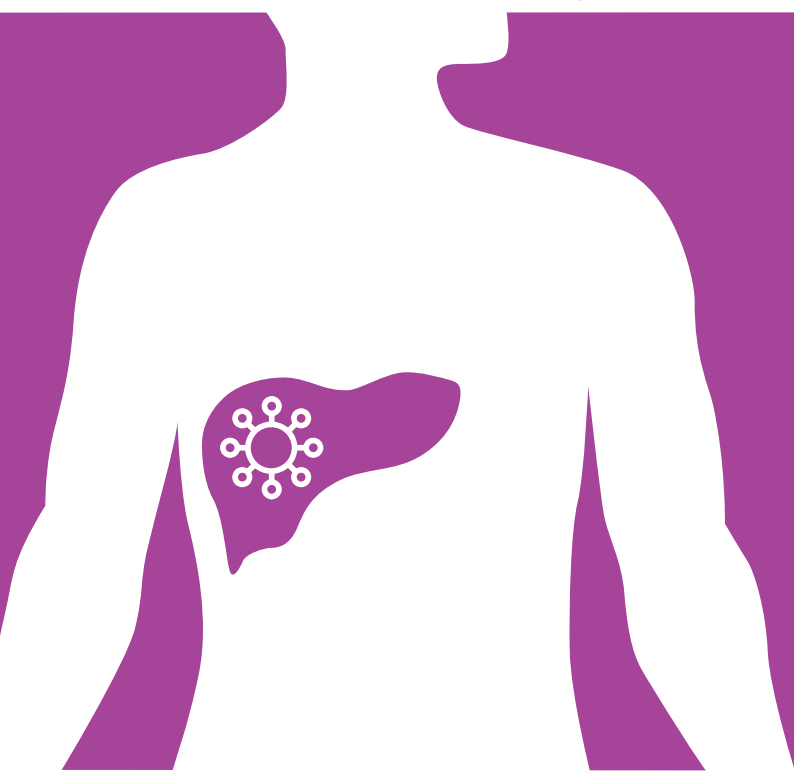


# TRAINING MANUAL FOR TREATMENT ADVOCATES



HEPATITIS **C** VIRUS & COINFECTION WITH HIV

## 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 the 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.

This publication was supported by a grant from the Open Society Foundations. Thanks to our contributors, to TAG's board and staff, and to TAG's generous donors, who have made this work possible.

**Written by:** Karyn Kaplan and Tracy Swan

**Edited by:** Andrea Benzacar, Lei Chou, and Tim Horn

**Designed by:** Lei Chou

# TAG

**Treatment Action Group**

261 Fifth Avenue, Suite 2110

New York, NY 10016 U.S.A.

[www.treatmentactiongroup.org/hcv](http://www.treatmentactiongroup.org/hcv)

TRAINING MANUAL FOR TREATMENT ADVOCATES:

Hepatitis C Virus and Coinfection with HIV

© Treatment Action Group 2013

ISBN 978-0-9895740-0-6

permission to use w/o copyright

## TABLE OF CONTENTS

Section 1. About Hepatitis.....	3
Section 2. About the Liver.....	7
Section 3. Transmission: How You Get It, How You Prevent It.....	11
Section 4. Natural History: What Happens to People with Hepatitis C?.....	14
Section 5. HCV Diagnostics.....	17
Section 6. HCV Diagnostics for Making Treatment Decisions.....	21
Section 7. HCV Treatment and Side Effects.....	24
Section 8. How to Tell if HCV Treatment Is Working.....	28
Section 9. Treatment for People Who Use Drugs or Alcohol Users and Treatment Issues for HIV/HCV-Coinfected People.....	32
Section 10. Fighting for New HCV Drugs.....	35
Appendix	
Handout on working with your health care providers.....	36
“Track your labs” sheet.....	38
Handout on viral hepatitis.....	39
Drugs and IL28B fact sheets.....	43

# TRAINING MANUAL FOR TREATMENT ADVOCATES:

## **Hepatitis C Virus and Coinfection with HIV**

The purpose of this manual is to provide information for you and your community. This information can be used to advocate for access to prevention and diagnosis of, and care and treatment for, hepatitis C virus (HCV).

The information here is written by and for people who are not medical specialists. We are treatment activists who learned about hepatitis C because it was a problem for people in our communities. We designed it to help you understand basic information about hepatitis C and coinfection with HIV: how it is transmitted, how to prevent hepatitis C, how a person can find out if he or she has hepatitis C, what happens to both HIV-negative and HIV-positive people who have hepatitis C, information used for making treatment decisions, and treatment options.

This manual is organized into short sections, and each section can be shared with a small group of people in less than one hour.

There are **discussion points** and **action steps** at the end of each section. The discussion points are intended to start conversations about the key issues raised in each section. The action steps are intended to start conversations about how to translate the key issues into advocacy in the community and to allow participants to find solutions together.

## SECTION 1: ABOUT HEPATITIS

### Hepatitis Means “Swollen Liver”

**Hepatitis** is a general term for swelling (inflammation) of the liver (*hepa* comes from the Greek word for liver, and *itis* means swelling). Many things can cause your liver to become swollen, including

- drinking a lot of alcohol;
- taking certain medications or herbs;
- inhaling toxic fumes;
- autoimmune diseases that cause the immune system to attack healthy tissue in the body; or
- infections, including viral hepatitis.

### Viral Hepatitis

There are six different hepatitis viruses: Hepatitis A, B, C, D, E, and G. These viruses were named alphabetically, in the order that they were discovered. Each of these viruses acts differently. Most people who have viral hepatitis don't know it, because they don't have any symptoms, but some people do have jaundice (yellow skin and eyes), appetite loss, nausea, vomiting, dark urine and pale stool, fever, aches, fatigue, and liver or abdominal swelling.

#### Hepatitis A (HAV)

HAV infection is usually not serious, but it can make some people feel very ill. There are no treatments for HAV because the body usually clears the virus by itself, and people recover without treatment. It rarely causes liver damage, and HAV is very rarely fatal.

#### Hepatitis B (HBV) and Hepatitis C (HCV)

HBV and HCV are the two most serious hepatitis viruses. Although some people can clear HBV and HCV without treatment, HBV and HCV become chronic (lifelong) infections for most people. Treatments are available for chronic HBV and HCV, and some people can even be cured. Although not everyone with chronic HBV or HCV will need treatment, some people will develop serious liver damage, liver cancer, or liver failure if they go without treatment, although this takes many years. Most deaths from liver disease are caused by chronic HBV and HCV.

#### Hepatitis D (HDV)

HDV only occurs in people who already have HBV. Some people may have been infected with both viruses at the same time. A person cannot get HDV unless they already have hepatitis B. About 20 percent of people will clear HDV without treatment. The other 80 percent develop chronic HDV infection, which worsens HBV, and can lead to cirrhosis (serious liver scarring that can lead to liver failure) or sudden liver failure.

### Hepatitis E (HEV)

HEV goes away without treatment, and often has no symptoms. It is usually not serious, but can become life-threatening during pregnancy, particularly in the third trimester.

### Hepatitis G (HGV)

HGV, often called **GB virus C** (GBV-C), does not make people sick or cause liver damage.

## Viral Hepatitis Can Cause Serious Liver Disease

Chronic HBV and HCV are “silent” illnesses; usually, people do not have symptoms until they have serious liver damage, which takes many years to develop. Many deaths from serious liver disease can be prevented with earlier diagnosis and treatment. Learning more about viral hepatitis and sharing the information with your community can help save lives.

## Vaccines Can Prevent HAV and HBV

Hepatitis A and hepatitis B can be prevented with vaccines. There is no HCV vaccine, although researchers are working to develop one. People can become infected with more than one hepatitis virus at the same time, and they can also be coinfecting with HIV. Coinfection with more than one virus can make you sicker, which is why people who have chronic HCV or HIV should be vaccinated against HBV and HAV.

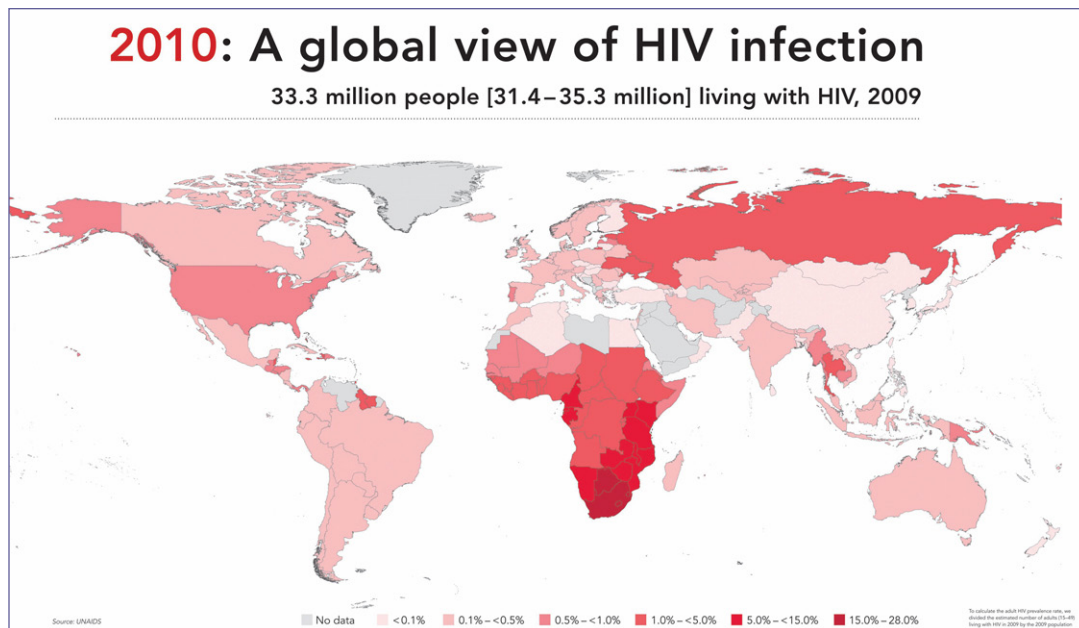
## HIV and Viral Hepatitis Epidemiology: Who Has It?

**GLOBAL HCV PREVALENCE:** Worldwide, an estimated **185 million people** have HCV.



Source: Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat. 1999 Jan;6(1):35-47.

**GLOBAL HIV PREVALENCE:** Worldwide, an estimated **34 million people** are HIV-positive.



Source: UNAIDS. Report on the Global AIDS Epidemic. 2010. Available at: [http://www.unaids.org/documents/20101123\\_2010\\_HIV\\_Prevalence\\_Map\\_em.pdf](http://www.unaids.org/documents/20101123_2010_HIV_Prevalence_Map_em.pdf) (Accessed on 2013 September 28).

## GLOBAL PREVALENCE OF HIV/HCV COINFECTION

Globally, approximately 10–30 percent of people with HIV are coinfecting with HCV.

In countries where injection drug use is the biggest risk factor for HIV transmission, as many as 7 of 10 people living with HIV are coinfecting with HCV. These include countries in Asia, Eastern Europe, and the Middle East.

In countries where sexual behavior is the biggest risk factor for HIV transmission, HCV coinfection is less common, but still a concern: about 1 in 10 people with HIV are coinfecting with HCV.

## HCV IN THE UNITED STATES

There is not enough information on how many people have HCV in the U.S. The lack of reliable data is a barrier in fighting the HCV pandemic. Even in the United States, data on HCV are not sufficient, especially in key populations such as people who inject drugs (PWID).

According to the Centers for Disease Control and Prevention (CDC), approximately 3.2 million people in the United States have chronic HCV infection. Hepatitis C is most common among “baby boomers”—those born between 1945 and 1965—the majority of whom were likely infected during the 1970s and 1980s, when rates were highest.

## HCV and African Americans in the United States

Hepatitis C is more common among African Americans than Mexican American or white Americans (this information comes from the third National Health and Nutrition Examination Survey [NHANES], which did not include homeless or incarcerated persons; information on members of additional racial and ethnic groups was classified as “other”). Overall, NHANES estimated that 1.8 percent of people in the United States have been infected with HCV, but rates were twice as high in African Americans versus whites (3.0% vs. 1.5%) and lowest among Mexican Americans (1.3%). The highest rates of HCV were found among African American men between 40 and 49 years of age: 13.6%.

## HCV and Social Conditions

HCV is more common among people with less than 12 years of education, and those living below the poverty line, regardless of race or ethnicity.

Although no one has done a formal survey of HCV among incarcerated persons, studies in Maryland and California have reported rates (30% and 34%) that are far higher than that of the general population, and experts estimate that each year almost 1.5 million people with HCV go through correctional facilities.

### ADVOCACY EXERCISE

#### Discussion Questions:

1. Do you know someone who has gotten sick from viral hepatitis?
2. Do you know if you've been vaccinated against HAV and HBV?

#### Action Steps:

1. How can you use this training manual to share information about viral hepatitis with others in your community?
2. Do you know how to find more information about HCV in your country or region?



## SECTION 2: ABOUT THE LIVER

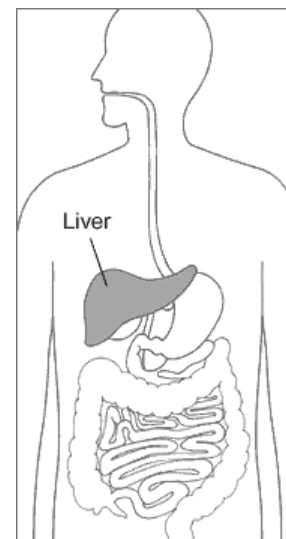
The liver is an organ in the body that has many critical functions. When the liver becomes very damaged (such as by chronic viral hepatitis), it cannot work properly. Liver damage can lead to life-threatening complications, such as cirrhosis, liver cancer, and liver failure.

### The Liver Performs Many Important Functions

The liver is the biggest organ inside the human body, found on the right side, underneath the rib cage. Your liver works as a filter and processing plant for your body. Anything you eat, drink, and inhale passes through the liver. Your liver also breaks down herbal remedies, vitamins, and drugs—whether or not they are legal.

Each day, your liver

- filters waste from the blood;
- stores vitamins, minerals, and iron;
- changes food into energy;
- makes bile (a liquid that your body uses to digest fat);
- helps balance sugar and hormone levels;
- makes cholesterol; and
- creates the hormone that helps to produce platelets, which stop bleeding by clotting blood.



### Immune Response to Viral Hepatitis Infection Causes Liver Damage

HCV does not directly cause liver damage—the way a person’s immune system responds to the virus is what can cause liver damage. The immune system tries to get rid of infected liver cells by surrounding them and walling them off; over time, this creates scarring in the liver. Although the liver grows new cells, cells that are already scarred cannot become unscarred. As the scarring worsens, the liver hardens, making it more difficult for blood and other important fluids to pass through it. These fluids, which are usually filtered by the liver, can build up to toxic levels in the bloodstream when the liver is too damaged to function.

Liver damage from HCV happens slowly, usually over decades. It can take from 15 to 50 years for an HIV-negative person who has chronic hepatitis C to develop cirrhosis.

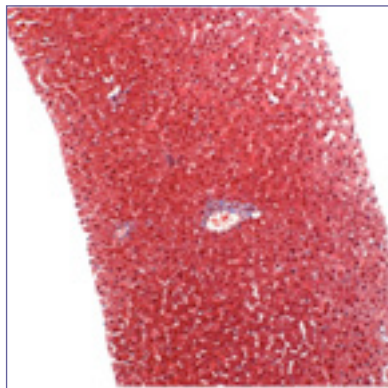
### Some things cause faster liver damage from viral hepatitis:

- Being HIV-positive—especially if you got HCV after getting HIV;
- Being coinfecting with HBV and HCV;
- Drinking alcohol, especially heavily;

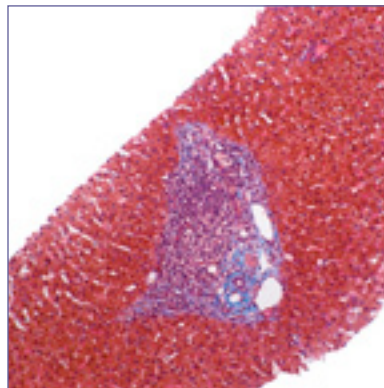
- Age over 40;
- Having fat in your liver (a condition called **steatosis**), usually in overweight people, heavy drinkers, or people with metabolic disorders;
- Being male (but researchers don't understand why); and
- The amount of time you have had hepatitis C—the longer you've been infected, the more likely you are to develop liver damage.

Having chronic HCV does not always mean that you will have serious liver damage, or that you need treatment. Some people live with hepatitis C for many years and will never have liver damage.

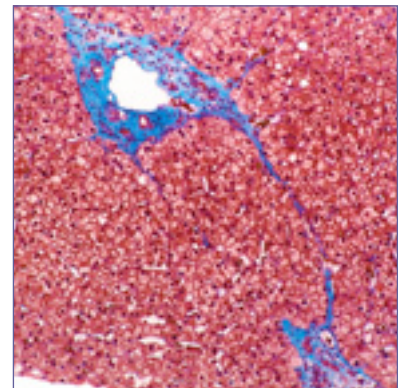
### Stages of Liver Damage



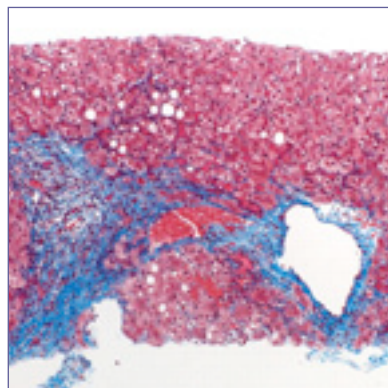
No Fibrosis (F0)



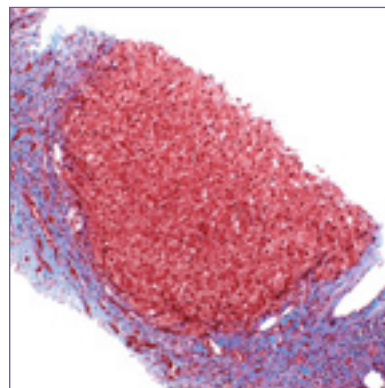
Mild Fibrosis (F1)



Mild-Moderate Fibrosis (F2)



Moderate-Severe Fibrosis (F3)



Cirrhosis (F4)

Source: Faria SC, Ganesan K, Mwangi I, et al. MR imaging of liver fibrosis: current state of the art. *Radiographics* 2009;29:1615–1635.

Some people develop mild liver scarring, called **fibrosis**. Having HCV and being overweight can cause fat to build up in the liver, a condition called **steatosis**. People with steatosis are at higher risk for liver damage.

**Compensated cirrhosis** means the liver is still able to function even though it is scarred. People with compensated cirrhosis are at risk for liver failure, liver cancer, and other serious complications. Liver failure, also called **decompensated cirrhosis**, or **end-stage liver disease** (ESLD), means that the liver can no longer do its job, and that a liver transplant is necessary.

Liver cancer (also called **hepatocellular carcinoma**, or HCC) is very serious. It is very difficult to treat, especially if it is not caught early. Although there is not a standard test for liver cancer, doctors use a combination of tests to screen for liver cancer, and researchers are working to develop better methods for early detection of liver cancer.

Preventing development or progression of liver disease by getting rid of HCV is the primary goal of HCV treatment. It is important for people to find out if they have HCV, because treatment doesn't work as well in people who already have cirrhosis. People with cirrhosis remain at risk for liver cancer even after they have been cured of HCV, and should be screened regularly.

### **Alcohol: Harmful to the Liver**

Alcohol is hard for the liver to break down, even in people who don't have hepatitis C. In people with HCV, alcohol hurts the liver by increasing inflammation and scarring, which leads to cirrhosis. Heavy drinking increases the risk for cirrhosis in people with all types of viral hepatitis, including HCV.

Even though experts have not agreed on a safe amount of alcohol, many recommend complete abstinence from alcohol, or limiting it to a small amount on special occasions. Doctors do agree that the less that a person with hepatitis drinks, the better. Some studies found that men who drink 50 grams of alcohol (4 to 5 servings of mixed drinks, shots, glasses of wine, or small bottles of beer) a day or more, and women who drink 30 grams of alcohol (2 to 3 servings) a day or more, are at higher risk for liver damage than people who drink less or not at all.

Quitting or cutting down on drinking can be very difficult, but drinking less—or not at all—may be the most important thing a person with hepatitis C can do to prevent liver damage.

### **Street Drugs**

People who regularly use heroin, cocaine, and crystal methamphetamine may not be getting enough sleep or eating well, and may be under a great deal of stress. People who don't have access to clean injection equipment are at risk for infections such as HIV, HBV, and HCV (including reinfection after being cured of the virus). For these reasons, using street drugs—especially on a daily basis—can have a negative overall impact on a person's health. However, there is not enough information to say whether or not street drugs actually cause or worsen liver damage in people with chronic hepatitis.

### **Street Drugs and the Liver**

Since heroin, cocaine, and crystal methamphetamine are illegal, there is very little research or information on whether or not these drugs cause liver damage in people with chronic hepatitis. Most research on street drugs has been done *in vitro* (in a test tube), not *in vivo* (in the human body). What happens inside the human body is often very different from what happens in a test tube, so it is hard to know how the results from an *in vitro* study relate to what actually happens in a person's body.

The purity of "street drugs" (illicit drugs) varies. The other substances that are added to street drugs may be harmful to the liver, although the drug itself may not be. This makes it more difficult to know the impact of street drug use on chronic hepatitis.

Some researchers have found that daily marijuana use (one joint or more per day over several years) can cause fibrosis faster in people with chronic HCV, but other studies have not reported a link between liver scarring and marijuana use. Occasional use of marijuana has not been found to be

harmful. In fact, one study found that smoking marijuana during HCV treatment helped people to deal with side effects and complete their treatment.

### **Prescription Drug Use**

Some people use prescription drugs to get high. This can be risky because they may interact with other medications, causing lowered or increased drug levels in a person's body. If drug levels are too low, medications may stop working, and in some cases—such as with HIV medications and antibiotics—drug resistance can develop because there is not enough drug in a person's system to stop viruses and bacteria from reproducing. Drug levels that are too high can also be dangerous, since they can increase drug toxicity and side effects, or cause an overdose.

For example, benzodiazepines such as midazolam interact with alcohol; caffeine; sleeping pills; some antidepressants and anti-anxiety drugs; some antibiotics; hormonal contraception (birth control pills); some of the drugs used to treat TB, fungal infections, high blood pressure, and heart problems; and even cold medications (among others).

### **Drug Overdose**

The risk of overdosing on certain prescription anti-anxiety and pain medications like benzodiazepines, opioids, and anesthetics (including alprazolam, diazepam, midazolam, triazolam, fentanyl, and lidocaine) may be higher in people with hepatitis-induced cirrhosis, since drugs such as these are broken down by the liver.

### **Other Drugs**

Some antibiotics, traditional medicines, herbs, and food supplements can be hard on the liver. Additionally, some medications should not be taken at the same time as certain HCV drugs or will need to have their doses adjusted. It is very important that your health care provider and pharmacist know about all of the medications and supplements you are taking, including those you buy both with and without a prescription, to help prevent serious drug interactions.

## **ADVOCACY EXERCISE**

### **Discussion Questions:**

1. Do you know someone who has died from liver cancer? Can serious illness and deaths from liver disease be prevented?
2. In places where HCV treatment is not available, what can people do to improve their liver health?

### **Action Steps:**

1. Do you know where people in your community can get testing and treatment for liver disease? If not, how can you find out?
2. Where can people find support and harm reduction services if they want to stop or decrease alcohol or drug use?

## SECTION 3. TRANSMISSION: HOW YOU GET IT, HOW YOU PREVENT IT

### Hepatitis C (HCV) is spread by direct blood-to-blood contact

HCV is a bloodborne virus, spread when infected blood directly enters a person's bloodstream. HCV is a very small virus, much smaller than HIV, so there is a lot of it even in a tiny amount of blood, but—unlike HIV—the **hepatitis C virus can stay alive on surfaces outside of the body for days. HCV is 10 times more infectious than HIV.** Bleaching syringes can prevent HIV, but it does not work as well to stop HCV; Sterilization of injection equipment, with heat, is the most effective way to kill HCV. Since most PWIDs don't have consistent and easy access to clean injection equipment, and HCV is not easy to kill, hepatitis C is common among people who inject drugs (PWID).

### The most common ways to catch HCV are:

- Sharing *anything* that another person has used to inject drugs with, including needles, cookers, ties, cotton, straws, water, or measuring syringes;
- Getting a tattoo with any shared, unsterilized equipment: needles, ink, or inkwells;
- Getting a contaminated blood transfusion or blood product (more common in some countries than others; in the United States, risk was virtually eliminated in 1992);
- Undergoing surgery or other invasive medical procedures (vaccination, blood draws or donations, endoscopy) with unsterilized, shared equipment, or kidney dialysis in a facility that does not practice infection control;
- From mother to infant; the risk is about four percent, but if the mother is also HIV-positive, the risk is higher—up to 20 percent;
- Having unprotected sex with a person who has HCV; and
- Needlestick injury (for health care providers) or other occupational hazard.

When possible, avoid sharing toothbrushes, razors, manicuring equipment, or any other personal care items that may have come in contact with another person's blood.

HCV cannot be passed by sharing eating utensils or by eating food made by a person with HCV. It cannot be passed by drinking from the same glass as someone with HCV.

HCV is not spread by casual contact (kissing, hugging, holding hands, etc.).

### Sharing noninjection drug equipment (straws and pipes)

It may be possible to get HCV from sharing straws and pipes (used for cocaine, heroin, crystal methamphetamine, etc.). Straws may contain tiny amounts of blood from the inside of someone's nose, and people may have burns on their lips from a hot pipe.

Although it is not always possible, it is important to use clean injection equipment (needles, measuring syringes, cookers, cotton, water, and ties) every time you get high.

**A person who already has HCV can get infected again—this is called *reinfection*—even after being successfully treated.**

*You can also be infected with more than one type of hepatitis C virus at the same time.* Not sharing your injection equipment or using clean/new equipment protects you and the people that you are getting high with.

### **HCV can be spread during unprotected anal and vaginal sex with a person who has HCV**

Although the hepatitis C virus has been found in semen and vaginal fluid, it is mainly found in blood. No one is sure whether there's enough HCV in semen and vaginal fluid to pass the virus to other people, but we do know that people have become infected from unprotected sex. HCV is more common among sex workers, men who have sex with men (MSM), and people who have had more than one sex partner.

The risk for sexually transmitted HCV is greater when blood is involved, even when the amount is too small to see. So all of the following can put a person at risk for HCV: rough, unprotected anal and vaginal sex; fisting (also called ***fist-fucking***; when a person puts his/her hand and forearm into another person's asshole [also called ***anus***] or vagina); group sex; and sex with a woman during her period. Using a condom with water-based lubricant for anal and vaginal sex, and latex gloves with plenty of water-based lubrication for fisting, can reduce the risk of sexually transmitted HCV.

### **Outbreaks of sexually transmitted HCV among HIV-positive gay men have been reported in several countries**

Outbreaks have been reported so far in Europe, Australia, and the United States. Several factors seem to be involved, including

- rectal bleeding;
- unprotected anal sex;
- longer, rougher intercourse;
- fisting;
- sex with many partners and group sex;
- being infected with another sexually transmitted infection, such as syphilis;
- meeting sex partners through the internet;
- use of noninjection “party drugs”, such as ecstasy, crystal methamphetamine, and cocaine, which can lower inhibitions; and
- recent rectal surgery.

Sometimes, people who don't have HCV themselves can wind up passing it to other people. For example, a person fisting with multiple partners can have blood from one partner on their hand; this blood can enter the bloodstream of other partners through tiny cuts or rips inside his or her anus or vagina.

## **HCV can be passed from mother to infant, in the womb, or during labor and delivery**

If the mother has HCV—but not HIV—there is about a four percent risk that her baby will have HCV. The risk of mother-to-infant transmission (MTIT) of HCV is higher—up to 20 percent—if the mother is also HIV-positive.

Pregnant women coinfecting with HIV and HCV can reduce the risk of passing HIV and HCV to their infants by taking antiretroviral therapy. HIV treatment takes care of the mother's health, and greatly lowers the risk of passing HIV and HCV to the infant.

Unfortunately, it is not possible to use HCV treatment during pregnancy because one of the drugs—ribavirin—causes birth defects, and the other—interferon—is dangerous for infants and children under two years old. Because ribavirin and interferon should not be used by pregnant women, the two newer hepatitis C drugs—boceprevir (Victrelis) and telaprevir (Incivek), which must be combined with interferon and ribavirin—also cannot be used.

Fortunately, researchers are studying new drugs and drug regimens that do not involve ribavirin or interferon. If these drugs are shown to be safe for pregnant women and their babies, they will likely be studied in combination to see if they can reduce the risk of mother-to-child transmission of HCV.

Unlike HIV, the hepatitis C virus has not been found in breast milk. HIV-negative mothers who have HCV can safely breastfeed their infants as long as their nipples do not have any cuts or cracks.

### **ADVOCACY EXERCISE**

#### **Discussion Questions:**

1. Do people in my community know how to protect themselves against HCV?
2. Are clean syringes, injection equipment, and condoms easy to get in my community?
3. How well is HCV controlled in health care settings in my country?
4. Is harm reduction equipment (like clean tattooing and injection equipment) available in jails and prisons?
5. Do MSM with HIV have information about sexually transmitted HCV?

#### **Action Steps:**

1. How can we help make clean syringes and condoms more available in jails and prisons, and in general?
2. How can we begin educating people about sexual transmission of HCV?

## SECTION 4. NATURAL HISTORY: WHAT HAPPENS TO PEOPLE WITH HEPATITIS C?

### HCV has two stages: acute and chronic (lifelong)

Acute infection is a term for the first six months after a person gets HCV. Most people—80 percent—don't feel sick at all during acute HCV, and don't know that they have HCV.

### The symptoms of acute HCV may include

- jaundice (yellow skin and eyes);
- fever;
- feeling tired and weak;
- nausea, vomiting, stomach pain, and appetite loss; and
- dark urine.

### HCV is not always chronic

HCV is not always a lifelong infection. Some people (15–45%) will get rid of the virus without treating it, usually during acute infection. The medical term for this is **spontaneous viral clearance**. HIV-negative people, women, children and young adults, and people who have symptoms during acute HCV are more likely to spontaneously clear HCV. HIV-positive people are less likely to clear HCV without treatment; experts think that up to 20 percent of HIV-positive people will get rid of their HCV without treatment versus 15–45 percent in HIV-negative people.

### HCV treatment is most effective during acute infection

Finding out that you have HCV during acute infection can make a big difference, because HCV treatment is much more likely to work—meaning it will get rid of the virus—during acute HCV. Usually, experts suggest that people who have acute HCV should wait for about 12 weeks before they start HCV treatment, since they may spontaneously clear HCV and won't actually need treatment.

### At least 55% of HIV-negative people and at least 75% of HIV-positive people develop chronic HCV

Most people who get HCV develop a chronic (lifelong) infection. Many do not have any symptoms at all, but the most common symptoms are being forgetful and feeling tired and/or depressed. Sometimes people with very mild liver damage have symptoms. There is no clear link between having symptoms and having liver damage. Many people don't have any symptoms until they have very serious liver damage.

### Chronic HCV does not always cause serious liver damage

Having chronic HCV does not always mean that you will have serious liver damage, or that you need treatment. Some people live with HCV for many years and will never have serious liver damage.



Liver damage from HCV happens slowly, usually over decades. It can take from 15 to 50 years for an HIV-negative person who has chronic HCV to develop cirrhosis after becoming infected with the virus. People who get HCV when they are over 40 seem to progress more quickly, probably because a person's immune system tends to slow down as they age. People who drink alcohol, especially heavy drinkers, are more likely to develop liver damage.

People with severe liver damage (**cirrhosis**) are at risk for very serious complications, such as liver cancer and liver failure. (For more information about liver damage, see section 2, About the Liver.)

### **HIV/HCV Coinfection: Impact of HIV on HCV**

HCV is a serious problem for HIV-positive people. HIV increases the risk for liver damage from HCV. In fact, coinfecting people are twice as likely to get cirrhosis as people with HCV alone. HIV speeds up the rate of liver damage from HCV; some coinfecting people have gotten cirrhosis in less than 10 years.

HCV is treatable, no matter what a person's HIV status is, but HCV treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV) does not work as well for HIV-positive people.

### **HIV treatment can help to slow down liver damage from HCV**

HIV treatment, also called **antiretroviral therapy**, or ART, may help keep the liver in good condition by keeping the immune system strong. Coinfecting people with less than 200 CD4 cells are at the highest risk for serious liver damage from HCV.

### **HIV/HCV Coinfection: Impact of HCV on HIV**

We know that HIV can accelerate progression of HCV, but so far, no one is sure about the impact of HCV on HIV. Experts do agree that being coinfecting with HCV makes treating HIV more complicated. A liver that is damaged from HCV may cause HIV medications to become less effective and, importantly, more toxic. This is because a healthy liver is required to effectively process medications and remove them from the body.

HCV coinfection triples the risk for liver toxicity (also called **hepatotoxicity**) from HIV meds. It is important to know which drugs are easier on the liver than others. However, many studies in HIV/HCV-coinfecting people have shown that the benefits of HIV treatment outweigh the risks (see Treatment Issues for HIV/HCV-Coinfecting People in section 9).

## **ADVOCACY EXERCISE**

### **Discussion Questions:**

1. Do you know people in the community who have died from HCV?
2. When and how did they find out they had HCV? Was it already “too late?” What options were available to them for treatment or support?
3. Which groups of people living with HIV/AIDS may not have regular access to health and HIV care?
4. If HCV treatment doesn’t work as well for people with HIV, should coinfecting people have access to HCV treatment?

### **Action Steps:**

1. What can we do to prevent more deaths from HCV?
2. How can we get more people tested for HCV?

## SECTION 5. HCV DIAGNOSTICS

The first step in dealing with HCV is to find out as much as you can. One way to do this is by getting some laboratory tests from the medical provider. These tests can tell

- if a person has been infected with HCV;
- which strain (genotype) of HCV the person has;
- IL28B genotype, which predicts response to HCV treatment with PEG-IFN and some newer HCV medications;
- the amount of virus (viral load) in the bloodstream;
- if the liver has been very damaged; and
- how well HCV treatment is working.

### HCV Screening Tests and What the Results Mean

Step 1: HCV ANTIBODY TEST	
<p><b>POSITIVE RESULT</b> There are three potential meanings:</p> <ol style="list-style-type: none"> <li>1. The person may have acute HCV; or</li> <li>2. may have chronic HCV; or</li> <li>3. was infected in the past, but has cleared HCV and is no longer infected.</li> </ol> <p><b>The person needs a viral-load test to confirm.</b></p>	<p><b>NEGATIVE RESULT</b> There are three potential meanings:</p> <ol style="list-style-type: none"> <li>1. The person has never been infected; or</li> <li>2. may have been recently infected (within the last two weeks); or</li> <li>3. may have chronic HCV (if the person is HIV-positive, especially with a CD4 count &lt;200 cells/mm<sup>3</sup>).</li> </ol> <p><b>The person needs a viral-load test to confirm.</b></p>
Step 2: HCV RNA (VIRAL LOAD) TEST	
<p><b>DETECTABLE RESULT</b> There are two potential meanings:</p> <ol style="list-style-type: none"> <li>1. The person may be recently infected, and has acute HCV; or</li> <li>2. may have chronic HCV.</li> </ol> <p><b>The person needs a second confirmatory viral-load test.</b></p>	<p><b>UNDETECTABLE RESULT</b> There are three potential meanings:</p> <ol style="list-style-type: none"> <li>1. The person has never been infected; or</li> <li>2. was once infected in the past, but has now cleared HCV; or</li> <li>3. was recently infected but is still in the process of clearing the infection.</li> </ol> <p><b>The person needs a second confirmatory viral-load test.</b></p>
Step 3: Second Confirmatory HCV RNA (VIRAL LOAD) TEST in Six Months	
<p><b>DETECTABLE RESULT</b></p> <p><b>The person has chronic HCV.</b></p>	<p><b>UNDETECTABLE RESULT</b></p> <ol style="list-style-type: none"> <li>1. The person has never been infected;</li> <li>2. was infected in the past but has now cleared HCV.</li> </ol> <p><b>The person does not have HCV.</b></p>

## Two different blood tests are used to diagnose HCV: antibody test and viral-load test

Diagnosing HCV is different from diagnosing HIV, although both viruses can be diagnosed with blood tests. A positive HCV-antibody test result does not always mean that someone has chronic HCV—it simply means that a person was infected with HCV in the past, and may still be infected—because people who get rid of HCV without treatment (called **spontaneous viral clearance**) usually stay HCV antibody-positive for years.

A viral-load, or HCV RNA, test looks for the actual virus—not antibodies—in a blood sample. This is the only way to determine if someone has chronic HCV. If there is hepatitis C virus in a person's blood, that person is currently infected with HCV. If the test does not find the hepatitis C virus in a person's blood (called **undetectable**), that person should get tested again, six months later. If the second test result is also undetectable, it means that HCV has been cleared.

HCV viral loads are usually much, much higher than HIV viral loads, but a high viral load does not mean that HCV is more serious, or that liver damage will happen faster. For people with chronic HCV, viral load is a very important test if treatment is prescribed. The test helps determine if treatment is working, if it should be stopped, and if it succeeds in curing the infection. So, for a person on HCV treatment, viral-load testing is done just before starting treatment, during treatment at specific intervals, and after treatment ends.

## A negative HCV-antibody test result usually means a person doesn't have HCV—but not always

Sometimes an HCV-antibody test result is negative, even when someone does have chronic HCV. This happens for two reasons. If a person just got infected with HCV, he or she may not have antibodies yet. After hepatitis C virus has entered a person's bloodstream, the immune system responds by making antibodies. These are sticky, Y-shaped proteins that wrap themselves around invaders, either disabling them or marking them so that the immune system can destroy them. It takes six to 24 weeks for a person to make antibodies to HCV (often called the **window period**). HCV-antibody test results may also be negative in HIV-positive people who have HCV. This can happen when a person has less than 200 CD4 cells, because their immune system is not able to make antibodies. *So anyone with a CD4 count of less than 200 cells/mm<sup>3</sup>, who has signs or symptoms of hepatitis, such as elevated liver enzymes, yellow skin or eyes, or fatigue, or who has been at risk for HCV, should have an HCV viral-load test, even when an HCV-antibody test is negative.*

## Viral-Load Tests

There are two different types of HCV viral-load tests: **qualitative** (measures whether or not there is HCV virus in a person's blood; results are either detectable or undetectable), and **quantitative** (measures how much hepatitis C virus there is in a person's blood).

- **Qualitative testing** can pick up very small amounts of HCV in a person's bloodstream. It is usually used to diagnose HCV, and sometimes used to measure response during HCV treatment.
- **Quantitative testing** is usually used to see how much virus a person has in his or her bloodstream before starting HCV treatment, and sometimes used to measure response during HCV treatment.

## Hepatitis C viral load does not determine the need for HCV treatment

In HIV, a person's viral load can be used to help make a decision about when to start antiretroviral therapy, but HCV is different. For example, HCV viral loads are reported as international units rather than copies per milliliter. They are much higher than HIV viral loads—sometimes in the tens of millions. Coinfected people usually have even higher HCV viral loads than people with HCV alone. For people who are used to the scale of HIV viral loads, the HCV viral load can be very upsetting. But having a high HCV viral load does not mean that a person needs to start HCV treatment, or that he or she has more liver damage, or that liver damage will develop more quickly.

## HCV treatment is more likely to work for people with a low HCV viral load

New treatments may cure HCV regardless of the viral load. The HCV viral load is one of the things that predict whether or not HCV treatment is likely to work. The lower the HCV viral load is, the more likely that HCV treatment will work. Viral-load testing is also used during and after HCV treatment, to see if treatment is working (for more information, see section 7, HCV Treatment and Side Effects).

## Getting More Information about the Health of Your Liver

### Liver Enzyme Tests (ALT and AST)

Liver enzymes are proteins that do different jobs in the body. When a person's liver is injured, increased numbers of these enzymes leave the liver cells and enter the bloodstream. Health care providers check liver enzyme levels using a group of blood tests, sometimes called **liver function tests** (LFTs). These tests do not actually measure liver function, and the results cannot predict or tell someone how much liver disease they have.

Alanine aminotransferase (ALT; SGPT) and aspartate aminotransferase (AST; SGOT) are two liver enzymes. ALT is made in the liver. If a person's ALT keeps increasing over time, it may be a sign of hepatitis C progression. AST is made in the heart, intestines, and muscles. Alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, albumin, and prothrombin time (PT) are other important liver enzymes.

Many things can cause abnormally high liver enzyme levels, such as: liver toxicity from prescription and over-the-counter medications, herbs, vitamins, and supplements; exposure to toxic fumes; heavy alcohol consumption; acute or chronic viral hepatitis and certain other infections; and while a person is detoxing from drugs or alcohol.

Some HIV medications are broken down by the liver, and can cause abnormally high liver enzyme levels. All HIV-positive people who are taking ART or TB drugs—whether or not they are coinfecting with hepatitis B or C—should have their liver enzyme levels checked regularly as some HIV medications, TB treatment and other drugs can be hard for the liver to break down.

When liver enzyme levels are higher than normal for several months, it can be a signal that the liver is inflamed or damaged. Normal liver enzyme levels do not mean that a person's liver is healthy—some people may have normal liver enzyme levels for years although they have serious liver

damage. It is a good idea to keep a record of your liver enzyme levels over time. If the level goes up and stays up over several tests, it may be a good time to discuss HCV treatment with your doctor, as other causes for abnormal enzyme elevations are ruled out.

### **ADVOCACY EXERCISE**

#### **Discussion Questions:**

1. Do you know where people can get tested for HCV in your community?
2. Are there free testing sites? If not, how much are the tests?
3. Do healthcare providers explain what the tests are and what the results mean?

#### **Action Steps:**

1. What can we do to make HCV testing easier to access?

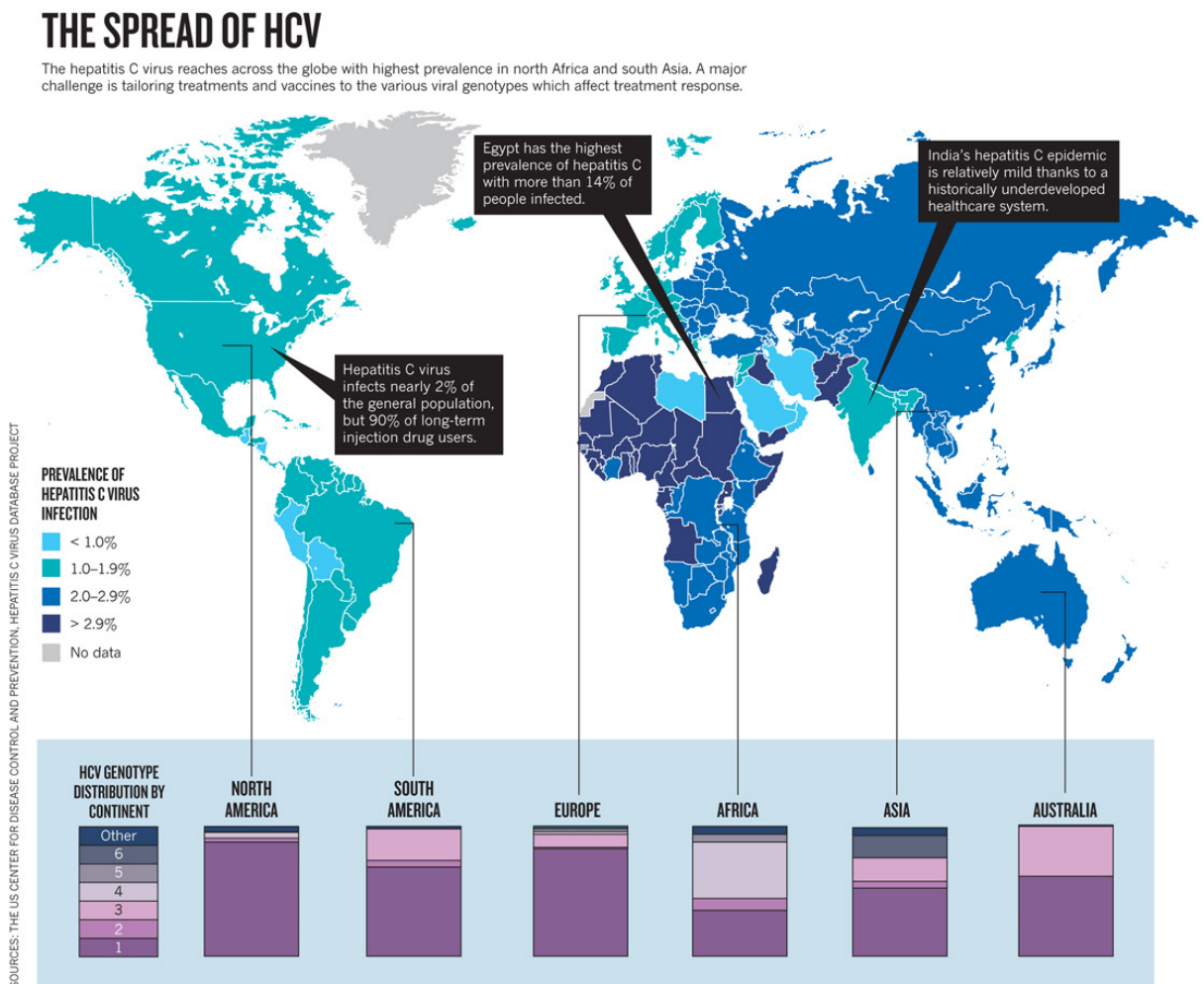
## SECTION 6. HCV DIAGNOSTICS FOR MAKING TREATMENT DECISIONS

### HCV Testing

There are different viral strains of HCV, called **genotypes**. There are at least six different HCV genotypes, each given a number (1, 2, 3, etc.) in the order of discovery. Within each HCV genotype there are slight differences, called **subtypes**; these are given a letter of the alphabet (a, b, c, d, etc.), so for example someone may be diagnosed with HCV genotype “3a.” A person can be infected with more than one HCV genotype, and people who already have HCV can get infected again (**reinfected**) with a different genotype.

**It is very important to have an HCV genotype test before starting HCV treatment, because some genotypes respond differently to treatment than others**

Health care providers can order a blood test to see which HCV genotype—or genotypes—a person has. It is very important to have an HCV genotype test before starting HCV treatment, because some genotypes don't need to be treated for as long as others.



Source: Gravitz L. Introduction: a smouldering public-health crisis. Nature. 2011 Jun 8;474(7350):S2–4. doi: 10.1038/474S2a.

Genotype 3 is most common in Thailand. People who have genotype 3 are more likely to have steatosis (fat in the liver); this can make treatment less effective. Genotype 1 is most common in the United States. People with genotype 1 are more likely to have high hepatitis C viral loads. HCV treatment is less likely to work for people with a high viral load.

However, new treatments are in development, many specifically made to work against genotype 1. Some of these may be more effective for people with genotype 1b (vs. genotype 1a), so it is important to ask your doctor about your subtype. New treatments are also in development for other genotypes.

Since some HCV genotypes are harder to treat than others, it is important to avoid getting reinfected with HCV when possible.

### Interleukin-28B (IL28B) Genotype Testing

IL28B is a gene in our body that plays a role in the immune system's defense against certain viruses. Everyone gets one IL28B gene from each parent—either "C" or "T." In turn, a person can either have the IL28B "CC," "CT," or "TT" genotype. You can find out your IL28B genotype through a blood test (called the **IL28B genotype test**).

People with the IL28B CC genotype are more likely to be cured by HCV treatment with peginterferon than people with the TT genotype. Cure rates among people with the CT genotype fall somewhere in between. New treatments that are not influenced by IL28B genotype are being developed.

Because IL28B is inherited, your ancestry can help determine which genotype you have.

Ancestry	Percentage Likely to Have IL28B CC Genotype
African	23–55%
European	53–86%
South Asian	65–98%
East Asian	90–100%

A person's IL28B genotype never changes, so this test needs to be taken only once. Knowing your IL28B genotype can be helpful to you and your doctor when discussing treatment options. Your IL28B genotype may determine what medications you take and how long you need to take them.

For more information about IL28B and treatment response, see the fact sheet in the appendix.

### Liver Biopsy

A liver biopsy is the best way to find out what condition a person's liver is in, because health care providers can see how much inflammation (**grade**) and scarring (**stage**) there is in a sample of liver tissue. During a liver biopsy, a very small piece of liver tissue is removed with a needle. The tissue is then examined to see how much damage there is, and what is causing the damage. Usually, a person will stay in the hospital for a few hours afterward to make sure that there are no complications.



There are drawbacks to liver biopsy. If the tissue sample is not large enough, or is taken from a less damaged part of the liver, the results will not be accurate. Biopsy is expensive, and many people are not able to have a biopsy done for this reason. Liver biopsy can also be painful. There is a small risk of complications—such as internal bleeding, or missing the liver and piercing a nearby organ—and a much, much smaller risk of death.

It is always important to ask how much experience a doctor has had in performing biopsies, what kind of pain medication will be offered, and how long the hospital stay is. It may be helpful for you to ask someone who has had a liver biopsy how it was, and if they recommend the doctor who did it.

### **Cirrhosis can be diagnosed without a liver biopsy**

Health care providers can use a combination of blood tests instead. Some liver specialists, particularly in Europe, are also using a machine called FibroScan that looks at liver stiffness using sound waves. It is difficult to diagnose mild or moderate liver disease without doing a biopsy, however, and FibroScan is not widely available in most countries.

### **Liver biopsy is not always necessary**

Sometimes, people do not get a biopsy before starting HCV treatment. Often, this is because of the cost, or because there is no experienced doctor available to perform one. Liver damage from HCV can develop faster in HIV-positive people, so some health care providers think it is a good idea to go ahead and treat coinfecting people whether or not they have had a biopsy.

## **ADVOCACY EXERCISE**

### **Discussion Questions:**

1. Are all the different HCV tests for making treatment decisions available? Is cost a problem? Are the tests covered under your insurance plan?
2. Do doctors take the time to explain test results?

### **Action Steps:**

1. What kind of tools can help people understand test results?
2. What can we do to increase access to expensive tests?
3. With whom can we make alliances to increase our understanding of and access to these important tests?

## SECTION 7. HCV TREATMENT AND SIDE EFFECTS

Figuring out when to begin HCV treatment can seem confusing. Because treatment can cause side effects and there is no guarantee that it will work, it is recommended only for people who show clear signs of worsening liver disease. Not everyone with chronic HCV will experience progressive liver disease, but in people who do, treatment should be started before the liver becomes severely damaged (which can cause liver failure).

In the future, when new medications that are easier to take and better tolerated become available, treatment may be recommended for people with HCV regardless of their liver disease status (also doing away with liver biopsies). Until then, however, people with HCV must weigh the known risks of current therapy against the benefits in deciding when to start treatment.

Treating HCV is never an emergency. HCV treatment is recommended for people who already have some liver scarring and inflammation, because they are at risk for cirrhosis. HCV treatment is not recommended for people with very advanced liver damage, because it can cause liver failure. People in this situation need a liver transplant. Treating HCV may be more important for HIV-coinfected people because they may get liver damage more quickly than people with HCV alone. Successfully treated HCV can also improve liver health and make HIV drugs easier to tolerate.

### **HCV treatment requires a combination of drugs**

HCV is currently treated with a regimen containing at least two drugs: pegylated interferon (PEG-IFN) and ribavirin. These medications are generally taken for 12 to 72 weeks. The length of treatment depends on how people respond to it after 12 weeks, which HCV genotype they have, how high their HCV viral load is, and their HIV status.

Where available, people with HCV genotype 1 should also receive a third drug: telaprevir or boceprevir. These new drugs are very expensive and may be even more difficult to access. These are taken three times a day and are combined with PEG-IFN and ribavirin for 4-44 weeks. The length of treatment containing all three medications depends on the drug used, whether or not someone is starting HCV treatment for the first time and the amount of liver damage.

All of these drugs can cause side effects that can be very serious. It is important for anyone who is thinking about treating their HCV to learn about the risks and benefits of HCV treatment. One of the best ways to do this is to talk with people who have been on HCV treatment.

### **Pegylated Interferon (PEG-IFN)**

Interferon is a protein made by the human body. It sends virus-fighting messages to the immune system. With HCV, a much larger dose of man-made interferon is given for treatment. Pegylation means that a molecule has been attached to the interferon, keeping it in the body longer and making it more effective. Before interferon was pegylated, people had to inject it three times per week (for up to 48 weeks). PEG-IFN is just one injection per week. PEG-IFN is more effective as well as more convenient than standard interferon. There are two different brands of PEG-IFN. One comes as a powder, is dosed by body weight, and needs to be mixed with water before each injection

(PegIntron, by Merck). The other brand (Pegasys, by Roche) comes premixed and is not dosed by weight. Both need to be refrigerated. **Standard, unpegylated interferon is no longer the standard of care, and should not be used.**

### **Ribavirin (RBV)**

Ribavirin is from the same family as some of the drugs used to treat HIV, called **nucleoside analogues**, but it does not work as an HIV treatment. Ribavirin works against HCV when used with PEG-IFN and is currently part of the standard of care in treating HCV. It is not very effective by itself and should not be used alone. Ribavirin is given as pills or capsules, twice a day. The dose depends on a person's weight.

### **Protease Inhibitors**

Telaprevir (Incivek) and boceprevir (Victrelis) are protease inhibitors. They are also known as **direct-acting antivirals** (DAAs), as they were designed, studied, and approved specifically to treat HCV.

When combined with PEG-IFN and RBV, these drugs can increase the chances of curing HCV genotype 1. In fact, they are approved only for people with HCV genotype 1. New drugs are being developed for other HCV genotypes.

Telaprevir is combined with PEG-IFN and RBV for 12 weeks (all three drugs may be stopped after four weeks if treatment does not appear to be working). PEG-IFN and RBV are then continued, without telaprevir, for another 12 or 36 weeks. Telaprevir is taken in two capsules every 7–9 hours for a total of six capsules a day, or in three capsules every 12 hours.

Boceprevir is added to PEG-IFN and RBV after four weeks of treatment. If treatment is not working, all drugs may be discontinued after 12 weeks. If treatment is working, all three drugs will be taken for another 12 to 36 weeks. Boceprevir is taken in four capsules every 7–9 hours for a total of 12 capsules a day.

The duration depends on the person's hepatitis C treatment history, health of his or her liver, and response to treatment as measured by viral load.

See drug fact sheets in the appendix for more information.

### **New HCV Drugs in Development**

Current HCV treatment does not cure everyone, and treatment success depends on many factors. Also, dosing is complicated, treatment can take many months to complete, and it may have many, sometimes serious, side effects. Now that we know more about how HCV reproduces in the body and causes liver disease, researchers have been able to develop many new treatments for hepatitis C, most of which are still under investigation (they are not yet approved for use). As these medications become approved and available, drug combinations that include PEG-IFN and RBV may not be needed for everyone.

These new drug combinations may be:

**Easier to take.** Most medications in development can be taken by mouth, either once or twice a day. Some medications will be combined in single-tablet formulations (called **fixed-dose combinations**, or FDCs).

**Highly effective.** These medications, when used in combination with each other (and without PEG-IFN or RBV), are expected to work better than current treatment. This may be especially true for people who cannot tolerate PEG-IFN, do not respond well to interferon, or have cirrhosis.

**Effective against many HCV genotypes.** Current medications are not as effective for people with some HCV genotypes. The hope is that new medications will be equally effective for people with all genotypes.

**Safe and tolerable.** PEG-IFN and RBV can be very difficult for some people to tolerate, to the point where HCV treatment must be stopped. Treatment regimens containing only DAAs may have fewer side effects. Even if PEG-IFN and/or RBV must still be used, the addition of DAAs may shorten the length of therapy, potentially reducing the duration and severity of side effects.

As with HIV drugs, the new HCV drugs will need to be taken regularly—missing doses can lead to drug resistance.

As a result of activist advocacy, drug companies have agreed to study a number of these new drugs in people coinfecting with HIV, people with cirrhosis, and other “harder-to-treat” groups who have traditionally been left out of HCV drug development trials.

### **Access to HCV treatment is an important advocacy issue**

HCV treatment is expensive. High prices and patent protections keep them out of reach for most who need them.

A generic version of ribavirin is available, but not of telaprevir or boceprevir. Generic versions of PEG-IFN, called **biosimilars**, are available in some countries, but regulatory guidance and safety and effectiveness studies are lacking, making it hard to determine the quality of these generics, and to register them outside of the producer countries.

## **ADVOCACY EXERCISE**

### **Discussion Questions:**

1. Do you know which HCV drugs are available in your country?
2. If available, do you know how much they cost?

### **Action Steps:**

1. What can you do to make more information about these treatments available for people who need them?
2. What can we do to make HCV treatment more accessible?

## SECTION 8. HOW TO TELL IF HCV TREATMENT IS WORKING

### HCV treatment can get rid of the virus, but it does not always work

The main goal of HCV treatment is to completely get rid of, or cure, the virus.

Treating—and curing—HCV can reduce the risk of cirrhosis, liver cancer, liver failure, and liver disease–related deaths.

Regular monitoring after successful treatment may be important, especially for people who have cirrhosis before they begin therapy. They are still at risk of developing liver cancer.

Here are some terms that people use to describe how well HCV treatment with PEG-IFN and RBV is working.

**RVR (rapid virological response):** means that a person has no detectable hepatitis C virus in the blood after four weeks of treatment. An RVR is a good predictor of a cure, but people who do not have an RVR may still be cured after a full course of treatment.

**EVR (early virological response):** means that a person’s HCV viral load drops by 99 percent (also called a **2-log drop**) from pretreatment levels after 12 weeks on treatment.

If a person does NOT have an EVR, they are extremely unlikely to be cured. People who do not have an EVR usually stop HCV treatment at this point. Therefore, access to HCV viral-load testing after 12 weeks of treatment is very important: if treatment isn’t working, there is no need for someone to stay on it and suffer the side effects, and no need to pay for an entire year of treatment.

**ETR (end-of-treatment response):** means that a person has no detectable virus after finishing HCV treatment.

**SVR (sustained virological response):** means that a person has no detectable HCV during treatment and remains undetectable 12 weeks (called **SVR-12**) or 24 weeks (called **SVR-24**) after finishing treatment. SVR-12 is a good indicator of SVR-24, because HCV usually comes back within 12 weeks. An SVR-24 is still considered a cure.

These terms, and the times when the response to treatment is measured, will change when new HCV drugs are used.

It is important for people who were not cured after treatment (called **treatment-experienced**) to know what happened, so that they can decide what to do when new treatment becomes available, as the effectiveness of the new treatment may be different depending on how a person responded to prior treatment. Here are some terms used to describe prior treatment history.

**Breakthrough:** This happens when a person’s viral load becomes undetectable at one point on treatment, but becomes detectable at a later point in treatment. In this case, it is a good idea to have a second viral-load test to confirm that HCV RNA is indeed detectable. If it is, the person should discontinue treatment.

**Partial responder or nonresponder:** Someone whose viral load drops, but does not become undetectable after 24 weeks of treatment.

**Null responder:** Someone who sees little or no reduction in HCV viral load during treatment.

**Relapser:** Someone who has an end-of-treatment response but whose HCV comes back after finishing treatment. This has happened to about 18 percent of people who have been on treatment. Usually the virus will reappear in the bloodstream within 12 weeks of finishing treatment.

### How Well Does HCV Treatment Work?

PEG-IFN/RBV	PEG-IFN/RBV + DAA	DAAs-only
Genotype 2	Genotypes 1, 2,3, 4, 5, and 6	Some combinations will work for all genotypes
Low viral load	May not differ based on viral load	May not differ based on viral load
CC genotype	Some difference between genotypes	Less difference between genotypes
Less effective for African Americans	May not differ by race	May not differ by race
HIV-negative	No difference with HIV status	Unknown
Treatment adherence is important	Treatment adherence is very important	Treatment adherence is very important
Less effective in people with cirrhosis	Less effective in people with cirrhosis	Less effective in people with cirrhosis
Less effective in people who are overweight	Unknown	Unknown
Less effective in people who have insulin resistance/ type 2 diabetes	Unknown	Unknown

Note: *Unknown* means the treatment has not been well studied in people with these characteristics.

Even though experts know a lot about the factors that predict whether or not HCV treatment will work in general, no one can predict how an individual will respond to HCV treatment. Researchers are still trying to determine whether these factors continue to be important when treating people with the newer drugs (DAAs) now in clinical trials. For example, some treatments may treat several or all genotypes equally effectively.

Results from clinical trials can give people an idea about how well HCV treatment works, but results do not always apply in the real world. People in clinical trials are picked carefully; often they don't have other medical conditions that are common among people with HCV, may have less liver damage, and be in better health overall. This happens for two reasons: one, it is safer to try new treatments in the healthiest possible people; and two, sometimes people who are unlikely to respond to a treatment are excluded from trials to make the results look better.

### Response to PEG-IFN/RBV by HIV Status and HCV Genotype

SVR	HCV Only (%)	HIV/HCV (%)
Genotype 1 (PEG-IFN/RBV)	42-44	14-38
Genotype 1 (PEG-IFN/RBV+DAA)	64-75	74*
Genotype 2 (PEG-IFN/RBV)	80-90	Up to 72
Genotype 3 (PEG-IFN/RBV)	60-70	~60

\*From one phase II study using telaprevir and PEG-IFN/RBV

## Side Effects of HCV Treatment

The side effects of PEG-IFN and ribavirin can make it difficult for people to stay on treatment, although they are different for each person. In general, side effects are worse for people who have more serious liver damage, and/or are HIV/HCV-coinfected. Some people have trouble working during HCV treatment.

It is very important to talk with other people who are, or have been on HCV treatment. Their experience and support can be very helpful. Ask your health care providers about how they manage side effects before you start HCV treatment.

### Common Side Effects

Flu-like symptoms, such as feeling weak or feverish, and having aching muscles and joints, headache, nausea, and appetite loss are very common. These are usually worse for the first day or two after injecting PEG-IFN, so people often take their weekly PEG-IFN when they can rest for a day or two afterward. These side effects can be managed by taking low-dose acetaminophen (paracetamol; Tylenol) and anti-nausea drugs, and drinking plenty of water.

Weight loss is common during HCV treatment. Eating smaller, light meals throughout the day may boost energy.

Many people feel very tired during HCV treatment. Taking regular naps, doing light exercise whenever possible, and taking methylphenidate (Ritalin) or bupropion (Wellbutrin) may help with fatigue.

### Mental Health and Depression

It is important to have access to peer support and mental health care before starting HCV treatment, since PEG-IFN can cause anxiety, irritability, insomnia, mania, and mood swings. In addition, both PEG-IFN and RBV can cause mild to very serious depression. In rare cases, people have become suicidal. People who have been seriously depressed in the past are more likely to become depressed during HCV treatment, but it can happen to anyone.

Sometimes people take antidepressant medication before starting HCV treatment, because it may take time to find the right medication. Other people prefer to wait and see if they become depressed during HCV treatment. Antidepressants have their own side effects, so some people prefer to avoid using them unless they need to.

### Changes in Blood Cell Counts

PEG-IFN can cause low white blood cell counts (called **neutropenia**; these white blood cells fight infections), low red blood cell counts (called **anemia**; these red blood cells carry oxygen through the body), or low platelets (called **thrombocytopenia**; these help blood to clot). Coinfected people are more likely to develop neutropenia, anemia, and thrombocytopenia during HCV treatment. The addition of a protease inhibitor to PEG-IFN and RBV can increase the risk of experiencing these side effects, or make them worse.



## **Anemia**

Usually, people who have anemia feel very, very tired. When anemia develops during HCV treatment, doctors can reduce the ribavirin dose (which may make HCV treatment less likely to work). Zidovudine (Retrovir; AZT), an HIV drug, can also cause anemia, so it is important for HIV-positive people to avoid zidovudine while they are on HCV treatment.

## **Neutropenia**

This can increase the risk of getting a bacterial infection. Usually, doctors treat it by reducing the PEG-IFN dose.

## **Thrombocytopenia**

HIV can cause thrombocytopenia, and sometimes people with serious liver damage have thrombocytopenia because the liver cannot help to make platelets. When people get thrombocytopenia during HCV treatment, they usually take a lower dose of PEG-IFN. If thrombocytopenia becomes very serious, HCV treatment should be stopped.

## **Other Potential Side Effects from Adding a Protease Inhibitor to PEG-IFN/RBV**

Adding telaprevir can also cause an increase in bilirubin and uric-acid levels, rash (reported as very serious in 4% of clinical trial participants), itching, hemorrhoids, itching and burning in and around the anus, nausea, vomiting, diarrhea, dysgeusia (a bad or strange taste in the mouth), and fatigue.

Boceprevir can also cause fatigue, nausea, vomiting, diarrhea, rash, dysgeusia, headache, dizziness, jaundice, and elevated liver enzyme levels.

### **ADVOCACY EXERCISE**

#### **Discussion Questions:**

1. How can we increase access to HCV care and treatment?
2. What are the other services that we need, such as: peer support programs, better access to opioid substitution therapy (OST) and mental health programs?
3. Does your country have HCV treatment guidelines?

#### **Action Steps:**

1. What are our most important arguments for increasing access to HCV treatment to policymakers?
2. What can we do to get a clinical trial for hepatitis C treatment that works for people in my community (e.g., people with genotype 3)?

## SECTION 9. TREATMENT FOR PEOPLE WHO USE DRUGS OR ALCOHOL USERS AND TREATMENT ISSUES FOR HIV/HCV COINFECTION

Some doctors may refuse, or be reluctant to treat, people who are using illicit drugs and alcohol—even when they need treatment and are ready and willing to undergo therapy.

### Drug Use

Although many doctors think that it is not possible to treat HCV in people who are using drugs, several studies have shown otherwise. These studies found that people who use drugs could be successfully treated for HCV, when their side effects were treated and when counseling from peers and mental health staff, methadone or buprenorphine, clean injection equipment and addiction treatment were available on request. Access to clean injection equipment is also critical to help prevent reinfection.

### Alcohol Use

Studies have found that both lifetime and recent alcohol use among people with HCV undergoing treatment can reduce the chance of being cured of the virus. However, many of these studies involved people being treated with non-pegylated interferon, which is considered inferior and harder to take compared with the current standard of care. Plus, the studies didn't measure adherence. In fact, a more recent study suggests that poor treatment adherence, not alcohol consumption, worsens treatment outcomes.

### Marijuana

Marijuana may have both positive and negative health effects for people with HCV.

Daily marijuana use may increase fat buildup in liver cells (*steatosis*), which can worsen fibrosis, according to one study. Researchers have also found that some people with HCV who have used marijuana daily for many years have more serious liver damage than those who don't use the drug or use it occasionally, although other studies have not confirmed this finding.

Modest marijuana use may be beneficial for some people undergoing HCV treatment. In one study, it helped to reduce side effects, which allowed more people to complete treatment—and be cured of the virus—compared with those who didn't.

There are many new treatments for HCV being studied; hopefully, some people will be able to get access to HCV treatment through clinical trials, but it is important to learn about the risks and benefits of the trial first. Some trials are better than others.

### HCV and HIV Treatment Issues for HIV/HCV-Coinfected People

Ideally, all HIV-positive people should be tested for HCV and offered treatment if needed.

HCV progresses more quickly in people who are also HIV-positive, so access to HCV treatment is especially important for people with coinfection.

Coinfected people with a CD4 cell count of more than 500 cells/mm<sup>3</sup> may treat HCV first, but most people start HIV treatment before treating HCV, because many people don't find out that they are HIV-positive until after their CD4 count is below 200 cells/mm<sup>3</sup>. HIV treatment can keep the immune system healthy, which slows HCV progression.

There is not very much information on how safe HCV treatment is or how well it works for people with less than 200 CD4 cells/mm<sup>3</sup> who are also taking ART. This is an important question, because people with low CD4 cell counts are at higher risk for liver damage from HCV.

### **PEG-IFN and CD4 Cell Count**

PEG-IFN can lower the absolute CD4 cell count (but not the percentage of CD4 cells), even when someone is on ART. This can be frightening, but it is temporary. The CD4 cell count goes back up after stopping PEG-IFN.

### **Antiretrovirals (ARVs) and Liver Toxicity**

Many ARVs are broken down by the liver. Some ARVs are more harmful to the liver than others, especially when a person is coinfecting with HCV. Liver toxicity is more likely for coinfecting people with serious liver scarring. Having liver enzyme levels checked regularly is very important for coinfecting people who are taking ARVs, because these can pick up liver problems caused by HIV drugs or other causes.

Although all drugs used to treat HIV may cause liver problems, some are more likely to cause damage than others. Nevirapine, a non-nucleoside reverse transcriptase inhibitor, should not be used in women with a CD4 cell count above 250 cells/mm<sup>3</sup> and men with a CD4 cell count above 400 CD4 cells/mm<sup>3</sup>. Darunavir, an HIV protease inhibitor, can be toxic to the liver. Careful monitoring of liver enzyme levels is recommended for people using this drug.

Curing HCV treatment can lower the risk of liver toxicity from ARVs by slowing or stopping liver scarring.

### **Drug Interactions**

Some ARVs should not be used during HCV treatment because they interact with ribavirin, telaprevir, or boceprevir.

**Didanosine (ddl; Videx)** should not be used with ribavirin because the combination can cause lactic acidosis (when lactic acid builds up in the blood), and pancreatitis; both conditions can be life-threatening. Using ddl during HCV treatment has caused liver failure in people with cirrhosis.

**Zidovudine (AZT; ZDV; zidovudine; Retrovir)** can cause anemia, as can ribavirin. The combination increases the risk of anemia, so AZT should be avoided during HCV treatment.

**Stavudine (d4T; Stavir)** may cause fat loss (called *lipoatrophy*), and increase weight loss when used during HCV treatment. When possible, d4T should not be used during HCV treatment.

Note that some of these medications may be combined with other HIV medications in single-tablet formulations (also called **fixed-dosed combinations**). The names of these fixed-dose combinations may be different from those listed above.

**HIV protease inhibitors boosted with ritonavir** should not be taken at the same time as boceprevir. Telaprevir can, however, be taken at the same time as ritonavir-boosted atazanavir.

ARVs	Boceprevir	Telaprevir
Atazanavir + ritonavir	No	Yes
Darunavir + ritonavir	No	No
Lopinavir + ritonavir	No	No
Efavirenz	No	Yes, but only if a higher dose of telaprevir is used
Raltegravir	Yes	Yes
Tenofovir	Yes	Yes
FTC or 3TC	Yes	Yes

**Efavirenz (also known as EFV or Sustiva; it is also found in the fixed-dose combination tablet Atripla)** should not be taken at the same time as boceprevir. It can, however, be taken at the same time as telaprevir as long as the dose of telaprevir is increased to 1,125 mg, three times per day.

It is very important that health care providers know all of the medication a person with HCV or HIV is taking to make sure there are no drug interactions. These can greatly increase the risk of side effects and make HCV or HIV treatment less effective.

A complete listing of drug-drug interactions is available at: [www.hep-druginteractions.org](http://www.hep-druginteractions.org).

### ADVOCACY EXERCISE

#### Discussion Questions:

1. How can we get better, less toxic ARV regimens that work with HCV treatment?
2. Is it difficult for coinfecting people to change ARV regimens where you are?

#### Action Steps:

1. How can we increase access to HCV care and treatment for HIV-positive people and people who use drugs?
2. How can we address other barriers to HIV and HCV treatment access, including discrimination in health care settings, lack of comprehensive harm reduction services, and the criminalization of people who use drugs?

## SECTION 10. FIGHTING FOR NEW HCV DRUGS

There are many new oral HCV drugs, called **direct-acting antivirals** (DAAs), being developed. They work by attacking different parts of the hepatitis C virus, making it impossible for the virus to reproduce. There are different classes of DAAs, each targeting a specific part of the HCV life cycle. Certain DAAs will be used with PEG-IFN and RBV (but for a shorter time) or just RBV, and some will be used with each other.

Sometimes drug makers will sell older drugs at a lower price, making them accessible in some middle-income countries. Some of these drugs work only for people with a certain HCV genotype, and they are less effective and have worse side effects than newer drugs. Cheaper treatment may wind up costing more to people with HCV and health care systems, because:

- People may need to switch their ARVs to avoid drug interactions with DAAs, but certain HIV drugs may not be available everywhere;
- Several tests are needed, to monitor safety and see whether treatment is working;
- More medical visits are needed;
- Side effects make it difficult for many people to complete treatment;
- Some drugs need to be taken every eight hours, with food; others are taken every 12 hours, making adherence difficult; and
- Treatment duration depends on whether or not someone has an early response; this uncertainty makes it difficult for people who are considering HCV treatment, and for medical providers, who need to put aside sufficient time for patient management.

It is important to learn about the local and national epidemics where you are so that you can advocate for the best possible HCV treatments. For example, most HCV DAAs can be used with opioid substitution therapy (OST), but some cannot be used with certain ARVs—these may be the ones that are available in your country. Some DAAs work only against a single genotype; others may not have been studied in many people with the genotype—or genotypes—that are most common in your country. Some regimens are simple—fixed-dose combinations that require less monitoring during treatment.

### ADVOCACY EXERCISE

#### Discussion Questions:

1. What do we know about HCV in our area?
2. What do we need to know about new HCV drugs?

#### Action Steps:

1. How can we create or improve access to the DAAs that are right for us?

## APPENDIX

### **Working with Your Health Care Providers**

You have the right to be involved in decisions about your own health.

#### **Find a good doctor/health care provider**

Many people who use drugs find it difficult to feel safe talking about their drug use with their doctor. Also, some doctors (and other health care providers) are more comfortable working with people who use drugs than others. Ask your friends if they have a good doctor that you can talk to. If you can't find a good doctor right away, at least you will learn about which health care providers to avoid, or what to be ready for in the case that you meet a doctor who does not want to treat people who use drugs. Consult your local harm reduction center or PLWHA network office for lists of health care providers they suggest.

#### **Ask questions**

Don't be afraid to ask questions about any tests or treatments that your health care provider suggests. Your health care provider should let you know about the risks and benefits of medications. The provider should tell you about the possible side effects, how common these are, and what can be done to help you get through hepatitis C treatment. You can be prepared by writing down some of your questions before your appointment.

#### **Be clear about needs and responsibilities**

Direct communication between you and your health care provider is important. Your health care provider can give you better care when you are honest about what you need. It may take time to develop a relationship with your health care provider, and it is not always possible. Since changing providers is not always an option, it is important to ask your provider what his or her needs and expectations are, as well as to share your own needs and expectations.

If you need any drugs with abuse potential, such as pain and antianxiety medications, talk with your doctor or health care provider in advance. Ideally, you can make an agreement about how often you get the medications, what to do if you need a higher dose, and how long you will be using them; make a plan to taper off of pain medication in advance, if needed. While the legal and policy environments make it difficult for people who use drugs to feel safe sharing personal information such as this with a health care provider, it is important to remember that your provider must respect your confidentiality and must treat you and your concerns with respect. If you feel your rights have not been respected, you may contact your local harm reduction center or network center for people living with HIV/AIDS (PLWHA) to ask for help in negotiating this issue with your provider or health care institution.

#### **Keep appointments**

Try not to miss appointments with your health care provider, even if you are using drugs. Some health care providers will use your reliability in attending appointments as a factor in their decision about treating your HIV or hepatitis C. If you need to miss an appointment, try to call ahead of time to cancel and reschedule.

When you are on treatment, it is even more important to keep appointments, because your health care provider needs to monitor your health, response to treatment, and any side effects.

## **Be prepared**

Make a list of questions in advance. Bring a friend or family member with you who can help you remember what your health care provider told you. Your doctor may not have much time to speak with you, so make sure to ask him or her to direct you to someone who can answer your questions, or schedule another appointment.

## **Share information with your health care provider**

If you are using any other medications, vitamins, or herbs, tell your health care provider or bring them with you to show your provider. Keep an updated list, and tell your health care provider if you are starting a new medication. Some may be toxic to the liver, or have interactions with other drugs that you're taking, which can make them less effective or increase side effects.

Tell your health care provider about any side effects you are having, even if they seem insignificant to you. They may be the sign of a more serious problem. For example, feeling tired may be a symptom of anemia (low red blood cell count), and can also be caused by PEG-IFN, ribavirin, and zidovudine.

## **Monitor your health**

Ask for copies of your lab work, and keep track of any changes so that you can ask your health care provider about them. Use the lab work sheet provided at the end of this section to keep track of your lab results over time.

## **Clinical trials**

Your health care provider may suggest that you participate in a clinical trial. Sometimes trials offer access to experimental or approved treatments that are not available otherwise, but it is important to get as much information as you can about the possible risks and benefits before you decide to enter a trial.

Health care providers are not always the best source of information about a trial (sometimes people get paid for enrolling people in a study, or their job depends on whether or not people sign up for a trial). Besides asking about risks and benefits, the most important questions for your health care provider are:

- What kind of treatment do you suggest if I decide not to enter the trial?
- Are there other options?
- If so, can you describe them?

Joining a trial is not an emergency; you have some time to learn more about whether or not it is the best option for you. Ask to take a copy of the informed consent document (it describes the known risks and benefits of participating in the trial), and read it over. Some NGOs may have more information about the trial; it's always a good idea to get a few different opinions, especially from community members and advocates. At the end of this manual, we provide a list of PLWHA groups, harm reduction organizations, and NGOs that can help you with this and other issues.

## Track Your Lab Work

Lab Tests	Date	Date	Date	Normal Ranges
CD4 count				From 0 to 1,600 cells/mm <sup>3</sup>
HIV viral load				From undetectable to over 1 million IU/mL
HCV viral load (HCV RNA)				From undetectable to over 10 million IU/mL
ALT (or SGPT)				<p>Women: 19 units/L Men: 30 units/L</p> <p>Alanine aminotransferase (ALT) is made by the liver. When ALT is abnormally high, it may be a signal that the liver is inflamed or damaged, especially if it stays high over time. ALT is not a good indicator of liver damage, since levels can be normal in people with serious liver damage, and they may go up and down in people with HCV. Certain drugs, including some ARVs, may increase ALT.</p>
AST (or SGOT)				<p>Women: 9–25 units/L Men: 10–40 units/L</p> <p>Aspartate aminotransferase (AST) is made in the heart, intestines and muscles. It does not always show liver damage by itself; AST is used with other tests to monitor liver inflammation and damage.</p>
ALP				<p>Women: 30–100 units/L Men: 45–115 units/L</p> <p>Alkaline phosphatase is found in tissues throughout the body, including in the liver. Abnormally high ALP is a signal of diseased or damaged tissue. When ALP that comes from the liver is abnormally high, it is a sign of liver disease.</p>
GGT				<p>Women: &lt;45 units/L Men: &lt;65 units/L</p> <p>Gamma-glutamyl transferase (GGT) is made in the bile ducts, the tubes carrying bile from the liver to the gallbladder and intestines. Liver disease, heavy drinking, and some medications can cause abnormally high GGT levels.</p>
Bilirubin (direct)				<p>0.0–0.4 mg/dL (U.S.) 0–7 umol/L (SI units)</p> <p>Direct bilirubin is produced in the liver. If bile ducts are blocked, direct bilirubin will seep into the bloodstream (and sometimes the urine). Liver disease, or certain medications, may increase the level of direct bilirubin in the bloodstream.</p>
Bilirubin (total)				<p>0.0–1.0 mg/dL (U.S.) 0–17 umol/L (SI units)</p> <p>Indirect bilirubin travels from the bloodstream to the liver, to be broken down into a form that dissolves in water. Abnormally high levels of indirect bilirubin may signal liver disease.</p>
Albumin				<p>3.1–4.3 g/dL (U.S.) 31–43 g/L (SI units)</p> <p>Albumin carries drugs, hormones, and waste products through the bloodstream and keeps fluid in the body. Abnormally low albumin levels are a sign of liver damage.</p>
PT				<p>11–13.5 seconds (1–2 times above this range is abnormal: INR 2–3)</p> <p>Prothrombin time (PT) is a measurement of how long it takes for blood to clot. The liver helps produce platelets, which clot blood. A longer PT means that the liver is not functioning normally.</p>



## HEPATITIS A (HAV)

**The virus is found in:** feces (stool; shit)

**You CAN get hepatitis A when:** feces from a person with hepatitis A virus get into your mouth.

This can happen when

- drinking water containing sewage (when a sewage pipe breaks, or during flooding);
- eating food handled by someone with HAV who didn't wash their hands after using the bathroom;
- eating raw shellfish or fish from contaminated water;
- eating raw fruit and vegetables in areas where sanitation is poor; or
- having unprotected sex—**rimming** (kissing or licking someone's asshole; mouth to asshole).

**You CANNOT get hepatitis A from:** casual contact (kissing, shaking hands, or sharing glasses or eating utensils).

**You can only get infected with HAV once.** Globally, the World Health Organization estimates there are 1.4 million cases every year. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that 17,000 people got hepatitis A in 2010. Cases of HAV have been dropping in the U.S. since 1995, when the HAV vaccine became available.

**You can protect yourself against hepatitis A by:** getting vaccinated. Recommendations vary from country to country. Some countries recommend the vaccine for all children over one year of age. Some countries also recommend the vaccine for travelers to countries where HAV is common and other people who may be at risk, including men who have sex with men and people with chronic hepatitis B or chronic hepatitis C. Cost varies.

**Symptoms:** Most children don't feel sick at all; some adults have symptoms, including nausea, vomiting, diarrhea, fever, fatigue, rash, jaundice (yellow skin and eyes), liver pain, and dark brown urine.

**Hepatitis A is not a chronic (lifelong) infection:** it goes away by itself, usually within two months.

**You can find out if you have already had hepatitis A by:** getting blood tests that tell if you have already been infected, or if you need the vaccine.

**Treatment:** There is no treatment for HAV; almost everyone can clear the virus without treatment.

**Outcome:** VERY rarely is HAV life-threatening, but people with HCV are at risk for liver failure if they get HAV.

## Hepatitis B (HBV)

**The virus is found in:** blood, semen, and vaginal fluid (very small amounts of HBV have been found in breast milk and saliva).

**You CAN get hepatitis B:** in the same ways as HIV (although it is 50–100 times more infectious than HIV), from

- sharing drug use– or tattoo equipment: including needles, water, cookers, cotton, measuring syringes, and tattoo ink and inkwells;
- needlestick accidents or other occupational exposures;
- unprotected anal, vaginal, or oral sex with a person who has HBV;
- improperly sterilized medical or dental equipment;
- mother-to-child during birth; and
- sharing personal care items that may have blood on them, such as razors and toothbrushes.

**You CANNOT get hepatitis B from:** casual contact (kissing, shaking hands, or sharing glasses or eating utensils).

**You can only get infected with HBV once.**

The World Health Organization (WHO) estimates that 2 billion people worldwide have been infected with HBV and about 600,000 people die every year from liver disease and cancer caused by the infection. The Centers for Disease Control and Prevention (CDC) estimates that 38,000 people became infected with HBV in 2010 in the United States, and 2 million people are living with chronic HBV. New HBV infections have dropped dramatically in many countries where the vaccine is widely available.

**You can protect yourself against hepatitis B by:** getting vaccinated, or with an injection of hepatitis B immune globulin (HBIG) within 24 hours of exposure.

In the United States, HBV vaccination is recommended for infants; unvaccinated persons who are less than 19 years old; people with multiple sex partners, or a partner who has HBV; people who inject drugs; HIV-positive people; and people with chronic liver disease, among others. The WHO recommends that all infants receive the hepatitis B vaccine.

**Symptoms:** Most children do not have symptoms; some adults (30–50%) have symptoms during the first few months after getting HBV (also called the **acute phase**): nausea, vomiting, appetite loss, fever, fatigue, abdominal and joint pain, liver swelling, and jaundice (yellow skin and eyes). In very rare cases, symptoms may be very severe and can be fatal (called **fulminant hepatitis**).

**Hepatitis B:** becomes a chronic (lifelong) infection in about six percent of healthy adults. Hepatitis B is more likely to become chronic in people infected at birth or during childhood (90%), and in HIV-positive people (30–90%).

**You can find out if you have hepatitis B by:** blood tests; they can tell if you cleared hepatitis B without treatment, if you just got it, or if you have chronic hepatitis B.

**Treatment:** Chronic hepatitis B can be treated with the oral antiviral drugs entecavir and tenofovir, or with PEG-IFN. Treatment can suppress HBV, but less than 10 percent of people will clear it. Since hepatitis B often comes back when people stop oral antivirals, HBV treatment is usually lifelong. It is important to talk to your doctor before stopping or switching HBV medications so you can avoid hepatitis B flare-ups, which can be life-threatening.

**Outcome:** If untreated, about 25 percent of people with chronic HBV will develop cirrhosis (serious liver scarring), liver cancer, or end-stage liver disease, but this takes many years. Hepatitis B is worse in people coinfecting with hepatitis C.

### **HIV Coinfection**

- All HIV-positive people should be screened for HBV and get the HBV vaccine if they don't have HBV.
- HIV makes HBV worse; it is more likely to become chronic, progresses more quickly, and is harder to treat.
- Because some HIV drugs are also active against HBV, but not strong enough to fully control HBV, HIV/HBV-coinfecting people should only use HIV regimens that contain tenofovir to prevent developing HBV drug resistance.

U.S. brand-name combination pills containing tenofovir include Truvada, Atripla, and Stribild.

## Hepatitis C (HCV)

**The virus is found in:** blood (very small amounts have been found in semen and vaginal fluid).

**You CAN get hepatitis C when:** blood from a person with HCV enters your bloodstream, from:

- Sharing drug use— or tattoo equipment, including needles, measuring syringes, water, cookers, cotton, and tattoo ink and inkwells. Since hepatitis C is a much smaller virus than HIV, there is more of it in a drop of blood. Bleach doesn't kill it. Up to 90 percent of current and former injection drug users have hepatitis C;
- Unprotected sex (especially if you have a sexually transmitted infection such as herpes, syphilis, or HIV) that involves blood (rough anal or vaginal sex, fisting, etc., are riskier);
- Mother-to-child during birth;
- Needlestick accidents;
- Improperly sterilized medical or dental equipment; and
- Sharing personal care items that may have blood on them, such as razors and toothbrushes.

**You CANNOT get HCV from:** casual contact (kissing, shaking hands, or sharing glasses or eating utensils).

**You can be reinfected:** This means you can get HCV more than once, even if your immune system cleared the virus on its own or you were cured using hepatitis C treatment.

Worldwide, at least 185 million people have been infected with hepatitis C. In the United States, roughly 3.2 million people are living with chronic hepatitis C.

**You can protect yourself against hepatitis C by:** using clean injection and tattooing equipment, getting checked and treated for other sexually transmitted infections, using condoms for vaginal and anal sex and gloves for fisting. There is no HCV vaccine (but researchers are working on preventive and therapeutic vaccines).

**Symptoms:** Most people have no symptoms when first infected; about 20 percent will have nausea, abdominal pain, appetite loss, fatigue, jaundice (yellow skin and eyes), and dark urine.

**Hepatitis C:** becomes chronic (lifelong) in 55–85% of people; the rest clear the virus without treatment, usually within six months of becoming infected.

**You can find out if you have hepatitis C:** by taking blood tests. They can tell you if you cleared hepatitis C without treatment, if you just got it, or if you have chronic hepatitis C.

**Treatment:** Hepatitis C can be treated—and cured—with a combination of pegylated interferon and ribavirin, and in some cases by adding another drug (called a **protease inhibitor**), but HCV treatment does not always get rid of the virus, and the side effects can be severe. New therapies are currently in development.

**Outcome:** Twenty to 30 percent of chronically infected people will develop cirrhosis (serious liver scarring) over decades. Each year, one to five percent of people with cirrhosis develop liver cancer. Hepatitis C is worse in people who are coinfecting with hepatitis B.

### HIV Coinfection

- All HIV-positive people should be screened for HCV.
- HIV makes HCV worse: HCV is more likely to be chronic, progresses more quickly, and is harder to treat in people with HIV.

# INCIVEK (telaprevir)

## What is Incivek?

Incivek is a hepatitis C virus (HCV)–fighting protease inhibitor that works for people with genotype 1. Incivek blocks an important step in the hepatitis C virus life cycle. The HCV protease enzyme works like a pair of scissors; it cuts viral proteins into smaller pieces so that they can be put back together again into new virus particles (called **virions**). Hepatitis C protease inhibitors work by binding to the virus’s protease enzyme—just like inserting something between scissor blades so they cannot cut.

## How is it used?

Incivek is not strong enough to work by itself; it must be used with pegylated interferon and ribavirin (PEG-IFN+RBV). These medications work together to get rid of hepatitis C by helping the immune system to get rid of HCV-infected cells, and making it difficult for the virus to reproduce.

Adding Incivek to PEG-IFN+RBV increases cure rates among people who are being treated for the first time (called **treatment-naive**) and people who have already been treated for HCV (called **treatment-experienced**).

PEG-IFN, RBV and Incivek are started at the same time.

- **PEG-IFN** is injected, once weekly.
- **RBV** pills or capsules are taken twice daily, dose is according to your weight.
- **INCIVEK** comes in boxes of seven daily-dose blister packs. The daily dose is six pills—two 375 mg capsules every 7 to 9 hours—with a snack or meal that contains at least 20 grams of fat (3 table-spoons of peanut butter, 2 ounces of cheese, or a bagel and cream cheese). It is important not to miss doses of Incivek.

The length of time on treatment varies, depending on someone’s past HCV treatment history, whether or not a person has cirrhosis, and how well it is working (called **response-guided therapy**), measured by how much, and when the amount of hepatitis C virus in the bloodstream (called **HCV RNA** or **viral-load**) drops.

## RESPONSE-GUIDED THERAPY

Response to Treatment	Combination and Treatment Duration
<b>Treatment-Naive People or Treatment-Experienced People Who Are Prior Relapsers</b>	
Undetectable HCV RNA at week-4 and week-12	Incivek+PEG-IFN+RBV for first 12 weeks, followed by PEG-IFN+RBV only for another 12 weeks. <b>Total 24 weeks.</b>
Detectable HCV RNA <1000 IU/mL at week-4 and/or week-12	Incivek+PEG-IFN+RBV for first 12 weeks, followed by PEG-IFN+RBV only for another 36 weeks. <b>Total 48 weeks.</b>
<b>Treatment-Experienced People Who Are Prior Partial or Null Responders</b>	
Undetectable or HCV RNA <1000 IU/mL at week-4 and/or week-12	INCIVEK+PEG-IFN+RBV for first 12 weeks, followed by PEG-IFN+RBV only for another 36 weeks. <b>Total 48 weeks.</b>
<b>People With Cirrhosis</b>	
Undetectable or HCV RNA <1000 IU/mL at week-4 and/or week-12	INCIVEK+PEG-IFN+RBV for first 12 weeks, followed by PEG-IFN+RBV only for another 36 weeks. <b>Total 48 weeks.</b>

## STOPPING RULES:

All people should **discontinue treatment** if they have HCV RNA >1000 IU/mL at week-4 or week-12, or if they have detectable HCV RNA (any level) at week-24.

## How well does Incivek work?

The likelihood of being cured depends on several things.

**Adherence**—or taking your medication as prescribed—is important, to lower the risk of drug resistance and treatment failure.

In clinical trials of Incivek, about 74% of treatment naïve people were cured. African Americans, people with cirrhosis, and people with an IL-28B CT or TT genotype were less likely to be cured.

Re-treatment with Incivek, PEG-IFN and RBV is more likely to work for people who **relapsed** (when HCV reappears after treatment) and **partial responders** (when HCV drops by 99% during treatment, but is still detectable at week 24) than **null responders** (when HCV RNA does not drop by 99% by week 12). Retreatment is more likely to work for partial and null responders who do not have cirrhosis.

## Side effects

**Make sure and talk with your health care provider about possible side effects and how they will be managed.** PEG-IFN and RBV have many side effects, and Incivek worsens some of them. Most people have at least one of these side effects, and they range from mild to very serious. Known side effects of Incivek include a drop in white blood cells, thrombocytopenia (a drop in platelets), and an increase in bilirubin and uric acid levels, itching, hemorrhoids, anorectal itching and discomfort, nausea, vomiting, diarrhea, dysgeusia (a bad or strange taste in the mouth) and fatigue.

Rash can be a very serious (sometimes even life-threatening) side effect from Incivek, although this happens rarely. If you develop a rash that seems to be spreading or a rash with fever, contact your healthcare provider immediately

Incivek causes anemia (a drop in red blood cells). Get a blood test to check for anemia before starting treatment, and again during treatment with Incivek, at least at weeks 2, 4, 8, and 12.

## Does Incivek work for people who also have HIV?

**Yes, but it does not mix with many HIV drugs** (see drug-drug interactions).

In a clinical trial in HIV/HCV coinfecting people who had never been treated for hepatitis C, approximately 74% were cured after 48 weeks of treatment (12 weeks of Incivek plus PEG-IFN+RBV, followed by 36 weeks of PEG-IFN+RBV).

Other clinical trials are looking at Incivek in treatment experienced HIV/HCV coinfecting people.

## Incivek and other medications: drug-drug interactions

**Incivek should not be used with certain drugs. Talk with your health care provider and pharmacist before starting—or stopping—any medications.** For people on methadone or buprenorphine, monitoring is recommended, and a dose adjustment may be needed.

For people with HIV, Incivek can be used with Norvir-boosted Reyataz or Isentress, plus Viread with Emtriva or Epivir. If using Atripla (or Sustiva plus Viread with Emtriva or Epivir), the dose of Incivek must be increased from 750 mg to 1125 mg. Incivek increases levels of some statin—or cholesterol-lowering—drugs, so it cannot be used with certain statin drugs. Incivek should not be used with several other drugs, including migraine medications, St John's Wort, certain sedatives, hypnotics and neuroleptics, PDE5 inhibitors (for treatment of pulmonary hypertension), and some anti-tuberculosis medications. **A complete listing of drug-drug interactions is available in Incivek's prescribing information, and at: [www.hep-druginteractions.org](http://www.hep-druginteractions.org).**

## Is there anyone who cannot use Incivek?

People with certain serious medical conditions, women who are pregnant, nursing, or trying to become pregnant, and people taking certain medications (see Incivek and other medications). Incivek has not been studied in people under 18 years of age.

## Access to Incivek

Vertex's patient assistance program (for uninsured people; income eligibility criteria apply) and co-pay assistance.

Call 855-837-8394 or go to [www.incivek.com](http://www.incivek.com)

**Access to pegylated interferon and ribavirin** (for uninsured people; income eligibility criteria apply)

**Pegasys and Copegus:** Genentech's patient assistance programs. Call 888-941-3331.

**Peg-Intron and Rebetrol:** Merck's patient assistance programs. Call 866-363-6379.

## What Is Drug Resistance?

Each day, hepatitis C makes billions of copies of itself. Some of these copies are not identical to the original (also called **wild-type**) virus. They have changes in their genetic structure, which are called **mutations**. Mutations happen at random, but the more a virus reproduces, the more likely it is that some copies will have mutations. Mutations can make it easier—or harder—for a virus to reproduce, and can prevent drugs from being effective.

When people skip their HCV medications, the virus has an opportunity to reproduce—and some of these virions may have mutations. Once a person begins taking HCV medication again, it will kill the wild-type virus, but it may not be able to kill all the virions, because some of them may have mutations that cause drug resistance. This can lead to treatment failure.

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.

**TAG**

Treatment Action Group  
[www.treatmentactiongroup.org/hcv](http://www.treatmentactiongroup.org/hcv)

# VICTRELIS (boceprevir)

## What is Victrelis?

Victrelis is a hepatitis C virus (HCV) –fighting protease inhibitor that works for people with genotype 1. Victrelis blocks an important step in the hepatitis C virus life cycle. The HCV protease enzyme works like a pair of scissors; it cuts viral proteins into smaller pieces so that they can be put back together again into new virus particles (called *virions*). Hepatitis C protease inhibitors work by binding to the virus’s protease enzyme—just like inserting something between scissor blades so they cannot cut.

## How is it used?

Victrelis is not strong enough to work by itself; it must be used with pegylated interferon and ribavirin (PEG-IFN+RBV). These medications work together to get rid of hepatitis C by helping the immune system to get rid of HCV-infected cells, and making it difficult for the virus to reproduce.

Adding Victrelis to PEG-IFN+RBV increases cure rates among people who are being treated for the first time (called *treatment-naive*) and people who have already been treated for HCV (called *treatment-experienced*).

HCV treatment begins with 4 weeks of PEG-IFN+RBV; this is called the *lead-in*. After the lead-in, Victrelis is added.

- **PEG-IFN** is injected, once weekly.
- **RBV** pills or capsules are taken twice daily, dose is according to your weight.
- **VICTRELIS** comes in daily-dose bottles. The daily dose is 12 capsules—four 200 mg capsules every 7 to 9 hours, with a snack or meal. It is important not to miss doses of Victrelis.

The length of time on treatment varies, depending on someone’s past HCV treatment history, whether or not a person has cirrhosis, and how well it is working (called *response-guided therapy*), measured by how much, and when the amount of hepatitis C virus in the bloodstream (called *HCV RNA* or *viral-load*) drops.

## RESPONSE-GUIDED THERAPY

Response to Treatment	Combination and Treatment Duration
<b>Treatment-Naive People</b>	
Undetectable HCV RNA at week-8 and week-24	PEG-IFN+RBV 4-week lead-in, followed by Victrelis+PEG-IFN+RBV for another 24 weeks. <b>Total 28 weeks.</b>
HCV RNA <100 IU/mL at week-8, Undetectable HCV RNA at week-24	PEG-IFN+RBV 4-week lead-in, followed by Victrelis+PEG-IFN+RBV for 32 weeks, then PEG-IFN+RBV only for another 12 weeks. <b>Total 48 weeks.</b>
<b>Treatment-Experienced People Who Are Prior Relapsers or Prior Partial Responders</b>	
Undetectable HCV RNA at week-8 and week-24	PEG-IFN+RBV 4-week lead-in, followed by Victrelis+PEG-IFN+RBV for another 32 weeks. <b>Total 36 weeks.</b>
HCV RNA <100 IU/mL at week-8, Undetectable HCV RNA at week-24	PEG-IFN+RBV 4-week lead-in, followed by Victrelis+PEG-IFN+RBV for 32 weeks, then PEG-IFN+RBV only for another 12 weeks. <b>Total 48 weeks.</b>
<b>Treatment-Experienced People Who Are Prior Null Responders</b>	
HCV RNA <100 IU/mL at week-12, Undetectable HCV RNA at week-24	PEG-IFN+RBV 4-week lead-in, followed by Victrelis+PEG-IFN+RBV for another 44 weeks. <b>Total 48 weeks.</b>
<b>People With Cirrhosis Regardless of Prior HCV Treatment History</b>	
HCV RNA <100 IU/mL at week-12, Undetectable HCV RNA at week-24	PEG-IFN+RBV 4-week lead-in, followed by Victrelis+PEG-IFN+RBV for another 44 weeks. <b>Total 48 weeks.</b>

## STOPPING RULES:

All people should **discontinue treatment** if they have HCV RNA  $\geq$ 100 IU/mL at week-12, or HCV RNA >10-15 IU/mL at week-24.

## How well does Victrelis work?

The likelihood of being cured depends on several things.

**Adherence**—or taking your medication as prescribed—is important, to lower the risk of drug resistance and treatment failure.

In clinical trials of Victrelis, about 65% of treatment naïve people were cured. African Americans, people with cirrhosis, and people with an IL-28B CT or TT genotype were less likely to be cured.

Re-treatment with Victrelis, PEG-IFN and RBV is more likely to work for people who **relapsed** (when HCV reappears after treatment) and **partial responders** (when HCV drops by 99% during treatment, but is still detectable at week 24) than **null responders** (when HCV RNA does not drop by 99% by week 12). Retreatment is more likely to work for partial and null responders who do not have cirrhosis.

## Side effects

**Make sure and talk with your health care provider about possible side effects and how they will be managed.** PEG-IFN and RBV have many side effects, and Victrelis worsens some of them. Most people have at least one of these side effects, and they range from mild to very serious. Known side effects of Victrelis include a drop in neutrophils (a type of white blood cells that fight bacterial infections), anemia (a drop in red blood cells), thrombocytopenia (a drop in platelets), fatigue, nausea, vomiting, diarrhea, dysgeusia (a bad or strange taste in the mouth), headache, dizziness, jaundice, and elevated liver enzyme levels.

## Does Victrelis work for people who also have HIV?

**Yes, but it does not mix with many HIV drugs** (see drug-drug interactions). In a clinical trial in HIV/HCV coinfecting people who had never been treated for hepatitis C, approximately 60% were cured after a 4-week PEG-IFN+RBV lead-in and 44 weeks of Victrelis plus PEG-IFN+RBV. Other clinical trials are looking at Victrelis in treatment experienced HIV/HCV coinfecting people.

## Victrelis and other medications: drug-drug interactions

**Victrelis should not be used with certain drugs. Talk with your health care provider and pharmacist before starting—or stopping—any medications.**

For people on methadone or buprenorphine, monitoring is recommended, and a dose adjustment may be needed.

For people with HIV, Victrelis lowers levels of Norvir-boosted HIV protease inhibitors, (Reyataz, Prezista, Kaletra), and Kaletra and Prezista lower Victrelis levels. Victrelis cannot be used with non-nucleosides (Atripla, Sustiva, Viramune, Intelence, Endurant, Complera). Victrelis increases levels of some statin—or cholesterol-lowering—drugs, so it cannot be used with certain statin drugs. Victrelis should not be used with many other drugs, including certain hormonal contraceptives, anti-seizure and migraine medications, St John's Wort and some anti-tuberculosis medications. **A complete listing of drug-drug interactions is available in the prescribing information for Victrelis, and at: [www.hep-druginteractions.org](http://www.hep-druginteractions.org).**

## Is there anyone who cannot use Victrelis?

People with certain serious medical conditions, women who are pregnant, nursing, or trying to become pregnant, and people taking certain medications (see Victrelis and other medications). Victrelis has not been studied in people under 18 years of age.

## Access to Victrelis

Merck's patient assistance program for uninsured people (income eligibility criteria apply). Call 866-363-6379.

Co-pay assistance (Victrelis only): [www.victrelis.com/boceprevir/victrelis/consumer/coupon.jsp](http://www.victrelis.com/boceprevir/victrelis/consumer/coupon.jsp)

**Access to pegylated interferon and ribavirin** (for uninsured people; income eligibility criteria apply)

**Peg-Intron and Rebetrol:** Merck's patient assistance programs. Call 866-363-6379.

**Pegasys and Copegus:** Genentech's patient assistance programs. Call 888-941-3331.

## What is Drug Resistance?

Each day, hepatitis C makes billions of copies of itself. Some of these copies are not identical to the original (also called **wild-type**) virus. They have changes in their genetic structure, which are called **mutations**. Mutations happen at random, but the more a virus reproduces, the more likely it is that some copies will have mutations. Mutations can make it easier—or harder—for a virus to reproduce, and can prevent drugs from being effective.

When people skip their HCV medications, the virus has an opportunity to reproduce—and some of these virions may have mutations. Once a person begins taking HCV medication again, it will kill the wild-type virus, but it may not be able to kill all the virions, because some of them may have mutations that cause drug resistance. This can lead to treatment failure.

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.

**TAG**

Treatment Action Group

[www.treatmentactiongroup.org/hcv](http://www.treatmentactiongroup.org/hcv)



# Hepatitis C and the IL28B Gene

## What predicts response to hepatitis C virus (HCV) treatment?

Many things help predict the likelihood of being cured (called *sustained virological response* or *SVR*) by pegylated interferon (PEG-IFN) and ribavirin (RBV). Making sure to take all medications as prescribed (called *adherence*) will really increase the likelihood of SVR.

Two of the strongest SVR predictors are virus-related: the amount of HCV in the bloodstream (called *viral load*) and the strain of HCV (called *genotype*). For example, HCV genotype 1 is harder to cure with PEG-IFN and RBV than genotypes 2 and 3. Medical issues (such as being HIV-positive, having liver damage, and being overweight) can also make HCV harder to cure.

PEG-IFN and RBV are less effective for African Americans and people of African ancestry than people of other races and ethnicities. Recently, researchers have discovered that this is mainly—but not completely—due to an inherited (*genetic*) factor, the interleukin-28B (IL28B) gene.

## What is the IL28B gene?

Genes are working parts of our body inherited from our parents. They determine eye, skin, and hair color as well as blood type, height, and race. The IL28B gene is involved in the immune response to certain viruses, including hepatitis C. There are three IL28B subtypes (called *genotypes*): CC, CT, and TT. **People with the CC genotype have a stronger immune response** to HCV infection than people with the CT or TT genotypes (called *non-CC genotypes*). This immune response makes people who have a CC genotype more likely to clear HCV without treatment (called *spontaneous viral clearance*), within months of becoming infected. People who have a CC genotype are also two to three times more likely to be cured by PEG-IFN and RBV, regardless of race or HIV status.

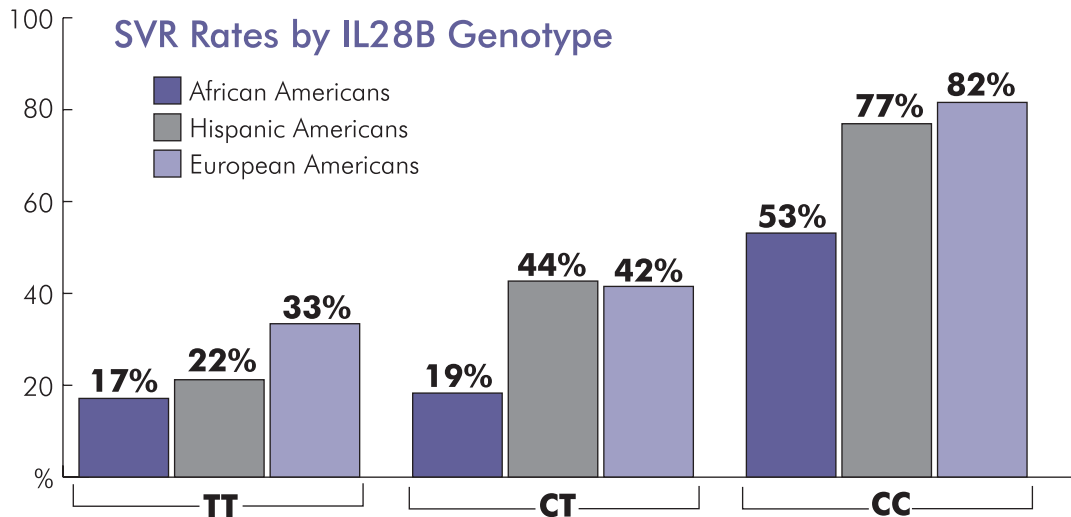
## Race and IL28B genotype

A person of any race or ethnicity could have any IL28B genotype, but African Americans and people of African ancestry are less likely to have the CC genotype than people of other races and ethnicities.

Ancestry	% Likely to Have IL28B CC Genotype
African	23–55
European	53–86
South Asian	65–98
East Asian	90–100

Source: Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature*. 2009 Oct 8;461(7265):798–801. doi: 10.1038/nature08463.

Although people with the CC genotype are more likely to be cured by PEG-IFN and RBV, race still influences the likelihood of being cured. SVR rates among people with the CC genotype are lower in African Americans and people of African ancestry than in people of other races. Researchers have not discovered other factors to explain the difference in SVR rates.



Adapted from Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009 Sep 17;461(7262):399-401. doi: 10.1038/nature08309.

## IL28B and new HCV drugs

Adding one of the new oral HCV drugs (called *direct-acting antivirals* or *DAAs*) to PEG-IFN and RBV or using a combination of DAAs will increase SVR rates in people with non-CC genotypes, regardless of race or ethnicity. It is still unclear whether IL28B genotype has a strong influence on cure rates from DAAs without PEG-IFN, or which DAAs are best for people with non-CC genotypes.

Regardless of your IL28B genotype, it is important to get a viral load test 4 or 12 weeks after starting HCV treatment, to see if it is working. People with an undetectable hepatitis C viral load at 4 or 12 weeks are more likely to be cured, especially if they have the IL28B CC genotype.

## How can I find out my IL28B genotype?

You can take a blood test to learn your IL28B genotype (called the *IL28B genotype test*). You only need to take this test once, because your IL28B genotype never changes.

- IL28B genotype may determine the type—and possibly length—of your HCV treatment. It can be important information for treatment decision-making.
- A person's IL28B genotype should never be used to withhold HCV treatment, since people with non-CC genotypes can also be cured.
- Soon, there will be more information about the best treatments for people with non-CC genotypes. Check with your medical providers.