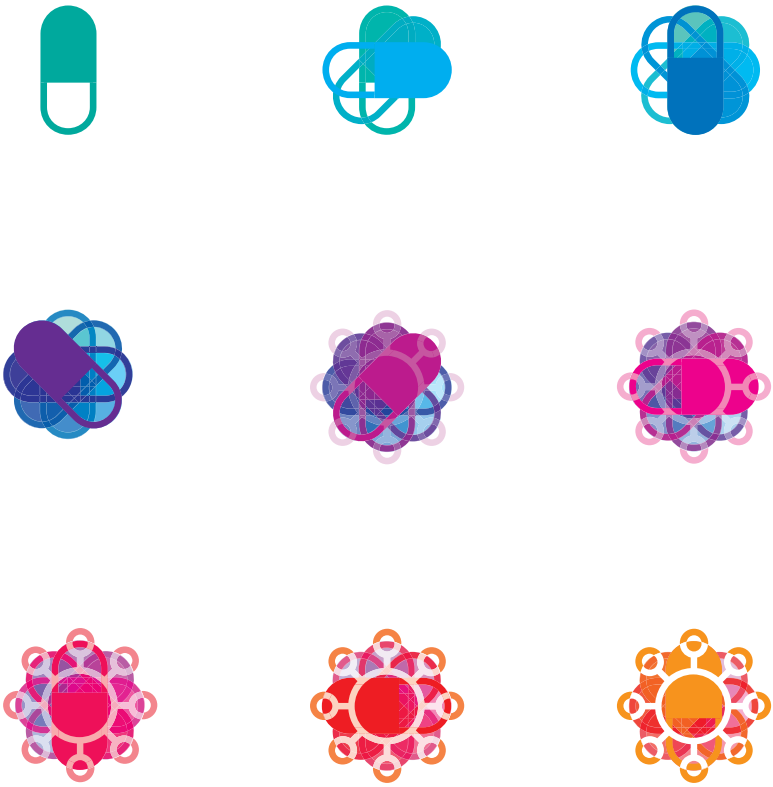
Guide to Clinical Trials for People with Hepatitis C

Second Edition



ABOUT TAG'S HEPATITIS/HIV PROJECT

TAG's Hepatitis/HIV Project draws from the core values and history of HIV activism, while incorporating hepatitis C-specific information into strategies targeting different constituencies, regions, and countries. The Hepatitis/HIV Project focuses on optimizing quality of, and broadening access to, HCV care and treatment for communities and individuals by continuing its domestic and international work with other activists, regulatory agencies, pharmaceutical companies, clinicians, and the patient community.

Guide to Clinical Trials for People with Hepatitis C
Second Edition
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We decided to write this guide based on both our work with people at risk for, or living with, hepatitis C virus (HCV) and our experience as AIDS activists. We created it with help from people living with hepatitis C and HIV/HCV and from our medical editors.

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Dedicated to Michael Carden

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This guide is dedicated to clinical trial participants everywhere.

INTRODUCTION

There are many new hepatitis C drugs being studied in clinical trials. People with hepatitis C have many options to choose from. Whether you have hepatitis C or another medical condition, deciding to participate in a clinical trial can be complicated. Having more information can help you decide whether or not to participate in a clinical trial, and which trial, or trials, may be right for you.

Some people are comfortable with a doctor's recommendation, while others prefer to make their own decisions about whether to participate in a clinical trial, and which trial is best for them. If you want to look for clinical trials or find out more about them, information is available online at www.clinicaltrials.gov.

The information in this guide is important because:

- People who participate in clinical trials are putting their bodies on the line. Regulations to protect trial participants vary from country to country. This guide was written in the United States, where there are federal regulations and guidelines to protect people from unreasonable risks during clinical trials. Trials in the European Union must follow the European Commission's Clinical Trials Directive, available online at: http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm#rlctd. Despite these safeguards, some risks are unavoidable when new treatments are being studied.

- If you decide to participate in a clinical trial, you should have information about all possible risks and benefits, so you can make the best choice for yourself.

- You need to feel comfortable asking questions and discussing all of your concerns with the research team.

- Most doctors have the best interests of their patients in mind, but some are paid to recommend, enroll, or refer people to trials. Learning about all your options can help you make the best decision for yourself, so it's always a good idea to ask what your doctor would recommend if you decide not to participate in a clinical trial. Sometimes it can help to get a second opinion from a doctor who is not involved in the trial.

- Some trials are riskier than others. For example, a clinical trial of a drug that has never been used in human beings may be riskier than a trial looking at how long to treat people with drugs that have already been approved.

The risks and benefits of enrolling in a clinical trial may depend on the type and stage of your hepatitis C, the drug or drugs that are being studied, as well as personal considerations.

This guide has eight sections:

SECTION 1. ABOUT CLINICAL TRIALS

Drug Development

Drug development is an uncertain process. Only one of 5,000 to 10,000 drugs that enter the first step of drug development (called ***preclinical trials***) is approved. The drug development process can take up to 12 years from beginning to end.

There are several steps, or ***phases***, of drug development. First, researchers identify a target (in this case, part of the hepatitis C virus). Then, they select compounds (which are chemical mixtures) that seem likely to work against the target, and they conduct additional tests in the laboratory.

Preclinical Trials

After promising compounds have been selected, preclinical trials begin in test tubes and animals. These trials focus primarily on safety; they check to see if the compound is harmful to any organs, look at the drug's effect on reproduction, and determine if it causes cancer. Preclinical trials help to identify what should be monitored when the drug is tested in people.

Preclinical trials also explore dosing. In animals, preclinical trials look at the relationship between the dose of a drug and its effects (whether or not it works, and if it causes side effects). This is called ***pharmacokinetics***. Animal trials also look at how the drug is absorbed, distributed, broken down (also called ***metabolized***), and eliminated (known as ***ADME***). Preclinical trials help to pinpoint the best dosing range to start with in human trials.

Clinical Trials

A clinical trial is an experiment done in people. Clinical trials of experimental drugs look at the following:

SAFETY: Is it safe?

Trials look at short-term and long-term side effects and toxicity. They find out if the drug, intervention, or treatment makes people feel sick, and if it causes short-term or permanent harm.

ACTIVITY: Does it do anything?

Trials monitor the response that a drug, intervention, or treatment produces. For example, Does the drug lower the amount of hepatitis C virus in the bloodstream?

EFFICACY: Does it work?

Trials assess whether the drug, intervention, or treatment produces a specific effect. For example, Can it cure the infection?

PHARMACOKINETICS: What does the body do to the drug?

Trials look for a dose that is effective and has the least possible side effects.

It is important to weigh the risks and the benefits of participating in a clinical trial. You may have special concerns, such as wanting to be treated near your home, not at a faraway clinic.

BENEFITS	RISKS
Gaining immediate access to a drug that may help (especially important to people with limited, or no other, treatment options)	Developing short-term or long-lasting side effects from an experimental drug (these range from mild to serious or life-threatening)
Undergoing monitoring and tests that are not available otherwise or not covered by insurance	Getting the placebo (a pill that does not contain any medication but looks identical to the experimental drug). However, there is also a risk to getting an experimental drug, because it may not always work, or can actually be harmful.
Contributing to the effort to find a better treatment or a cure for a certain disease	Being in the control arm of a trial (which compares the current treatment to the experimental drug) when the standard of care has changed. This means you will not have access to more effective treatment that is available outside of the trial.
Getting a very effective drug	Getting a drug that is not at all effective

BENEFITS	RISKS
Knowing that you are taking action to improve your health	Losing the opportunity to participate in future trials requiring that you have never been treated (this is called ***treatment-naive***) or because you have already received an experimental drug
Getting extra support from the research team to help you stay on treatment	Not getting the proper dose or length of treatment with an experimental drug (which can cause drug resistance; see About Drug Resistance and Treatment Adherence, page 24)
Being reimbursed to participate (this can range from a small stipend to thousands of dollars, depending on trial length, risks and procedures involved, and whether it is outpatient or inpatient)	Giving up more of your time for appointments and additional tests, and possibly having to go through a more complicated treatment

PHASE I

Phase I trials are the first trials in people. They mainly look at the safety of an experimental drug, which is compared to an identical, inactive substance (called a ***placebo***). Phase I trials are small (involving 20 to 80 people) and short-term (lasting days to weeks).

Although safety is the main focus in phase I trials, doctors and researchers also collect information about other things, such as how a drug is absorbed by the body, how it moves through the body, and how it moves out of the body. These trials look at what the body does to a drug, the effect of food on drug levels, as well as the side effects from a drug.

Phase I trials begin with a low dose of the drug (one that is much, much lower than the amount that was harmful to animals in preclinical trials). If the drug appears to be safe, the dose is gradually increased (called ***dose escalation***). These are called ***single ascending dose*** (SAD) and ***multiple ascending dose*** (MAD) trials.

Who can and cannot participate (called *inclusion* and *exclusion criteria*): Usually, phase I trials are open to healthy volunteers before people with the actual condition (in this case, hepatitis C). Some people are not allowed to participate in phase I trials such as children, people over 70 years of age, people with advanced liver disease or other illnesses, and pregnant or breast-feeding women.

If all goes well in the healthy-volunteer trials, people with hepatitis C can then enroll in phase I trials; usually this means people who have never been on HCV treatment.

Risk/benefit ratio: The more that is known about an experimental drug, the lower the risk of using it is. Although phase I trials are the first time the drug is tested in people, participating in phase I may be less risky than later-stage trials because the experimental drug is used for a short time at this stage, and there are many safeguards in place.

PHASE II

Drugs that are reasonably safe in phase I can advance to phase II. About two-thirds of drugs make it to phase II trials. Some trials are designed to move directly from phase I to phase II if there do not seem to be serious side effects (called ***phase I/II trials***).

Phase II trials are sometimes divided into two parts, known as IIa and IIb. The purpose of a ***phase IIa trial*** is to select the proper dose of a drug (more than one dose is usually studied) and to determine how often the drug needs to be taken (such as once daily versus twice daily, or even daily versus weekly). ***Phase IIb trials*** look at how well the selected dose, or doses, of a drug work (called ***efficacy***). Of course, safety is always closely monitored. In fact, phase II trials are usually the make-or-break point for a new drug; development is stopped if it becomes clear that the drug does not work or is too toxic.

Phase II trials are conducted at different sites and in different countries, and involve more than a hundred people. Hepatitis C trials need to follow people for at least 24 weeks after they have completed their treatment to see if it was successful, so final results may not be available for a couple of years.

Who can and cannot participate: Phase II trials are open to some people with hepatitis C virus. Eligibility may be limited to people who do not have ***cirrhosis*** (serious liver scarring), or people who have never been treated for hepatitis C. As with phase I trials, some people cannot participate in phase II trials. These include children, people with other illnesses, pregnant or breast-feeding women, people with advanced liver disease (including liver cancer or liver failure), and people who are waiting for, or have had, a liver transplant. Often, people who are taking certain medications are excluded, because the drugs they use have not been studied with the experimental drug, or because using them together is known to be harmful.

Risk/benefit ratio: Participation in a phase II trial can be risky, because people in phase II trials usually take the experimental drug for a longer period of time than in phase I trials.

PHASE III

Phase III trials (also called ***registration trials***) are the last step before drug approval. Phase III trials are randomized and controlled (see Trial Designs, page 13); they are often international, so that different groups of patients can be studied.

Phase III trials look at safety, monitor side effects, and test how well the drug works (usually in comparison to the current ***standard of care***—or best treatment available) in a large group (hundreds to thousands of people). They also study the best ways to use a drug, so that the drug's risks and benefits can be seen in, and applied to, a larger and more diverse group of people. Information from phase III trials goes into the labeling of approved drugs, so that doctors and patients can understand more about how to use them.

Who can and cannot participate: Phase III trials may have fewer restrictions than earlier trials; the elderly, and people with more advanced liver disease, may be eligible; people on a particular medication may also become eligible (if the company has already done a drug-drug interaction study and/or determined that the two medications can be safely and effectively used together). But participation in phase III trials may still be limited; for example, people who have already been on HCV treatment may be excluded.

Some groups of people cannot participate in phase III trials. Often, these are the same groups of people who were also ineligible for phase II trials.

Risk/benefit ratio: More is known about the drug, and the proper dose has been identified. Only 10% of drugs that make it to phase III fail, but there are still risks involved with participating in all phases of clinical trials, despite safeguards such as frequent monitoring.

PHASE IV

Phase IV trials are also called ***postmarketing trials***. These trials are done for several reasons. Sometimes, sponsors want their drug to be used in new groups of people who were excluded from earlier trials (such as HIV/HCV-coinfected people, children, or the elderly). Regulatory authorities may ask for longer follow-up, or for more information about drug safety and efficacy, in groups that were ineligible for, or underrepresented in, earlier trials. Often postmarketing trials look at women and children, people with advanced liver disease, people from certain racial and ethnic groups, or people with other illnesses.

Sometimes postmarketing trials look at different doses and durations of treatment to see if there is a better way to use a drug or a combination of drugs. These trials are important, since even the most well-designed development plan cannot address all questions about long-term safety and efficacy among all the different populations who will be using the drug.

Who can and cannot participate: Phase IV trials may be open only to certain populations, such as children, people who have cirrhosis, or liver transplant recipients, or they may compare treatment tolerability, safety, and outcomes in different populations (African Americans/Blacks and Latinos/Latinas, for example). Some people, such as pregnant or breast-feeding women, cannot participate in phase IV trials because they cannot use the study drugs for medical reasons (called ***contraindications***), or because they are not part of the group being studied.

Risk/benefit ratio: Phase IV trials usually do not open right away. Sometimes, the standard of care changes while a trial is open. This means that people who enroll in a trial may receive treatment that is less effective, or takes longer to work, than the new standard of care. Because the standard of care for hepatitis C is changing quickly, some people choose not to participate in trials unless they offer access to an experimental drug, or combination of experimental drugs.

In May 2011, the current standard of care for people with HCV genotype 1 changed with the approval of boceprevir (Victrelis) and telaprevir (Incivek), which are hepatitis C protease inhibitors (see Direct-Acting Antivirals, page 36). The ***control arm*** (or group that does not receive new treatments) in some hepatitis C treatment trials will now include one of these drugs plus peginterferon and ribavirin. Trials that opened before May 2011 use only peginterferon and ribavirin for the control arm. The standard of care for hepatitis C will continue to evolve over the coming years.

Trial Designs

A well-designed clinical trial should be able to provide information on the best way to use a single experimental drug—or combinations of experimental and approved drugs—while trying to keep risks low for trial participants. Trials ask questions, and use different designs to try to answer them. Knowing about the different types of trials, and the questions that are being asked in the trial, can help you make the best choice for yourself.

Some trials are ***randomized***, meaning people with similar characteristics such as age, weight, sex, race/ethnicity, and disease stage are assigned by chance—like flipping a coin—to receive a certain treatment. Sometimes these trials compare different doses of the same drug, to see which one is most effective and has the least side effects. Randomization helps to prevent bias (such as making sure that patients who are healthier or sicker get the experimental drug).

Some trials are randomized and ***controlled***; these trials compare the standard of care (plus placebo) to an experimental treatment. Participants in controlled trials will be randomized to receive either the standard of care that was current when the trial opened, or an experimental treatment. Clinical trials need to demonstrate that new drugs are safe. They also allow direct comparison of side effects, dose reductions, and drop-out rates between the current standard of care and the experimental drug.

In some randomized controlled trials, either the trial participants or the research team do not know who is receiving the experimental drug, and who is getting the placebo. These trials are called ***single-blinded***. In a ***double-blinded*** trial, neither the research team nor the trial participants know who is receiving the experimental drug or placebo. Blinding is used to lower the risk of trial participants dropping out or being treated differently by the research team.

Sometimes the research team and trial participants know what treatment they are receiving; trials like these are called ***open-label***. Sometimes open-label trials are randomized. Open-label trials are used to compare treatment strategies, or two very similar treatments—or used when there is no adequate placebo (peginterferon is a good example; substituting a placebo does not make sense because lack of side effects would make it obvious that peginterferon was not used).

Single-arm trials do not use a control arm; everyone gets the same treatment. Sometimes this design is used when there is already enough information on how well the standard of care works, or when the experimental treatment has already shown efficacy in earlier trials. Single-arm trials are also used when there is no other treatment available.

SECTION 2. ABOUT HEPATITIS C

What Is the Liver?

The liver is the largest internal organ. It is located on the right side of the body, under your ribcage. Your liver is a vital organ with several functions; these include filtering toxins, storing and breaking down fat, cholesterol, and carbohydrates, and making proteins and blood-clotting factors.

What Is a Virus?

Viruses are tiny infectious organisms that must enter the cells of another living being to make copies of themselves (called ***reproduction***).

What Is Hepatitis C?

Hepatitis C is a virus that enters the bloodstream and goes to the liver. If the immune system is unable to get rid of the virus, usually within a few months, hepatitis C becomes a lifelong infection unless it is cured with treatment (see Hepatitis C Testing, page 17, for more information).

Why Is Hepatitis C a Problem?

HCV can cause liver inflammation and scarring. Scarring happens because the immune system tries to prevent the virus from spreading by surrounding infected liver cells. Over time, scarring can become widespread. Mild-to-moderate liver scarring is called ***fibrosis***. Serious liver scarring that affects the liver's ability to function normally is called ***cirrhosis***. Experts estimate that 20% to 30% of people with chronic hepatitis C will develop cirrhosis over years to decades following infection. Even though all people with hepatitis C are at risk for liver cancer, it is more likely to develop in people who have cirrhosis. People with cirrhosis are also at risk for liver failure (called

decompensated cirrhosis). People with decompensated cirrhosis need a liver transplant.

Risk Factors for Cirrhosis

- **Alcohol** speeds up liver damage from hepatitis C, especially for heavy drinkers. The less alcohol a person drinks, the better for his or her liver.

- **Hepatitis B coinfection** can worsen liver damage from hepatitis C.

- **HIV coinfection** increases the risk for liver damage from hepatitis C, and also makes the damage happen faster. People with weaker immune systems (less than 200 CD4 cells) are at higher risk for liver damage from HCV. Keeping the immune system strong with HIV medication can help to slow down liver damage from hepatitis C.

- **Aging** is linked with liver damage. Liver damage is more likely to happen, and more likely to progress, in people who became infected with HCV when they were over 40 years of age than it is in younger people. This is because the immune system begins to slow down in people over 40 years of age, and liver cells may regenerate more slowly in older people.

- **Duration of HCV infection**: the longer a person has hepatitis C, the more likely it is that the virus has had time to cause liver damage. Experts estimate that cirrhosis can develop in 20 years, but this is different for everyone.

- **Metabolic factors**, such as obesity and insulin resistance (prediabetes), cause fat to build up in the liver; this is called ***steatosis***. Liver damage from hepatitis C is more likely in people who also have steatosis.

- **Being male** increases the risk for developing cirrhosis, although researchers are not sure why.

Hepatitis C Symptoms

Most people do not have symptoms when they become infected with hepatitis C, and people can have HCV for years without knowing it. The most common symptoms of chronic hepatitis C are fatigue, forgetfulness—which people often call ***brain fog***—and depression. These symptoms can happen whether or not a person has serious liver damage.

Once cirrhosis develops, people usually have symptoms. These include fluid build-up that causes swelling in the abdomen and legs, yellow skin and eyes (called ***jaundice***), itching, appetite and weight loss, and trouble sleeping. People with ***compensated cirrhosis*** (which means that the liver can still function despite scarring) can be treated for hepatitis C, and are eligible for most phase III trials.

Acute Hepatitis C

Curing HCV is most likely when it is treated within the first six months after a person becomes infected (this is called the ***acute phase***). Most people do not feel ill during acute hepatitis C, so many cases go undiagnosed. Future clinical trials will be exploring how best to treat acute HCV.

Hepatitis C Testing

Diagnosing hepatitis C is usually a two-step process, involving two different tests. The first test is for hepatitis C ***antibodies***, which are proteins made when a person's immune system responds to an infection. The second test looks for the hepatitis C virus itself, called ***HCV RNA***. Because some people (about one in four) clear hepatitis C on their own, without treatment, it is important to have both tests. Hepatitis C clinical trials require that participants undergo antibody and viral-load testing.

If you have been diagnosed with chronic hepatitis C, it means that antibodies to hepatitis C and the virus itself were found in your bloodstream.

Monitoring

During clinical trials, participants are monitored often—and thoroughly—to see how well the drugs are working, and if they are causing any laboratory abnormalities. Safeguards are in place, and you will be notified about abnormal lab test results.

Liver Enzyme Testing

Many people with hepatitis C already have elevated liver enzymes, which is a sign of liver inflammation. People with HCV usually have liver enzyme testing regularly. Liver enzyme levels are monitored even more often during HCV treatment, especially in clinical trials. Sometimes, medications used to treat hepatitis C can cause liver enzyme levels in the bloodstream to become abnormally high. Regular liver enzyme testing (and the additional monitoring done in clinical trials) is a safeguard, so that drugs can be stopped if there is a possibility that they are harming the liver (or other organs). This is one reason it's important not to miss trial visits (and to reschedule appointments if you need to).

Hepatitis C (Viral) Genotype

Genotype is another word for the genetic structure, blueprint, or code of all living things, including viruses. There are more than six hepatitis C genotypes, which were numbered in the order of their discovery. Each hepatitis C genotype has subtypes, which were lettered in the order of their discovery. In the United States, genotype 1 is the most common, and more people have genotype 1a than genotype 1b.

Before you enter a clinical trial, you will need a blood test to check your HCV genotype. Many hepatitis C treatment trials are for people with HCV genotype 1.

Race, Ethnicity, and IL28B (Host) Genotype

Peginterferon is more likely to work for Asian and Caucasian people than for African Americans or Latinos and Latinas. One of the reasons for this difference is genetic. Researchers have discovered a gene called IL28B that is linked to the outcome of HCV treatment. There are three possible variations of the IL28B genotype (since people inherit one copy of a gene from each parent): CC, CT, and TT.
A blood test for IL28B genotype is available.

The IL-28B CC genotype is found most often in Asians and Caucasians. People who have an IL28B CC genotype are most likely to be cured by peginterferon-based treatment, followed by people with a CT genotype. People with the TT genotype (which is more common among African Americans than Asians or Caucasians) are less likely to be cured by peginterferon-based treatment than people with the CC or CT genotype.

Clinical trials look at IL28B genotype, the amount of liver damage a person has, and how well a person is actually responding once he or she starts HCV treatment. These factors help doctors select the treatment regimen and duration most likely to cure hepatitis C. Ask if a trial requires you to have IL28B genotype testing, and if you can see your results; this information may help you make decisions about clinical trial participation.

Hepatitis C Viral Load

Hepatitis C viral-load testing (also called ***HCV RNA***) is used to diagnose HCV, to help predict treatment outcome, to monitor response during and after treatment, and sometimes to help determine how long a person needs be treated for HCV (see Stopping Rules, page 39, and Response-Guided Therapy, page 40).

Some trials provide HCV-RNA results; others do not. People may decide not to enter a trial unless they will be able to see their viral-load test results, because they want to know if they are responding to their HCV treatment as soon as possible. It's a good idea to ask whether or not you and the research team will have access to this information.

Checking for Liver Damage

There are different ways to assess liver damage, but many clinical trials require that you have a ***liver biopsy*** (removal of a small sample of liver tissue through a needle) within two or three years. Usually, people with bleeding disorders and people who have already been diagnosed with cirrhosis do not need to undergo liver biopsy.

Liver biopsy is a routine procedure, but it does have some drawbacks. It is not 100% accurate, can be painful, and carries a small risk of complications, such as internal bleeding or puncturing nearby organs. But it is the best way to find out how much liver inflammation (called ***grade***) and damage (called ***stage***) a person has.

Researchers are looking for less invasive ways to measure and monitor liver damage, such as groups of blood tests, and machines that look at liver stiffness using sound waves (called ***FibroScan***). Although these tests have not yet been approved in the United States as a biopsy substitute, they are sometimes used in clinical trials when biopsy is unavailable or inappropriate (such as in people with bleeding disorders).

Section 3. About Hepatitis C Treatment

What Is HCV Treatment?

The current standard of care for people with hepatitis C genotype 1 is a combination of three medications: peginterferon, ribavirin, and an HCV protease inhibitor. The standard of care for people with other HCV genotypes is peginterferon and ribavirin alone. But the standard of care for different HCV genotypes will change in the near future and continue to evolve with the development of new drugs.

Hepatitis C treatment with peginterferon and ribavirin works by getting rid of the virus in two ways. It stimulates the immune system to kill infected cells, and stops hepatitis C reproduction, to protect uninfected cells.

Adding an HCV protease inhibitor blocks an important step in the hepatitis C virus lifecycle, making it harder for the virus to reproduce (see What Is an HCV Protease Inhibitor?, page 22).

What Is Peginterferon?

Interferon is a protein, made by the immune system. Interferon helps to stimulate virus-fighting immune responses. Researchers discovered how to make interferon outside of the human body. Then, they attached a small molecule to interferon to make it last longer and work better—this is called ***pegylation***.

Pegylated interferon (also called ***peginterferon***) is both an antiviral and an immune-based therapy that is used to treat hepatitis C in combination with other drugs. Peginterferon is administered by a once-weekly injection for 24 to 48 weeks, depending on your HCV genotype, treatment history, and the condition of your liver (see Are You Experienced?, page 22).

What Is Ribavirin?

Ribavirin is an antiviral medication in pill, capsule, or liquid form that is used to treat hepatitis C in combination with other drugs. Although researchers are not exactly sure how ribavirin works against hepatitis C, they know that it is a very important part of HCV treatment, and that without it, cure rates are much lower. Ribavirin is taken twice a day for up to 48 weeks.

What Is an HCV Protease Inhibitor?

Boceprevir (Victrelis) and telaprevir (Incivek) are oral drugs. They are called ***protease inhibitors***, because they target hepatitis C's protease enzyme (see Protease Inhibitors, page 37). Either boceprevir or telaprevir—but never both—are used with peginterferon and ribavirin to treat hepatitis C genotype 1. Although both of these drugs are from the same family, they have different side effects and are used for different lengths of time. Cure rates vary according to which drug is used and other factors.

Other HCV drugs, called ***direct-acting antivirals*** (DAAs) prevent hepatitis C from reproducing by blocking certain steps in the HCV lifecycle (see About New HCV Drugs and Treatment Strategies, page 36).

Are You Experienced?

People who were treated with pegylated interferon and ribavirin (with or without other HCV drugs) but not cured are known as ***treatment-experienced***. This category also includes people who stopped HCV treatment because of severe side effects, and people who stopped HCV treatment without knowing the results.

There are different categories for treatment-experienced people, depending on what happened when they were treated in the past, and what they were treated with (if this information is available). The response to past treatment is one of the factors taken into account in clinical trials, because it helps to determine both the length and outcome of HCV treatment.

The United States Food and Drug Administration (FDA) has identified three categories for treatment-experienced patients:

> **Null Responder:** People who have less than a 2 $\log_{10}$ (or 99%) drop in HCV RNA after 12 weeks of peginterferon and ribavirin
>
> **Partial Responder:** People who have at least a 2 $\log_{10}$ (or 99%) drop in HCV RNA after 12 weeks of treatment with peginterferon and ribavirin, but in whom HCV RNA never becomes undetectable (this is sometimes called nonresponse)
>
> **Responder-Relapser:** People who have undetectable HCV RNA at the end of peginterferon and ribavirin treatment, but in whom HCV reappears, usually within three to six months of finishing treatment

Your HCV treatment experience is an important factor to consider before deciding to participate in a clinical trial. It is a good idea to ask your doctor if the drug, regimen, or strategy has been studied in treatment-experienced people, and what the results were. This can help you assess risks and benefits based on your past response to treatment (as well as other factors). For example, responder-relapsers are very likely to be cured by HCV treatment with peginterferon, ribavirin, and a protease inhibitor. On the other hand, null responders are less likely to be cured with peginterferon, ribavirin, and a hepatitis C protease inhibitor than are partial responders, and they are at higher risk for drug resistance if treatment fails (see HCV Reproduction and Drug Resistance, page 24).

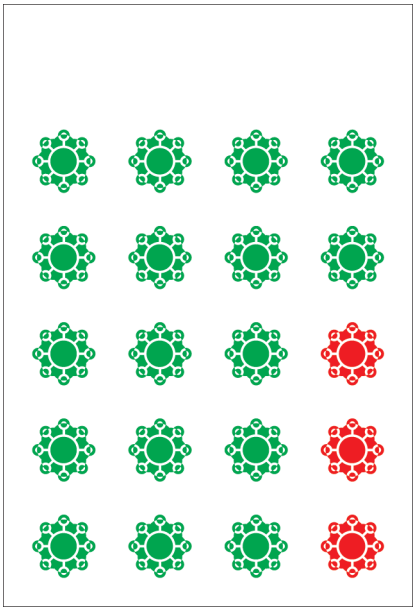
Cure rates among null responders are likely to increase with the use of new HCV drugs. Some trials have reported high cure rates among null responders treated with direct-acting antiviral combinations, with and without peginterferon and ribavirin.

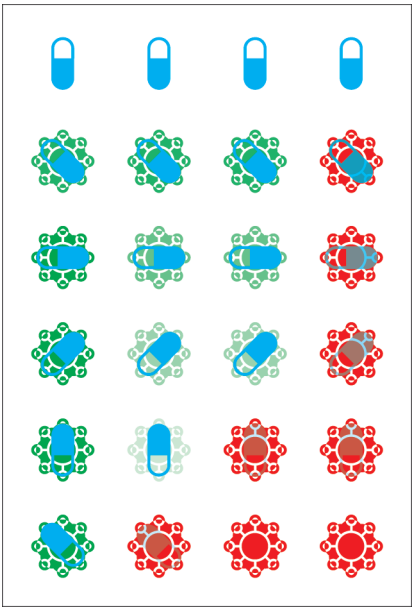
SECTION 4. ABOUT DRUG RESISTANCE AND TREATMENT ADHERENCE

HCV Reproduction and Drug Resistance

The hepatitis C virus finds liver cells (called ***hepatocytes***), enters them, and uses them to reproduce. Hepatitis C can reproduce many times in the same hepatocyte before it becomes worn out and dies.

Each day, hepatitis C makes billions of copies of itself. Out of all of these, there are usually some that are not identical to the original virus (these are called ***wild-type***, shown in green below). Copies with errors—or changes in their genetic structure—are called ***mutations***, shown in red below.

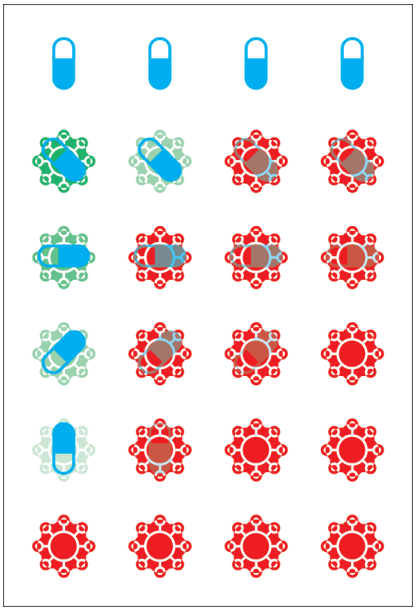


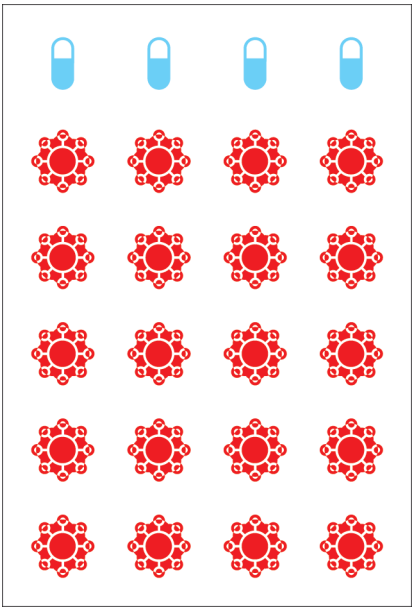


Mutations happen at random. The more the virus reproduces, the more likely it is that mutations will develop. Mutations can make it easier or harder for a virus to reproduce, and can prevent drugs from being effective.

Most people already have natural HCV mutations that cause resistance to certain HCV drugs, even though they have never taken the drugs. This does not mean that the drug won't work at all, but that the drug will not work by itself. Hepatitis C needs to be treated with a combination of drugs that attack it in different ways. These drugs help your immune system to kill infected cells, and they protect uninfected cells by preventing hepatitis C from reproducing.

If trial participants skip or stop taking their HCV medication, both wild-type HCV, and HCV with mutations that cause drug resistance, can multiply. Once a person begins taking his or her medication again, it will kill the wild-type virus, but it won't work against the resistant virus anymore.





Mutations can cause resistance to a single drug, to a whole family of drugs (called ***cross-resistance***), or to drugs from different families (called ***multiclass resistance***). Sometimes, the amount of drug-resistant virus shrinks over time after a person has stopped HCV treatment. But resistant virus may pop back up if the person tries the same drug, or one from the same family. No one is sure about how long HCV drug resistance lasts, or what impact it will have on a person's future treatment options.

People usually have many hepatitis C viral-load tests during HCV clinical trials to see if the treatment is working for them. Most hepatitis C clinical trials have ***stopping rules*** to lower the risk for drug resistance. This means that if a person's HCV becomes detectable after having been undetectable, or does not decrease by a certain amount within a certain period of time, that person needs to stop taking trial medications so that the virus does not continue to mutate.

What Is Adherence?

Adherence means sticking to, or staying with, something. For example, when you brush your teeth every day you are being adherent to your dental care regimen. If you miss brushing occasionally, you are less likely to have any dental problems than if you stop brushing your teeth for days at a time. The more times you miss brushing your teeth, the greater the impact on your dental health.

Adherence to medications is important. You need to be as adherent as possible so that you will get the best results from your treatment. But adherence can be difficult. Some people have a hard time taking a ten-day prescription of antibiotics, usually because they begin to feel better and think that the antibiotics have already done their job.

The most common reason why people miss doses is that they simply forget about their medication. In today's busy world, people may have difficulty with taking medication at regular intervals because of other responsibilities, such as work and childcare.

Adherence can be trickier when drugs need to be taken over a longer period of time, or when someone is taking several medications with different dosing schedules and food requirements. Side effects can make people not want to take medications regularly—or at all. Sometimes people stop taking medications because they are depressed—and depression can be a side effect of peginterferon as well as a symptom of hepatitis C itself (see About Side Effects, page 30).

Whether or not you are in a clinical trial, adherence to HCV treatment can be challenging. It can involve at least two drugs, which may have different dosing schedules and food requirements (from a light snack to a high-fat meal). Some regimens include peginterferon and/or ribavirin. Peginterferon is injected once a week. It seems like it would be easier to remember a once-weekly injection than remembering to take pills at different times each day, but using peginterferon less often may make it easier to forget. Ribavirin, a pill, is taken twice daily. HCV protease inhibitors and other direct-acting antiviral drugs are also pills; some need to be taken every 7 to 9 hours, while others are taken once or twice daily.

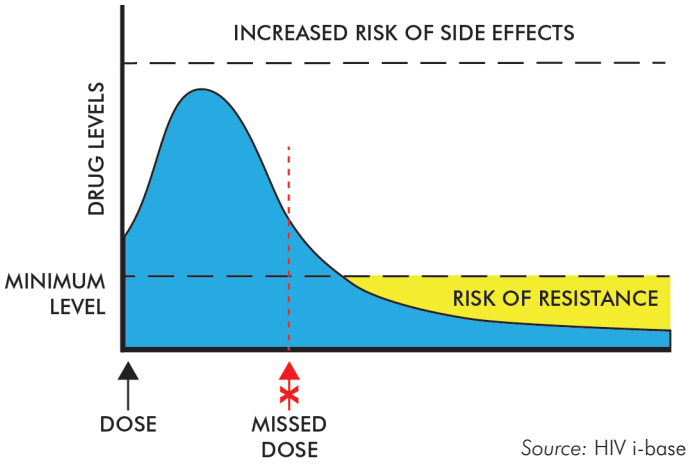
Sometimes your doctor will manage certain side effects from peginterferon and ribavirin by temporarily stopping or lowering your dose. This can make it difficult to remember your dosing schedule. It's helpful to remember two things: **hepatitis C can be cured, and you have control over the most important part of your treatment, which is adherence.**

Why Adherence Matters

Drugs are made to work according to their dose and how often they are taken, so it is important to take medication as instructed. Every drug is different, which is why some medications need to be taken at certain intervals, such as twice or three times a day.

Sticking to the dosing schedule will keep the amount of medication in your bloodstream within a certain range, so the amount of drug in your blood does not get too low or too high. Drug levels that are too

high can cause or worsen side effects. When drug levels get too low, the drugs may not be effective. With hepatitis C antiviral drugs, this means that if you skip a dose of your drug, the amount of drug left in your bloodstream gets so low that there is not enough drug left to stop HCV from reproducing, and you may develop resistance (see HCV Reproduction and Drug Resistance, page 24).



Source: HIV i-base

It is important not to get weighed down if you miss a dose of your medication. Take your medication as soon as you remember—unless it is too close to the next scheduled dose—then try to get back on schedule. Staying on a medication schedule takes time to get used to, but you can do it with a little support and confidence in yourself. Give yourself credit for getting treated. Although HCV treatment can be challenging, you can get through it!

Getting Help with Adherence

Make sure you completely understand your dosing schedule as soon as you get medication or a prescription from your doctor. Don't be afraid to ask your doctor and the research team for adherence support. They have ways to help you take your medication regularly. Remember, you won't be at the clinic every day—so, if possible, ask family and friends for help as well.

Think about how you can fit the dosing schedule into your lifestyle. Some medications need to be stored in the refrigerator, and others may need to be taken with food. Make sure to ask if your medications need to be taken with food, and if this means a snack or a full, high-fat meal, so that you can be prepared. Visible reminders can also help with adherence. Think about your routine, and any regular activities. For example, if you drink coffee first thing in the morning, keep a reminder by your coffee pot; if you watch television each evening, keep a reminder by your TV set. Some people like to use text messages and alarms to help them remember to take their medication.

Often, trials measure adherence. Different methods are used to track adherence. These include counting pills at each trial visit, keeping a medication diary, or using a pillbox marked with the days of the week and times when you need to take medication. Some trials use Medication Event Monitoring System (MEMS) caps, which count the number of times you open your bottle of medication and record it onto a microchip.

Over time, it may become easier to take your medication regularly, but sometimes it may become more difficult. If you are feeling challenged, let your doctor and support network know that you need any help. The good news is that HCV treatment is not lifelong—you will be taking medication for a year or less.

SECTION 5. ABOUT SIDE EFFECTS

What Is a Side Effect?

A side effect is any extra physical or mental symptom caused by a drug. In clinical trials, side effects are called ***adverse events*** or ***AEs***. These can be mild to life-threatening (called ***serious adverse events***, or ***SAEs***). All of the side effects that occur during clinical trials must be reported to the Food and Drug Administration.

Side effects of approved drugs are listed on their label, according to how often they were seen in clinical trials. Sometimes side effects are not reported until long after a drug has been approved. This is because certain side effects are rare, and drugs need to be studied in, or used by, thousands of people to see less common side effects. Since clinical trials are usually too small to pick up rare side effects, they are most often reported after the drug has been on the market.

In addition to the side effects reported in earlier trials, experimental drugs may have side effects that no one is yet aware of. When you participate in a clinical trial, you may experience unexpected drug side effects.

Information about the risks of participating in a clinical trial should be spelled out in a document called the ***informed consent***. You will be given the informed consent to read and sign before entering the trial (see Your Rights and Responsibilities in a Clinical Trial, page 42).

Managing Side Effects

During HCV clinical trials, people need to be monitored closely and seen regularly, so that side effects can be promptly and effectively managed. Open and honest communication is important. You don't need to be shy while discussing your concerns about side effects.

Ask your research team about all possible side effects, and how they will be managed, especially if you experience them late at night or over the weekend. Some people like to have this information in writing, because it can be difficult to remember.

Often, side effects are short-lived and happen while your body is adjusting to a new medication. **But it is very important to tell the research nurse or doctor about side effects right away, so they can see if your side effect is serious**.

If you are in a clinical trial and cannot tolerate the medications, you have the right to drop out of the trial. If you decide to leave the trial, it is important to explain why you decided to stop taking the medication. Some trials will continue to follow people even if they have stopped taking the medications.

Side Effects from HCV Treatment and Tips for Managing Them

Some HCV clinical trials involve peginterferon and ribavirin. These drugs have well-known side effects, and tolerating them can be hard. Luckily, there are many ways to get help with side effects from the research team. Joining a support group, or speaking with people who have been on HCV treatment, can be very helpful.

The most common HCV treatment side effects are:

- **Flu-like symptoms** (fever, aches and pains, headache, chills, appetite loss, and nausea) often happen during HCV treatment.

Usually, flu-like side effects from peginterferon are worse on the second and third day after injection. Sometimes, people who are working during HCV treatment inject their peginterferon on Friday night, so that they have the weekend to rest. Low-dose acetaminophen (Tylenol) is often used for aches, pains, and fever. Some people take antinausea medication; nausea can also be managed by avoiding greasy, spicy, or fried foods, sipping flat, caffeine-free soda, and by not lying down for an hour after meals.

Dronabinol (Marinol) is a man-made version of the active ingredient in marijuana. Dronabinol can help with nausea and stimulate your appetite. This can be important because weight loss is common during HCV treatment. Some trials may not allow use of dronabinol.

Dehydration can make people feel much, much worse during HCV treatment. Drinking plenty of water is important for lessening flu-like symptoms.

Fatigue is a common symptom of HCV, as well as a side effect from its treatment. Getting plenty of sleep, taking naps, and engaging in regular but light exercise (when possible) can help.

- **Emotional symptoms** (depression, anxiety, irritability, insomnia, mania, mood swings, and psychosis) can be side effects of peginterferon; ribavirin may also cause depression and irritability.

These side effects can range from mild to very serious. Although it happens rarely, some people have reported that they've felt like taking their own lives (and a smaller number of people have committed suicide during peginterferon treatment). People who have been depressed in the past are at higher risk of becoming depressed during HCV treatment. But people who have never been depressed before may also experience depression during HCV treatment.

It's important to have access to mental health care before and during HCV treatment, so that these side effects can be treated promptly if it becomes necessary. Usually, clinical trials involving peginterferon check with participants regularly to see if they have become depressed, or are experiencing any other mental health problems.

Some people decide to start taking an antidepressant before treating their HCV to prevent—or lessen—depression during treatment. Antidepressants and other mental health medications have their own side effects. Some experts think it is better to provide these drugs only if and when people need them. Certain psychiatric medications do not

mix well with HCV drugs, so before you start treatment, it is important to discuss any medications you use (including herbs and supplements) with your doctor. Ask your research team if they work with a mental health care provider, and how they can be of help if you need it.

- **Laboratory abnormalities** (such as low red or white blood cell counts, and low platelets—which help your blood to clot).

Sometimes, these side effects can show up in blood tests before you feel them. This is why clinical trials closely monitor participants. It is important to have regular blood tests during clinical trials. This helps the research team to identify and treat these laboratory changes as soon as possible.

Anemia (low red blood cell count)

Peginterferon, ribavirin, and some of the hepatitis C protease inhibitors can lower red blood cell counts (a condition called ***anemia***). Usually, anemia makes people feel weak and tired. Anemia can also cause shortness of breath and lightheadedness. If it goes untreated, anemia can become serious, and even life-threatening.

Anemia is managed in different ways. Severe anemia can be treated with a blood transfusion. Otherwise, your doctor may decide to lower the ribavirin dose or take you off it altogether (although this may have an impact on your response to treatment). Anemia can also be treated with injections of red blood growth cell factor (although many trials do not allow this). Ask your research team how anemia will be treated during the clinical trial.

Neutropenia (low white blood cell count)

Neutropenia is an abnormally low amount of neutrophils, a type of white blood cell that fights bacterial infections.

People with neutropenia are at higher risk for developing bacterial infections. Peginterferon can cause neutropenia, and boceprevir, an HCV protease inhibitor, may worsen it.

If a person's neutrophil count becomes too low during HCV treatment, his or her peginterferon dose is usually reduced, but sometimes neutropenia is treated with an injectable white blood cell growth factor. It is important to ask your research team how neutropenia will be managed.

Thrombocytopenia (low platelets)

Thrombocytes, or ***platelets***, help blood to clot so bleeding stops. ***Thrombocytopenia*** can be caused by serious liver damage (because the liver helps to make platelets) and by other medical conditions. Peginterferon can also cause thrombocytopenia, and boceprevir, an HCV protease inhibitor, may worsen it. Thrombocytopenia can be treated by lowering the dose of peginterferon, or with medication that increases the amount of platelets. If thrombocytopenia becomes severe, it can have life-threatening consequences such as intracranial hemorrhaging (bleeding inside of the skull). If severe thrombocytopenia develops during HCV treatment, all medications are usually stopped.

Liver enzymes

Liver enzymes are also closely monitored during clinical trials, because some HCV drugs can cause liver inflammation. Sometimes an increase in liver enzymes is temporary, but in serious cases, drugs may need to be stopped to prevent liver damage.

Bilirubin is a yellowish-brown substance left over after the liver breaks down old red blood cells; it is found in ***bile***, a fluid made by the liver. Many drugs, including some HCV protease inhibitors, can cause bilirubin levels to increase. When there is too much bilirubin in the bloodstream, a person's skin and eyes may turn yellow; this is called ***jaundice***.

- **Skin problems**

Some HCV drugs (including ribavirin, and boceprevir and telaprevir [HCV protease inhibitors]), can cause rash and itching. Most rashes are mild to moderate, but they can become serious, even life-threatening. Sometimes, the rash will appear in ***mucous membranes*** (such as the mouth, nose, anus, rectum, and the urethra, where urine and semen pass out of the body). It is important to let the research team know right away if you develop a rash, especially if your mucous membranes are involved. Ask what to do if this happens late at night or over the weekend. You may need to have the rash looked at right away, especially if you have a fever, a stuffy or runny nose, a cough, and aching muscles or joints. A rash can be managed in different ways, but sometimes drugs may need to be stopped.

- **Miscellaneous side effects**

Other common side effects of HCV treatment include bad or metallic taste in the mouth (called ***dysgeusia***), hemorrhoids and anal itching, nausea, diarrhea, dizziness, headaches, fatigue, skin reactions after exposure to sunlight, jaundice, and temporary hair thinning or hair loss.

SECTION 6. ABOUT NEW HCV DRUGS AND TREATMENT STRATEGIES

Research breakthroughs over the last decade have brought many new HCV drugs from the laboratory into human trials, and more are on their way. New trials are announced frequently. It is important to ask questions, so you can understand the risks and benefits of participating in a clinical trial based on your individual health status and treatment needs (see Questions, page 44).

New HCV drugs, when used in combination with pegylated interferon and ribavirin, have increased cure rates among people with genotype 1, and can sometimes shorten treatment from 12 months to 6 months. Despite this progress, there is still plenty of room to improve HCV treatment. Pharmaceutical companies are working on drugs and strategies to simplify treatment, reduce side effects, shorten treatment, and cure more people.

Clinical trials are exploring different treatment strategies, such as shortening duration of peginterferon (called ***interferon-sparing***); using peginterferon and ribavirin only as a rescue therapy when treatment with other drugs is not working; or using peginterferon-free and/or ribavirin-free regimens.

Direct-Acting Antivirals

Some of the new HCV drugs are called direct-acting antivirals (DAAs), because they target certain steps in the HCV life cycle to stop the virus from reproducing (also called ***replication***). There are many clinical trials of DAAs, because some types of these drugs have already worked. Other types of treatments are also being explored, such as therapies that stimulate the immune system to fight hepatitis C; gene therapy; and injectable silibinin (milk thistle extract).

There are different DAA drug families, called ***classes***. Each class targets a specific step in the HCV life cycle. A single DAA will not stop hepatitis C reproduction for too long, because HCV makes billions of copies of itself each day; some of these copies may be drug-resistant (see HCV Reproduction and Drug Resistance, page 24). DAAs need to be used in combination with each other or other drugs, including peginterferon and ribavirin.

DAA classes include protease inhibitors, NS5A inhibitors, non-nucleoside polymerase inhibitors, and nucleoside and nucleotide polymerase inhibitors.

Different treatment strategies are being explored, such as using peginterferon and ribavirin before, during, and after treatment with one or more DAA, or using DAA combinations without peginterferon.

Protease Inhibitors

Merck's boceprevir (Victrelis) and Vertex's telaprevir (Incivek) are the first generation of HCV protease inhibitors—and the first DAAs to receive FDA approval. Several other protease inhibitors are in development; most of them will work only for people with hepatitis C genotype 1.

The protease enzyme plays an important part in hepatitis C reproduction. The virus uses it like a pair of scissors to cut viral proteins into smaller pieces, so that they can be put back together as individual hepatitis C virus particles (called ***virions***). Protease inhibitors work by binding to the protease enzyme so it cannot cut—the same way that inserting something between scissors blades prevents cutting.

Known side effects of HCV protease inhibitors include low white- and red blood cell counts, low platelet counts, rash, anal itching and hemorrhoids, fatigue, nausea, vomiting, diarrhea, dysgeusia, headaches, dizziness, increased sensitivity to sunlight, jaundice, and elevated liver enzyme levels.

NS5A Inhibitors

NS5A is a protein that is part of HCV. Researchers have not discovered all of the functions of NS5A, although they know that HCV cannot reproduce without it. Some NS5A inhibitors work against all HCV genotypes, not just HCV genotype 1.

Known side effects of NS5A inhibitors include low white blood cell counts, headache, diarrhea, vomiting, dysgeusia, and liver enzyme elevations.

Polymerase Inhibitors

There are three types of polymerase inhibitors: nucleosides, nucleotides, and non-nucleosides. ***Nucleoside*** and ***nucleotide polymerase inhibitors*** are defective copies of HCV's own polymerase enzyme. Nucleoside and nucleotide polymerase inhibitors insert themselves into the hepatitis C virus as it is being made, but because they are not actually part of the virus, the virus cannot attach itself to them, and reproduction is prevented. In other words, these drugs create viral dead ends.

Nucleoside and nucleotide polymerase inhibitors work against all HCV genotypes.

Non-nucleoside polymerase inhibitors bind to different spots of the hepatitis C polymerase, thus changing its shape (like partially filling in the holes in Swiss cheese). They prevent the virus from reproducing in the same way that a motorcycle in the middle of a parking place prevents a car from being able to park there. Hepatitis C offers at least four different binding sites as targets for non-nucleoside polymerase inhibitors. Non-nucleoside polymerase inhibitors work against HCV genotype 1 only.

Side effects reported in trials of nucleoside/tide and non-nucleoside polymerase inhibitors include low white and red blood cell counts, nausea, vomiting, abdominal pain, flatulence, chills, headache, dizziness, fatigue, chest pain, muscle pain, rash, and increased sensitivity to sunlight.

The Lead-in

Lead-in means that people start out with one treatment before others are added. The lead-in can be used as a treatment strategy or as a screening strategy. In hepatitis C trials, peginterferon and ribavirin are usually used for lead-in, but sometimes a combination of DAAs is used instead.

The lead-in is used as a strategy to lower the hepatitis C viral load (and hopefully get rid of resistant virus) before adding an additional experimental drug or drugs. Researchers hope that the lead-in will lower the risk of resistance to an experimental drug.

Lead-in can also be used as a screening strategy, to see how well the backbone of a regimen (such as peginterferon and ribavirin) works for someone. This will identify people who do not respond to these drugs and prevent them from being exposed to the DAA alone or virtual monotherapy (meaning treatment with a combination of drugs, but only one that is working). Virtual or actual monotherapy can lead to drug resistance and unsuccessful treatment.

Stopping Rules

Stopping rules (also called ***futility rules***) are guidelines developed in clinical trials that are used to spot—as early as possible—when treatment is unlikely to work. Stopping rules are designed to lower the risk of drug resistance in people who are unlikely to respond to HCV treatment, and to prevent unnecessary side effects. Stopping rules are based on a person's response to treatment, measured by their hepatitis C viral load at certain time points. Stopping rules differ for individual drugs and may differ for treatment-naive versus treatment-experienced people.

Response-Guided Therapy

Response-guided therapy (RGT) means that the length of treatment is individualized. With response-guided therapy, treatment duration is planned according to the hepatitis C viral load at 4, 8, 12, or 24 weeks, depending on the treatment regimen. Some people will be able to shorten treatment, but the full 48 weeks of treatment is still recommended for people with serious liver damage and people who do not have an early response. There are specific terms developed for each time point, and each is related to the likelihood of a cure.

HCV Treatment: Milestones and Time Points

RVR: ***Rapid virologic response*** (RVR) means that HCV RNA cannot be detected in the blood after 4 weeks of treatment. RVR is a milestone for response-guided therapy.

eRVR: ***Extended rapid virologic response*** (eRVR) means that HCV RNA is undetectable at week 4, and remains undetectable through week 12. An eRVR is often used to determine the duration of treatment and predict the likelihood of a cure.

pEVR and **cEVR:** These stand for ***partial early virologic response*** (pEVR) and ***complete early virologic response*** (cEVR). A pEVR means that HCV RNA has dropped by at least 2 $\log_{10}$ (99%) after 12 weeks of treatment. A cEVR means that no hepatitis C virus can be detected in a person's bloodstream after 12 weeks of treatment. People who have a cEVR are more likely to be cured than people who have a pEVR.

Breakthrough: ***Breakthrough*** means that HCV RNA reappears during treatment after HCV RNA became undetectable. This can happen even when people adhere to medication, but it is more likely when people have skipped doses or stopped taking medication, or when drug resistance has emerged. Usually, a second HCV-RNA test is done to confirm viral breakthrough. In most cases, all drugs are stopped.

EOT: ***End-of-treatment response*** (EOT), means that a person has finished HCV treatment, and has an undetectable viral load. This does not mean that a person has been cured. A person is considered cured only when hepatitis C virus stays undetectable for six months after finishing treatment.

SVR-24: This means that hepatitis C has stayed undetectable (that is, there has been a ***sustained virologic response***) for ***24 weeks*** (six months) after the end of treatment. Most people are now using the term ***cure*** instead of ***SVR***.

SVR-12: This means that HCV has stayed undetectable (that is, there has been a ***sustained virologic response***) for ***12 weeks*** after the end of treatment. SVR-12 is considered a good predictor of SVR-24.

SVR-4: This means that HCV has stayed undetectable (that is, there has been a ***sustained virologic response***) for ***4 weeks*** after the end of treatment.

Relapse: ***Relapse*** means that HCV has reappeared in a person's bloodstream after the end of treatment.

SECTION 7. DECIDING TO PARTICIPATE IN A CLINICAL TRIAL

Your Rights and Responsibilities in a Clinical Trial

The informed consent process is one of the most important safeguards for clinical trial participants. During this process, you will be given a document—called an ***informed consent***—to read and sign before entering a trial. The informed consent should provide complete and detailed information about what is involved with participating in a clinical trial. It should also describe other treatment options, if they are available, to help you decide whether to participate in the trial.

The informed consent will explain the purpose of the trial, and the known risks and benefits involved with participation in the trial. Information about risks may include known or suspected drug toxicities, side effects, drug-drug interactions, possibilities of drug resistance and cross-resistance, and—of course—the risk of taking a drug that does not work.

The informed consent will describe your rights and responsibilities as a participant, as well as the responsibilities of the institution conducting the trial. The informed consent will also explain what to do and whom to call in case something happens to you during the trial.

You will get a complete explanation of what is expected from you as a participant. This includes every procedure that you will undergo; when, where, and how often you will need to go to appointments for the trial; and how long the trial will last.

The informed consent also includes information on which (if any) drugs and medical procedures are part of the trial, and on any medications, medical procedures, laboratory tests, or other expenses that you (or your insurance) will be expected to cover.

Some trials will provide, or reimburse for, childcare, transportation, and parking, if necessary; make sure to ask. Some trials pay participants. The amount of and schedule for payment should be included in the informed consent. Reimbursement is meant to cover the cost of your time. The amount offered reflects the risk involved, the number and type of procedures, and how long the trial is. If reimbursement is your main reason for participating in a clinical trial, make sure to carefully weigh the risks against the benefits. There are ethical safeguards in place—including the informed consent process—to prevent unnecessary and excessive risks, but these do not eliminate all of the risks involved.

Informed consent forms are legal documents. They are usually long, and often use unfamiliar medical terminology that can be difficult to understand. Don't rush. Make sure that your questions are answered thoroughly and clearly, in language that you can understand. Don't be embarrassed or ashamed to keep asking questions; the research team should be available to answer all of your questions.

It is okay to wait before signing the informed consent instead of doing it on the spot. Sometimes people like to ask a doctor, or family members, friends, or advocates, about a trial before deciding to participate. You have the right to ask for a copy of the informed consent so that you can take it with you and discuss it with other people. You may be able to talk to people who are participating in a trial, or who have done so in the past; their experiences can be helpful.

Do not sign the informed consent until you understand what is involved with participating in a clinical trial and have decided that it is the right thing for you to do. Although the informed consent is a legal document, it is not a binding contract. It should explain that you have the right to drop out of the trial at any time.

Once you have read and understood all the information, and you have decided to participate, you must sign and date the informed consent. Make sure to ask for a copy, so you can refer back to it if necessary.

SECTION 8. QUESTIONS

Participating in a clinical trial is a big decision, so it is important to have as much information as you need. Begin making a list of questions in advance, as they occur to you, so that you are prepared for appointments. If you can, ask a friend, family member, or other advocate to accompany you, so that you can talk with them afterwards.

Basic Questions

What is the purpose of the trial?

Who is going to be in the trial?

Why do researchers believe the experimental treatment being tested may be effective? Has it been tested before?

What kinds of tests and experimental treatments are involved?

How do the possible risks, side effects, and benefits in the trial compare with my current treatment?

How might this trial affect my daily life?

How long will the trial last?

Will hospitalization be required?

Who will pay for the experimental treatment?

Will I be reimbursed for other expenses?

What type of long-term follow-up care is part of this trial?

How will I know if the experimental treatment is working?

Will results of the trials be provided to me?

Who will be in charge of my care?

Source: Understanding Clinical Trials [Internet]. National Institutes of Health. Updated: September 2007. Cited: September 2012. Available from: http://clinicaltrials.gov/ct2/info/understand.

Here are some additional questions to get you started:

If I decide not to join this trial, what treatment do you recommend?

Where can I find more information about the trial?

If you were me, would you sign up for this trial?
If so, why? If not, why not?

Can I get the experimental drug or drugs if I don't participate in the trial?

Will I be able to get the experimental drug after the trial if I got the placebo?

Will I be able to continue taking the experimental drug after the trial ends?

Will I know if I am getting the experimental drug?

How do I know if the drugs in the trial will work?

Will I have access to my own results, and when?

When will I get the results?

How well do you think I will do?

What are my treatment options after the trial if I do not do well?

What do you think are the biggest risks involved with this trial?

Do you think these drugs are safe for me?

What side effects will I experience in the trial?

How will you help me to manage them?

If a bad side effect happens, what should I do and whom should I call, especially if this happens after hours or over the weekend?

Can I leave the trial if I get side effects?

Who is responsible if something happens to me during the trial?

Who is responsible if something happens to me soon afterwards that seems to be related to experimental drugs?

How many pills do I have to take every day?

How many times a day will I have to take pills?

Will I be injecting medication? If so, can you show me how, so that I know I'm doing it the right way?

If I don't want to inject the medication, can I come to the clinic to have it done?

Do I have to stop working in order to participate?

If I have to take time off from work, will I be reimbursed for it?

If I need childcare to participate, will I be reimbursed for it?

Is my personal information kept confidential?

What are my legal rights to my blood and tissue samples and my personal medical history?

Can I still visit you during the trial or call to ask questions?

Is there a support group, or do you know someone in the trial I can speak to?

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