cut-off between low and high viral load may be set too high. These studies have shown that people with a viral load under 400,000-600,000 IU/mL respond better to current medications compared to those who have a viral load above 400,000-600,000 IU/mL. More data is needed to confirm these observations.

Age
In the past, older age (especially people over 40 yo) was a negative predictor of treatment response. However, some newer therapies are overcoming this.

Disease Severity
The more the liver is damaged or scarred, especially cirrhosis, the less likely it is that people will respond to current HCV medications.

IL28B
IL28B or interleukin 28B is part of our natural immune system that triggers our body to make more of a type of natural interferon called lambda interferon. The presence of a certain variation of IL28B called CC genotype indicates a better chance of producing a stronger immune response. The stronger immune response translates to a higher rate of natural clearance and treatment cure.

Race
In general, Asians tend to have the highest response rates to current HCV medications followed by Caucasians and African Americans. The reason for the lower treatment response rates of African Americans is not completely understood, but the non-presence of IL28B CC genotype may be responsible for the higher rates of chronicity of HCV in African Americans and the lower HCV treatment response rate. Many studies have ruled out factors such as adherence and/or socio-economic issues as the reason. Studies are underway to determine additional reasons for the lower treatment response.

The addition of an HCV inhibitor to pegylated interferon and ribavirin therapy has greatly increased the response rates in everyone infected with HCV—including African Americans.

Metabolic Disorders
There are several conditions that decrease the chances of responding to HCV therapy, such as insulin resistance, obesity, metabolic syndrome, and steatosis:

- **Insulin resistance** occurs when the pancreas produces and releases insulin after a meal to enable cells to absorb and convert glucose (carbs/sugar) into energy. In an individual with insulin resistance the normal levels of insulin do not trigger the absorption of glucose into cells, leading to an excess of glucose in the bloodstream. It is further complicated as the pancreas makes and releases more insulin in response to the elevated glucose levels.

- **Obesity** is defined by certain measurements, such as BMI (body mass index), waist circumference and the measurement of actual body fat. A person is considered obese if their BMI is greater than 30. Studies have found that people who are obese do not respond as well to HCV medications as those who are at a healthy weight.
Predictors of Treatment Response

- **Metabolic Syndrome** is a group of conditions or risk factors (high blood pressure, obesity, elevated triglycerides, decreased HDL cholesterol) that increase the chances of developing heart disease, stroke and diabetes. In some studies it has been found that people with HCV and metabolic syndrome do not respond as well to current HCV medications.

- **Steatosis** is defined as fatty liver or fatty infiltrates in the liver. Steatosis can speed up disease progression and lower treatment response. Due to the high prevalence of steatosis in people with HCV genotype 3 it is recommended that pegylated interferon and ribavirin treatment duration should be extended from 24 weeks to 48 weeks. There are no drugs to treat steatosis at this time, but some good strategies to reduce or control steatosis are to maintain a healthy lifestyle by eating healthy and nutritious foods, and to balance the amount of food consumed with regular exercise. Alcohol can also contribute to steatosis.

**Prior HCV Treatment Response**

The type of prior treatment response with interferon plus ribavirin therapy is predictive of successful HCV treatment with HCV protease inhibitor triple combination therapy. People who have relapsed after a prior course of interferon plus ribavirin have a very high likelihood of responding to treatment with the new HCV inhibitor combination therapies. People who are considered prior partial-responders will respond well to the new HCV inhibitor combination therapy, but not as well as relappers. Prior null-responders are the least likely to respond to HCV inhibitor therapy.

**On Treatment Predictors**

**Adherence**

It is not surprising that taking all of the prescribed medications is a positive predictor of successful treatment outcome. However, it is sometimes difficult to remember to take the medications all of the time and serious side effects may require dose reductions of the medicines. This is why it is so important to manage any side effects as soon as they occur—before they become so severe that a dose reduction or discontinuation of therapy is required. Adherence to taking all the HCV medications is even more important because of the risk of developing HCV drug resistance.

**Rapid and Early Virological Response**

Studies have found that rapid virological response (RVR) and early virologic response (EVR) are important predictors of a successful treatment response. RVR is defined as becoming HCV negative after 4 weeks of treatment. EVR is defined as having a 2 log drop in viral load (example: 1,000,000 IU/mL to 10,000 IU/mL) after 12 weeks of treatment, and cEVR (complete EVR) is defined as undetectable HCV RNA (viral load) after 12 weeks of treatment. eRVR

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**Treatment Response Terms:**

- **Relapser** is defined as a person who becomes HCV RNA undetectable at end of treatment, but then becomes HCV detectable within 24 weeks from the end of treatment. People who have relapsed after a prior course of therapy have the best chances of successful therapy.

- **Prior partial-responders**—a person who has a 2 log_{10} drop in HCV RNA by treatment week 12, but who does not become HCV RNA undetectable by end of treatment. Example: 2 log_{10} drop (99% decrease): 1,000,000 to \leq 10,000. Partial-responders also have high cure rates with the new triple combination therapy.

- **Null Responder:** A person who does not achieve a 2 log_{10} drop of HCV RNA by week 12 of treatment. Null responders are less likely to respond to the new combination therapy.
Predictors of Treatment Response

(extended RVR) is defined as HCV RNA undetectable at treatment week 4 and 12. In addition to predicting treatment response, becoming HCV RNA negative at certain time points is used to dictate treatment duration for some of the HCV medications.

The predictors to treatment response listed above can affect treatment response and overall liver disease progression. Some of these predictors, such as genotype, viral load, age, race, gender, and disease severity, can not be changed. Other factors are within the realm of change by lifestyle modification. Starting and maintaining a healthy lifestyle that includes a diet and exercise program can be very difficult and challenging. Anyone with HCV should work closely with a medical provider to design a healthy nutrition and exercise program tailored to his or her individual needs.

Related publications:

- **Olysio (simeprevir) Package Insert** *(Highlights of Prescribing Information)*

- **Sovaldi (sofosbuvir) Package Insert** *(Highlights of Prescribing Information)*
  www.hcvadvocate.org/hepatitis/factsheets_pdf/sovaldi_pi.pdf

- **Patient Assistance Programs**
  www.hcvadvocate.org/hepatitis/factsheets_pdf/Patient_Assistance.pdf

For more information

- **American Association for the Study of Liver Diseases**
  www.aasld.org

- **Centers for Disease Control and Prevention**
  www.cdc.gov

- **Food and Drug Administration (FDA):**
  www.fda.gov

- **Mayo Clinic**
  www.mayoclinic.com

Visit our websites to learn more about viral hepatitis:

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