TRAINING MANUAL FOR TREATMENT ADVOCATES

HEPATITIS C VIRUS & COINFECTION WITH HIV

TAG
Treatment Action Group

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 affordable access to, HCV diagnostics, treatment, and care for communities and individuals by continuing its domestic and international work with other activists, regulatory agencies, pharmaceutical companies, clinicians, and the patient community.

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Hepatitis C Virus and Coinfection with HIV

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January 2018

TREATMENT ACTION GROUP

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Glossary

AASLD/IDSA	American Association for the Study of Liver Diseases/Infectious Diseases Society of America
Antibody	Part of a person's immune system that responds to viruses, bacteria, and other harmful substances
Acute	A person has had an infection for a shorter duration, which may have mild or no symptoms; acute HCV infection infection may result in some inflammation to the liver
ALP	Alkaline phosphatase, an important liver enzyme
ALT; SGPT	Alanine aminotransferase or serum glutamic-pyruvic transaminase, a liver enzyme
APRI	Aspartate aminotransferase (AST) to platelet ratio index, formula used to determine level of cirrhosis
ARV	Antiretroviral drugs
ART	Antiretroviral therapy
AST; SGOT	Aspartate aminotransferase or serum glutamic oxaloacetic transaminase, a liver enzyme made in the heart, intestines, and muscle
CD4	Cluster of differentiation 4, found on a type of white blood cell in the body. In blood tests, the CD4 count is used to determine how healthy the immune system is and to monitor a person's response to antiretroviral therapy for HIV. HIV infects CD4 cells. The lower the count, the more damage done by HIV. If the count goes lower than 200 cells per millionth of a liter, it can make a person more at risk to opportunistic infections, such as pneumonia
CDC	Centers for Disease Control and Prevention
Chronic	A person has had the infection for a longer period of time, causing more damage to tissue or infection organs
CL	Compulsory license
DAA	Direct-acting antiviral
DCV	Daclatasvir
EASL	European Association for the Study of the Liver
EBR	Elbasvir
ESLD	End-stage Liver Disease
FBC	Full blood count
FDC	Fixed-dose combination
g/dL	grams per deciliter
GGT	Gamma glutamyl transferase, an important liver enzyme
g/L	grams per Liter
G/P; GLE/PIB	Glecaprevir/Pibrentasvir
GZR	Grazoprevir
HAV	Hepatitis A virus
HBIG	Hepatitis B immune globulin, an injection used to protect against hepatitis B within 24 hours of exposure
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HGV	Hepatitis G virus, also known as GB virus C
HICs	High-income countries
HIV/AIDS	Human immunodeficiency virus/ Acquired immunodeficiency syndrome

INHSU	International Symposium on Hepatitis Care in Substance Users
IP	Intellectual property
IU/mL	International units per milliliter
L	Liter
LED	Ledipasvir
LMIC	Low- and middle-income countries
MAT	Medication-assisted treatment, also referred to as OST
mg	milligram
mg/dL	milligram per deciliter
MIC	Middle-income country
mm3	millimeters cubed
MSM	Gay, bisexual, and other men who have sex with men
NHANES	National Health and Nutrition Examination Survey
OST	Opioid substitution therapy, also referred to as MAT
PEG-IFN	Pegylated interferon
PLWHA	People living with HIV/AIDS
PoC	Point-of-care test
PT	Prothrombin time, measurement for how long it takes for blood to clot
RBV	Ribavirin
RDT	Rapid diagnostic test
RNA, NAT	HCV ribonucleic acid or HCV RNA test
RVD	Ravidasvir
SI	International system of units
SOF	Sofosbuvir
STI	Sexually transmitted infection
SMP	Simeprevir
SVR	Sustained virological response
TAG	Treatment Action Group
TB	Tuberculosis
µmol/L	micromoles per liter
VEL	Velpatasvir
VL	Voluntary license
VOX	Voxilaprevir
WHO	World Health Organization
WHO PQ	World Health Organization pre-qualification

FOREWORD

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 HCV because it was a problem for people in our communities.

A primary goal of the Training Manual is to increase advocates' knowledge about available HCV tests and treatments and to jumpstart discussions on advocacy strategies that can be used to open up affordable access for more people with HCV.

We designed it to help you understand basic information about HCV and coinfection with HIV: how it is transmitted, how to prevent HCV, how people can find out if they have HCV, what happens to both HIV-negative and HIV-positive people who have HCV, information used for making treatment decisions, and treatment options.

Direct-acting antivirals (DAAs) have emerged as all-oral, highly effective medications for treating hepatitis C. The World Health Organization (WHO) does not recommend pegylated interferon-based treatment as the standard of care. DAAs are the optimal standard of care, and it is inhumane that DAAs have not yet been approved or made available in some countries. A primary goal of the Training Manual is to increase advocates' knowledge about available HCV tests and treatments and to jumpstart discussions on advocacy strategies that can be used to open up affordable access for more people with HCV.

This manual is organized into short sections, and each section can be presented and shared by a trainer or peer educator with a small group of people in one to two hours.

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 light colored stool, fever, aches, fatigue, and liver or abdominal swelling. People with acute infection are infectious for a short period of time, often with no or mild symptoms like fatigue and vomiting, within the first six months of infection. Hepatitis A and E are not chronic, but other forms of the virus can become chronic if your body is unable to clear them on its own. Chronic infection by hepatitis B, C, D, E or G may cause more severe damage to the liver.

HEPATITIS A (HAV)

HAV infection is usually not serious, but it can make some people feel very ill. HAV is transmitted by feces (stool, shit) from a person with HAV getting into your mouth. This can happen from contaminated water, eating food handled by someone with HAV who did not thoroughly wash their hands, eating raw fish or shellfish-contaminated water, raw fruit and vegetables grown in places with poor sanitation, or having unprotected sex, such as mouth-to-anus play. 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. **(For more information, see Handout on viral hepatitis in the Appendix)**.

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. HBV is transmitted through blood, semen, and sometimes vaginal and rectal fluid. HBV and HCV are transmitted from sharing unclean injection equipment, cookers, cotton, tattoo equipment, tattoo ink, and inkwells; needlestick accidents or other occupational exposures; unprotected sex with someone who has HBV or HCV; improperly sterilized medical and dental equipment; mother-to-child during birth; and sharing personal care items that may have blood on them, such as toothbrushes and razors. **(For more information, see Handout on viral hepatitis in the Appendix).**

Treatments are available for chronic HBV and HCV. Most people can be cured from HCV, and HBV can be treated. Not everyone with chronic HBV or HCV will need treatment because they will spontaneously

clear the virus. However, some people with chronic HCV 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 because they are transmitted in the same ways. A person cannot get HDV unless they already have hepatitis B. People who inject drugs are more at risk, and HDV is not commonly found in low- and middle-income countries. 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 is transmitted though water contaminated by feces or through uncooked or under-cooked meat. Outbreaks have occurred among people who manage wastewater and sewage, as well as people caring for pigs and other livestock. 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. HGV is transmitted through blood. Contaminated blood or blood products, unsterile drug use, injection or tattoo equipment can transmit the virus.

Many deaths from serious liver disease can be prevented with earlier diagnosis and treatment.

Viral Hepatitis Can Cause Serious Liver Disease

Chronic HBV and HCV are "silent" illnesses; people can experience fatigue or depression but this may not stand out. Usually, people do not have specific 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. 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. People who have viral hepatitis can be coinfected with HIV.

HIV and Viral Hepatitis Epidemiology: Who Has It?

Worldwide, an estimated 71 million people have chronic HCV. Two-thirds of people living with HCV reside in low- and middle-income countries. Approximately, 400,000 people die each year, commonly from HCV that has progressed to liver disease and liver cancer. The estimate highlights the urgency for an effective global response with increased access to testing, treatment, and harm reduction services.

Map 1. Global HCV Prevalence

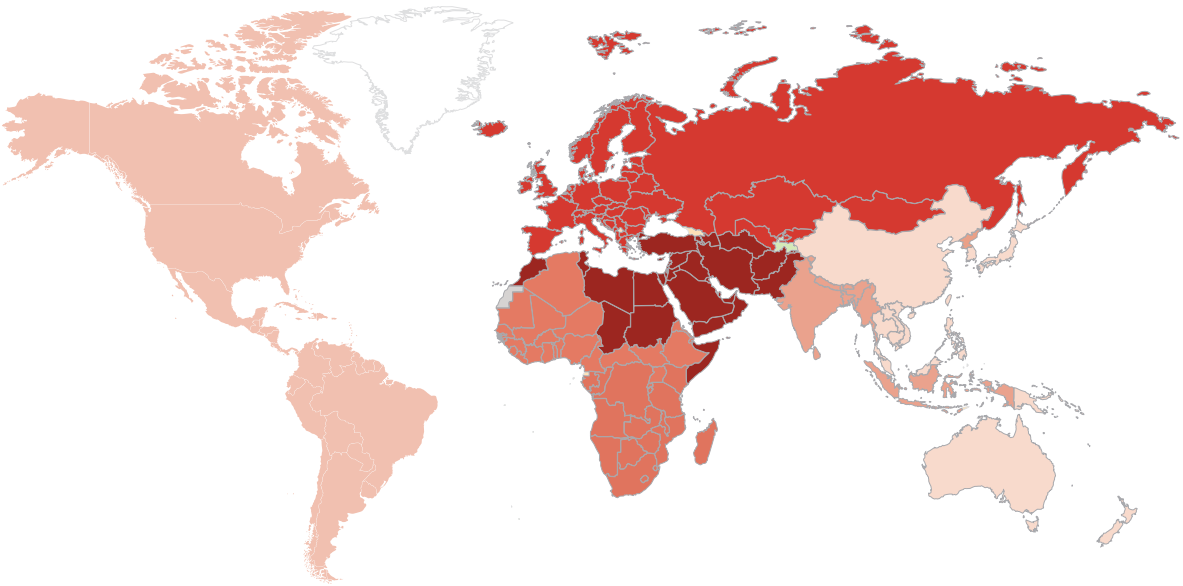
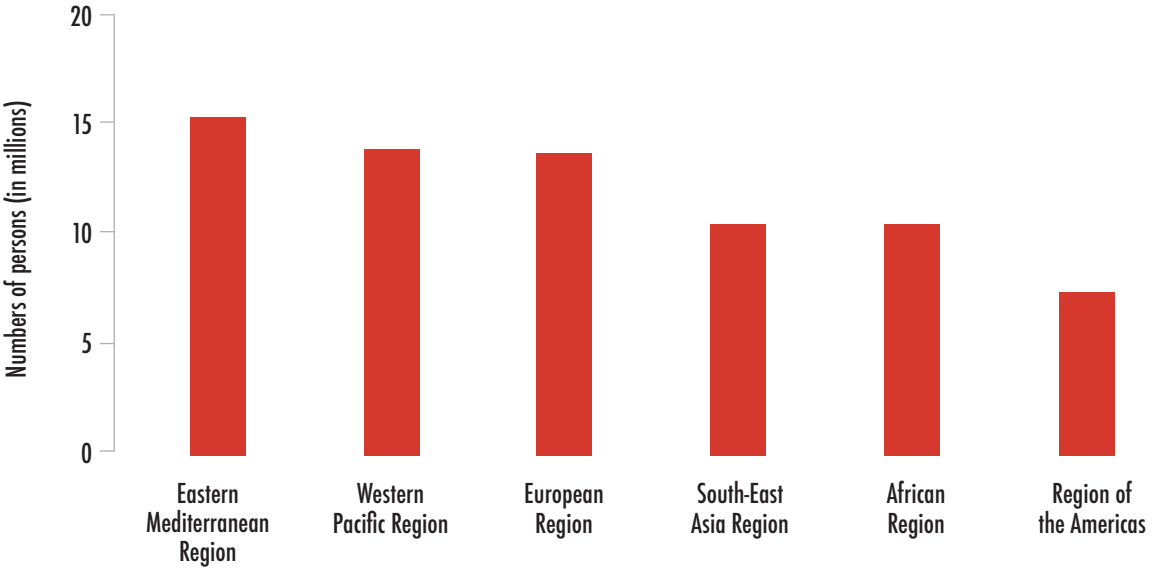


Figure 1 (with table). Prevalence of HCV infection (RNA confirmed positive) in the general population, by WHO region, with uncertainty intervals (in 2015)

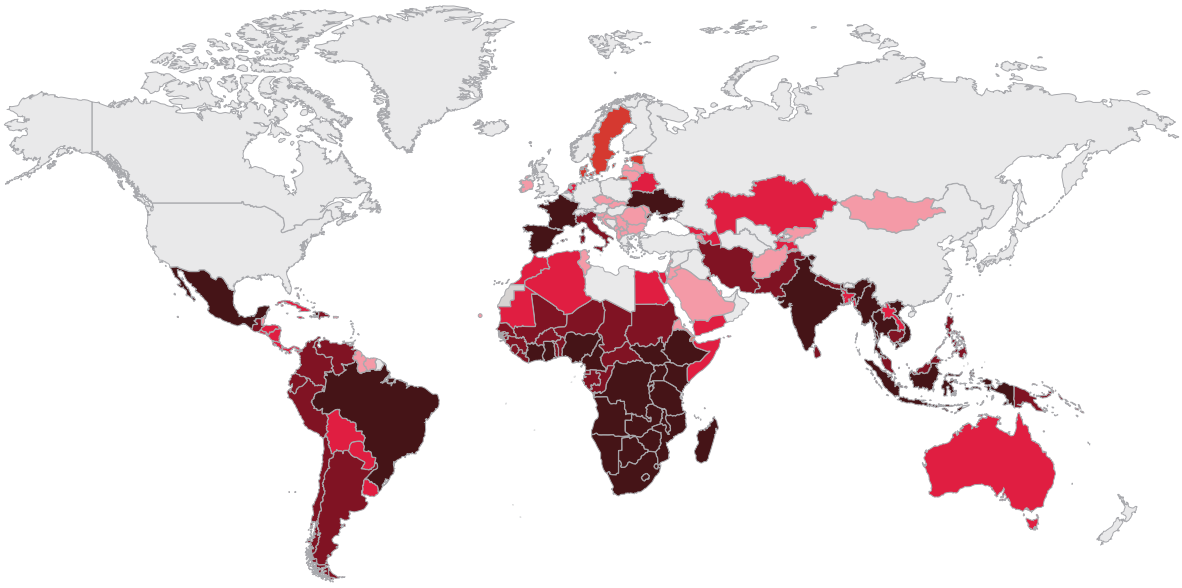


Source: WHO. Global Hepatitis Report. Geneva: WHO; 2017 April, pp.13-4.

	Estimates of the prevalance of HCV infection (%)			Estimated number of persons living with HCV (millions)		
		Uncertainty interval			Uncertainty interval	
WHO region	Best	Lower	Higher	Best	Lower	Higher
African Region	1.0	0.7	1.6	11	7	16
Region of the Americas	0.7	0.6	0.8	7	6	8
Eastern Mediterranean Region	2.3	1.9	2.4	15	13	15
European Region	1.5	1.2	1.5	14	11	14
South-East Asia Region	0.5	0.6	0.8	10	8	18
Western Pacific-Region	0.7	0.6	0.8	14	10	15
Total	1.0	0.8	1.1	71	62	79

Map 2. Global HIV Prevalence

Worldwide, an estimated 36.7 million people are living with HIV.



Sources: UNAIDS. AIDSinfo. 2017. http://aidsinfo.unaids.org/; Fact Sheet. 2017 July. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf (Accessed 21 October 2017).

GLOBAL PREVALENCE OF HIV/HCV COINFECTION

Globally, approximately 2.3 million people (or 6.2 percent) of the 36.7 million people living with HIV are coinfected with HCV. About 1.36 million of people who inject drugs have become infected with HCV and/or HIV.[1] HCV prevalence among men who have sex with men is lower at 6.4 percent. Prevalence is about 2.4 percent in people living with HIV who do not engage in behaviors that involve transmission of HCV-infected blood.[2]

In countries where the HIV epidemic is driven by injection drug use, as many as seven of 10 people living with HIV are coinfected with HCV. These include countries in Asia, Eastern Europe, and the Middle East.

HCV IN THE UNITED STATES

There is not enough information on how many people have HCV in the United States. The lack of reliable data and robust monitoring and surveillance systems, especially in key populations such as people who inject drugs, are barriers in fighting the HCV pandemic. According to the Centers for Disease Control and Prevention (CDC), approximately 3.2 million people in the United States have chronic HCV infection.[3] 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 before blood screening and identification of the virus. There are approximately 20,000 HCV-related deaths per year.

Young People Who Inject Drugs

Recently, the use of heroin[4] and synthetic opioids, including the highly potent and dangerous hydrocodone, oxycodone, fentanyl, and carfentanil, has sky-rocketed in the United States.[5] Using these drugs without a prescription is illegal, and due to the stigma and threat of arrest, people tend to use drugs in concealed places without sterile equipment. The sharing of unclean needles, measuring syringes, cookers, cotton, and water used to dissolve drugs, among other paraphernalia, puts people at risk of blood-borne infectious diseases like HIV and HCV. Younger people, who start by taking prescription opioids, may switch to street drugs like heroin once pills become scarcer. They may not have access to information on safe injection practices or ways to obtain clean syringes and other materials. Lack of access to clean injection equipment has exposed a new generation to HCV.

The largest increases of new HCV infections are occurring among young people who inject drugs, and are disproportionately affecting rural areas.[6] Opioid-related overdoses have also increased enormously, and are now considered the leading cause of death for Americans under the age of 50. Harm reduction programs and safe consumption spaces give people information on safe injection practices that can prevent transmission of HCV, as well as access to clean syringes and other materials for personal use. These programs can also prevent overdoses, provide medication-assisted treatment (MAT, also known as opioid substitution therapy), and increase people's access to HIV and HCV medications by linking them to care.

HCV and People of Color in the United States

The National Health and Nutrition Examination Survey (NHANES) is a series of surveys that tracks health and nutrition changes among a select group of adults and children in the United States over time. HCV is more common among African Americans than Mexican Americans or White Americans. This is true for both African-American men and women.[7] NHANES III 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 White Americans (3.2 percent vs. 1.5 percent, respectively).[8] The HCV prevalence rate is highest among African-American men age 40 to 49 years (13.4 percent) and Mexican American men age 50 to 59 years (10 percent).[9]

Additional studies estimate an average HCV ***antibody prevalence*** (testing positive for the virus) of 32.1 percent among homeless people, 11.5 percent among Native Americans served by the Indian Health Service, 4.5 percent among nursing home residents, and 0.48 percent among active military personnel.[10] In addition to the NHANES study, there are over 997,000 people who test positive for HCV antibodies.[11] Antibodies, or tiny proteins, are part of a person's immune response to help protect the body against intruders such as viruses, bacteria, and other harmful substances.

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.

HCV and Incarceration

An estimated 10.2 million people are incarcerated worldwide. The United States has the highest incarceration rate in the world, with more than 2.3 million people in U.S. prisons and jails. One in five people are locked up for nonviolent drug-related offenses.[12] Youth and immigrants held in juvenile justice and immigration detention centers are not reflected in these numbers.

The lack of options to test for HIV or HCV and the withholding of treatment in prisons allow the virus to spread to other prisoners or community members.

The prison system contributes to the transmission of infectious diseases, such as HIV, HBV, HCV, and tuberculosis (TB) due to overcrowding, lack of access to condoms, clean syringes or opioid substitution therapy, and limited testing and treatment services. Injection drug use is common among prisoners, and access to effective treatment for these infectious diseases, as well as for substance use disorders, is essential to curbing the epidemics. Compulsory drug detention centers in some countries add to the problem, as they use harsh punishments, have inhumane conditions, and deny access to treatment for substance use disorders or infectious diseases.

Approximately 15.1 percent of prisoners worldwide are living with HCV. However, very few prisoners have received treatment. This could be due to limited prison budgets for the expensive medications. Prisoners often move to multiple facilities during their sentences, and a significant number of prisoners[13,14] are released annually and reintegrate into society. The lack of options to test for HIV or HCV and the withholding of treatment in prisons allow the virus to spread to other prisoners or community members.

Treating substance use as a public health concern rather than a law enforcement issue, including the decriminalization of drugs for personal use, has been shown to reduce the incidence of HIV, and could reduce HCV.[15] Treating prisoners with HIV, HCV, and other infectious diseases while incarcerated, or linking them to care immediately when they return to the community, are critical components of HCV elimination. We can't end the HIV and HCV epidemics if we continue the war on drugs.

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?
3. Does your government offer HCV testing and treatment to key populations such as prisoners in your country?

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?
3. Have there been any campaigns to widen access to HCV treatment for key populations in your country?

NOTES

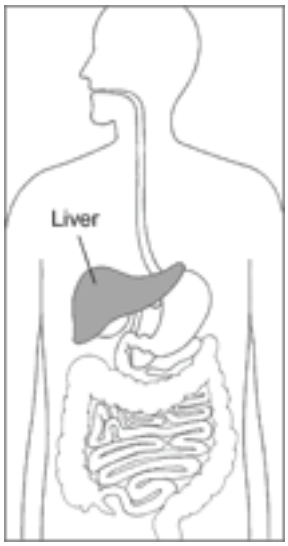
1. WHO. Global Hepatitis Report. Geneva: WHO; 2017 April.
2. *Ibid.*
3. Centers for Disease Control and Prevention (U.S.). Hepatitis C FAQs for Health Professionals. Atlanta: Department of Health and Human Services (U.S.), Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm (Accessed 2017 October 14).
4. Kounang N. "US heroin deaths jump 533% since 2002, report says," CNN [Internet]. 2017 September 8. Available from: http://www.cnn.com/2017/09/08/health/heroin-deaths-samhsa-report/index.html (Accessed 2017 November 8).
5. United Nations Office on Drugs and Crime. World Drug Report 2016. Available from: http://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf (Accessed 2017 November 8).
6. Centers for Disease Control and Prevention (U.S). Viral Hepatitis and Young Persons Who Inject Drugs. Atlanta: Department of Health and Human Services (U.S.), Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/hepatitis/featuredtopics/youngpwid.htm (Accessed 2017 October 14).
7. This information comes from NHANES study, which did not include homeless, incarcerated persons, nursing home residents, people living on Native American reservations, or active military personnel; information on members of additional racial and ethnic groups was classified as "other." There are also limitations in the geographic representation of the United States.
8. Armstrong GL, Wasley A, Simard EP, McQuillan GM, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006; 144:705–14.
9. *Ibid.*
10. Edlin BR, Eckhardt BJ, Shu MA, et al. Hepatol. 2015 Nov; 62(5):1353-63. doi: 10.1002/hep.27978.
11. Ibid.
12. Wagner P and Rabuy B. Mass Incarceration: The Whole Pie 2017. Prison Policy Initiative. Available from: https://www.prisonpolicy.org/reports/pie2017.html (Accessed 13 November 2017).
13. In the U.S. an estimated 641,000 prisoners (and 90 percent of prisoners in some jurisdictions) are released annually.
14. Wagner P and Rabuy B. Mass Incarceration: The Whole Pie 2017. Prison Policy Initiative. Available from: https://www.prisonpolicy.org/reports/pie2017.html (Accessed 2017 November 13).
15. Dolan K, Wirtz AL, Moazen B, et al. Global burden of HIV, viral hepatitis, and tuberculosis in prisoners and detainees. The Lancet. 2016

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 the blood.

Immune Response to Viral Hepatitis Infection Causes Liver Damage

Liver damage from HCV happens slowly, usually over decades, although it progresses more quickly in HIV-positive people.

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, although it progresses more quickly in HIV-positive people.

Some things cause faster liver damage from viral hepatitis:

- Being HIV-positive–especially if you acquired HCV after becoming infected with HIV;
- Being coinfected with HBV and HCV;
- Drinking alcohol, especially heavily;
- Age over 40, as older patients may have been infected longer;

- Having fat in your liver (a condition called ***steatosis***), usually in overweight people, heavy drinkers, or people with metabolic disorders;
- Being male (premenopausal women have more estrogen, which some researchers believe can have a protective effect); and
- The amount of time you have had HCV–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 HCV for many years and never develop serious liver damage.

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.

Figure 2. Stages of Liver Damage

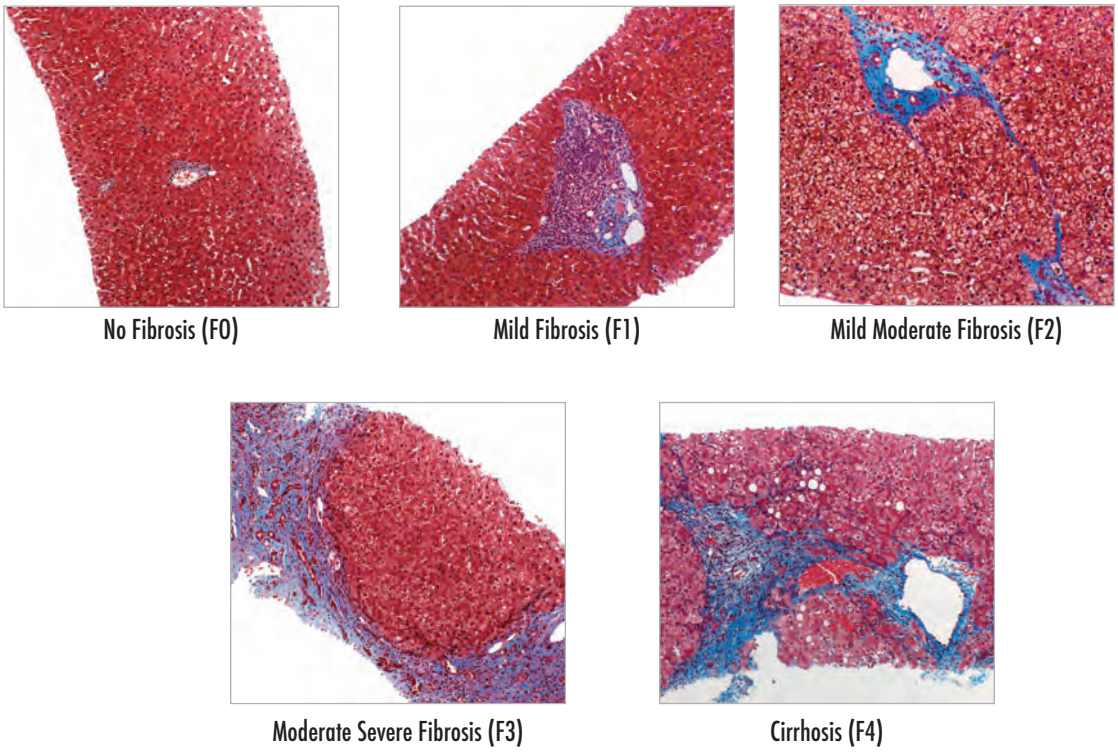


Figure 2 shows the progression of liver scarring, or fibrosis. The white splotches surrounded by blue and the darkened coloring show increases in scarring, notably around the arteries and veins in the liver. Stage F3 indicates significant inflammation around the central veins and tiny connective tissue. Stage 4 cirrhosis, or chronic liver disease, shows thickening of the tissue and loss of the ability to produce certain proteins and process nutrients, medications, and toxins. Source: Faria SC, Ganesan K, Mwangi I, et al. MR imaging of liver fibrosis: Current state of the art. Radiographics 2009; 29:1615-35.

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. Researchers are working to develop better methods for early detection of liver cancer.

Quitting or cutting down on drinking can be very difficult, but drinking less—or not at all—can help a person with HCV to prevent liver damage, particularly in places where treatment is not available. Getting cured is the most important thing!

Being cured is the primary goal of HCV treatment because it prevents the development or progression of liver disease. Getting tested for HCV is important because it is easier to cure before cirrhosis develops. 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. Some studies have found that men who drink 50 milliliters 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 milliliters 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—can help a person with HCV to prevent liver damage, particularly in places where treatment is not available. Getting cured is the most important thing!

Street Drugs

People who regularly use heroin, synthetic opioids, 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 could transmit infections such as HIV, HBV, and HCV through blood–this includes 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, synthetic opioids, 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 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.

Occasional use of marijuana has not been found to be harmful. One study done in the era of pegylated interferon treatment found that smoking marijuana during HCV treatment helped people to deal with side effects and complete their treatment.[1] Another study correlated daily marijuana use with reduced risk of ***nonalcoholic fatty liver disease***, or a build-up of fat in the liver, in HIV/HCV coinfected people.[2] By contrast, 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.

Prescription Drug Use

Some people use prescription medications, including prescription opioids like oxycodone and hydromorphone, to get high. This can be risky because they may interact with other medications, raising or lowering medications levels in a person's body. If medication levels are too low, they may stop working, and in some cases–such as with antibiotics–drug resistance can develop because there is not enough of the medicine in a person's system to stop viruses and bacteria from reproducing. Medication levels that are too high can also be dangerous, since they can increase drug toxicity and side effects.

Benzodiazepines, such as midazolam, interact with alcohol and can cause an overdose. Other drugs such as caffeine; sleeping pills; some antidepressants and antianxiety prescriptions; some antibiotics; hormonal contraception (birth control pills); some of the medicines used to treat tuberculosis, fungal infections, high blood pressure, and heart problems; and even cold medications (among others) can be dangerous when taken together.

Drug Overdose

The risk of overdosing on certain prescription antianxiety 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 because the liver breaks down these drugs. People who have recently completed detox programs or were released from incarceration are also at increased risk of overdose due to reduced tolerance to their drugs of choice.

Overdose Prevention

Overdose from prescription and street opioids is a leading preventable cause of death among people living with HCV who inject drugs.[3] Naloxone is a medication that can reverse an opioid overdose by blocking the effect of opioids in the body. It can be given as a nasal spray, or injected into muscle. Community members can be trained to administer naloxone and reverse overdose. Naloxone can be used when opioids have been used with other drugs, but it does not work for overdoses of benzodiazepines, cocaine, or amphetamines without opioids. People who have had an overdose reversed with naloxone remain at increased risk for overdose. An overdose is a medical emergency and the person should receive medical care as soon as possible.[4]

Along with opioid substitution therapy, also known as ***medically assisted treatment***, naloxone can prevent and reduce overdose deaths.

Other Medicines and Supplements

Some antibiotics, traditional medicines, herbs such as St. John's wort, and food supplements can be hard on the liver. Additionally, some medications should not be taken at the same time as certain HCV treatments 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?

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

HCV Is Primarily Spread by Direct Blood-To-Blood Contact

Hepatitis C is primarily a blood-borne 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 people who inject drugs don't have consistent and easy access to clean injection equipment or sterilization machines, and the virus is not easy to kill, hepatitis C is common among people who inject drugs.

The hepatitis C virus can stay alive on surfaces outside of the body for days. HCV is 10 times more infectious than HIV. Sterilization of injection equipment, with heat, is the most effective way to kill HCV.

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.

New research suggests HCV can also be present in semen, at least in HIV-positive men. According to one small recent study,[1] 11 of 33 men coinfected with HIV and HCV had the hepatitis virus in their semen. Though the semen contained only small numbers of HCV particles—between 50 to 6630 international units per milliliter (IU/mL)—the researchers noted than only 10 to 20 IU/mL are necessary for infection, particularly via anal sex without a condom. The same research team has also found HCV in rectal fluid,[2] meaning that HCV can potentially be spread from the receptive ("bottom") partner to the insertive ("top") partner.

More research is required to understand the prevalence of HCV in semen and the risk it poses, particularly among HIV-positive and HIV-negative men engaging in condomless anal sex.

The most common ways to catch HCV are:

- Sharing anything that another person has used to inject drugs, 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, this 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 with inadequate 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 condomless sex (barebacking) or fisting, particularly through anal sex with a person who has HCV. In the "chemsex" or "party-n-play" culture among MSM, a combination of street drugs are taken, facilitating sex with multiple partners and with more frequency, which can increase the risk of becoming infected with HIV, HCV, or other sexually transmitted infections (STIs);

- Having sex during menstruation with a person who has HCV;
- 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 Non-injection Drug Equipment (Straws and Pipes)

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

It may be possible to get HCV from sharing straws and pipes (used for cocaine, heroin, crystal methamphetamine, etc.). Although infection is less likely to occur than with injection equipment, 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.

A person who already has HCV can get infected again–this is called reinfection–even after being successfully being cured.

You can also be infected with more than one subtype of HCV at the same time (also known as ***genotypes***). Not sharing your injection equipment or using clean/new equipment protects you and the people with whom you are getting high.

Sexual Transmission of HCV

Sexual transmission of HCV isn't common, but can occur. Although the hepatitis C virus has been found in semen, rectal, and vaginal fluid, it is mainly found in blood. There are a limited number of studies examining infectiousness of semen and vaginal fluid. But people have become infected with HCV from condomless sex, and appears to be highest among MSM who are living with HIV. Why infection with HCV through sexual activity is more likely with HIV-positive MSM is not entirely clear.

The risk for sexually transmitted HCV is greater when blood is involved, even when the amount is too small to see. All of the following can put a person at risk for HCV: rough, unprotected anal and, in rare cases, vaginal sex; fisting (also called ***fist-fucking***; when a person puts his/her hand and forearm into another person's anus or vagina); group sex; and sex with a woman during menstruation.

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.

The incidence of HCV infection among HIV-positive MSM–the number of new infections that occur every year–has not been accurately determined, given that HCV testing is not performed regularly enough to produce useful data.

Several factors seem to be involved in the risk of HCV infection among MSM, including:[3]

- HIV infection;
- Rectal bleeding;
- Condomless 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.

Sexual transmission of HCV has been documented in a small number of HIV-negative MSM using pre-exposure prophylaxis (PrEP) to prevent becoming infected with HIV.[4] One important implication of this is the need to routinely test HIV-negative MSM using PrEP and engaging in anal sex without condoms for HCV.

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 the baby will have HCV. The risk of mother-to-child transmission of HCV is higher—up to 20 percent—if the mother is also HIV-positive and not on ***antiretroviral therapy*** (ART).

It's necessary to routinely test HIV-negative men who have sex with men using PrEP and engaging in anal sex without condoms for HCV.

Pregnant women coinfected 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, there is not enough information on the safety of HCV treatment with direct-acting antivirals during pregnancy and breastfeeding to recommend their use. So far there has only been one study showing that DAAs are safe for pregnant women, and there has been no research on using DAAs to prevent mother-to-child transmission. Ribavirin (RBV), which is sometimes used with DAAs, causes birth defects. Pregnant women or women who are trying to get pregnant should not use RBV ***(see Ribavirin Fact Sheet)***.

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?

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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 (20 to 40 percent)[1] will get rid of the virus without treating it, almost always within the first six months, during acute infection. The medical term for this is ***spontaneous viral clearance***. Women, children and young adults, HIV-negative people, and people who have symptoms during acute HCV infection are more likely to spontaneously clear HCV. HIV-positive people are less likely to clear HCV without treatment. Experts think that up to 25 percent of HIV-positive people will get rid of their HCV without treatment.

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. 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. People who get HCV when they are over 40 seem to progress to cirrhosis more quickly, probably because a person's immune system tends to slow down as they age and they may have been living with the virus longer. 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 About the Liver in Section 2)**.

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, coinfected people are twice as likely to get cirrhosis as people with HCV alone. HIV speeds up the rate of liver damage from HCV; some coinfected people have developed cirrhosis in less than 10 years.

HCV is curable, no matter what a person's HIV status is. While the older treatment, pegylated interferon (PEG-IFN) and RBV, did not work as well for people coinfected with HCV and HIV, DAA regimens are likely to work the same for people who are HIV-positive.

HIV treatment (or ART) is recommended for all people living with HIV. Although ART can keep the immune system strong and may slow liver damage from HCV, by itself it is not enough to stop HCV progression. Coinfected 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 coinfected with HCV makes treating HIV more complicated.

HCV coinfection can increase the risk for liver toxicity (also called ***hepatotoxicity***) from HIV medications. It is important to know which treatments are easier on the liver. However, most studies in HIV/HCV-coinfected people have shown that the benefits of HIV treatment outweigh the risks. Furthermore, the benefits of DAA treatment for HCV outweigh the risks for coinfected people **(see Treatment Issues for HIV/HCV-Coinfected 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?

Action Steps:

1. What can we do to prevent more deaths from HCV?
2. Which groups of people should we be screening for HCV?
3. How can we get more people tested for HCV?

NOTES

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SECTION 5:

HCV DIAGNOSTICS

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

- If a person has been infected with HCV;
- If the person is still infected with HCV;
- The amount of hepatitis C virus (viral load) in the bloodstream; and
- If the liver has been damaged.

HCV Screening Tests and What the Results Mean[1]

Step 1: HCV ANTIBODY TEST	
POSITIVE RESULT There are three potential meanings: 1. The person was recently infected with HCV or 2. May have chronic HCV; or 3. Was infected in the past, but has cleared HCV and is no longer infected. **The person needs a viral load test to confirm.**	**NEGATIVE RESULT** There are three potential meanings: 1. The person has never been infected with HCV 2. May have been recently exposed (within the last two weeks); or 3. May have chronic HCV (if the person is HIV-positive, with a CD4 count <200 cells/mm^3). **The person needs a viral load test to confirm.**
Step 2: HCV RNA (VIRAL LOAD) TEST	
DETECTABLE RESULT There are two potential meanings: 1. The person may be recently infected with HCV; or 2. May have chronic HCV. **The person should be assessed for HCV treatment.**	**UNDETECTABLE RESULT** There are two potential meanings: 1. The person has never been infected; or 2. Was once infected in the past, but has now cleared HCV. **The person should be assessed for follow up testing.**

What is screening?

Screening looks to see whether someone might have a disease. For HCV, screening means looking for ***antibodies*** instead of the virus.

What are antibodies?

Antibodies are Y-shaped proteins made by a person's immune system. They are part of the immune system's response to viruses, bacteria, and other harmful substances (called ***antigens***).

Antibodies attach themselves to antigens or infected cells and tag them so that other immune cells can find and disable them. It takes six to 24 weeks for a person to make antibodies to HCV (often called the ***window period***). Antibodies stay in a person's body long after the antigen that triggered them disappears (this is called ***immunological memory***). If the same antigen enters a person's body again, even years later, the immune system will remember it—and send antibodies to destroy it.

When HCV enters a person's bloodstream, it triggers an immune response. The immune system makes HCV-fighting antibodies. Sometimes, the immune system gets rid of HCV by itself (this is called ***spontaneous viral clearance***). About 20 to 40 percent of people with HCV will spontaneously clear the virus. This is more likely in young people (especially women), and people who do not have HIV.

Even when a person has cleared HCV or been cured by treatment, HCV antibodies remain in a person's blood for years, possibly for the rest of the person's life. That means they will always test positive for HCV antibodies, even if they don't have the virus in their bloodstream.

For antibody screening, a ***rapid diagnostic test (RDT)*** is available—this means the test can be done outside a medical center using oral fluid (saliva) or a fingerstick. In some cases, blood from your arm, or plasma (yellowish liquid of the blood that contains blood cells) can be used as samples.

What does a negative HCV antibody test result mean?

A negative antibody test result usually means that the person has not been infected with hepatitis C (unless they were infected very recently or have a weakened immune system).

The body needs at least two months, and sometimes up to nine months, to make antibodies. People with weakened immune systems from an illness or certain medications are not always able to produce antibodies. This might happen in people with autoimmune disorders (when a person's immune system attacks his or her own organs or tissues), HIV-positive people with a CD4 cell count below <200 cells/mm^3, and people taking immunosuppressants.

What does a positive HCV antibody test result mean?

A positive antibody test result means that a person has been infected with HCV. It does not mean that the person still has hepatitis C. A different test, to look for the actual hepatitis C virus, is needed to make a diagnosis.

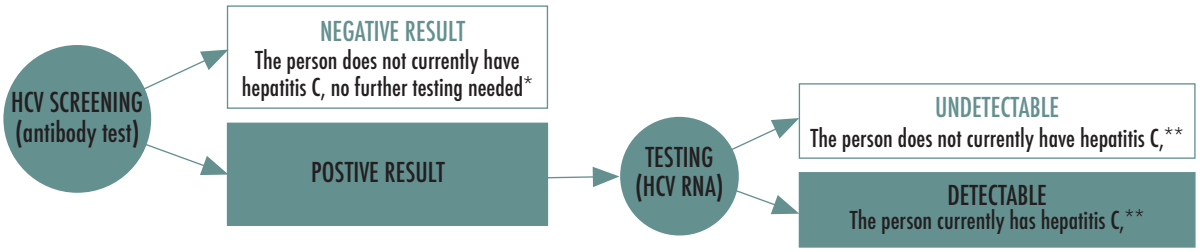
What is testing?

Testing will confirm—or rule out—whether someone has a disease.

How is a person tested for HCV?

Two different blood tests are used to diagnose HCV: the antibody test mentioned above and a viral load test. A viral load test, called an ***HCV ribonucleic acid or HCV RNA*** test is used to look for the hepatitis C virus in the bloodstream. Usually, the hepatitis C virus can be found in a person's bloodstream two weeks after they become infected.

Figure 3. Two HCV Blood Tests



*Except in case of recent risk (within six months) or in people with a weakened immune system.

**During the first six months after HCV infection, a person may spontaneously clear the virus; if there was a recent risk, repeat viral load testing to confirm chronic hepatitis C infection.

There Are Two Types of Viral Load Tests: Qualitative and Quantitative

Qualitative testing checks whether there is hepatitis C virus in the bloodstream. The test result is either positive (virus is ***detectable***) or negative (no virus can be detected).

Quantitative testing measures the amount of hepatitis C virus in the bloodstream. These tests, while not available in every country, are used during HCV treatment to see if it is working. Due to the effectiveness of DAAs, quantitative tests are not required to tell whether a person is cured. However, they may still sometimes be used. The test result is a number: the higher the number, the more virus was detected.

HCV Qualitative Testing

WHAT THE RESULT SAYS	Undetectable, the lower limit of detection (LLOD) varies; it can be as low as <5 IU/mL	Detectable, below the lower limit of quantification (LLOQ); the lowest amount of hepatitis C virus that the test can measure	Detectable
WHAT THE RESULT MEANS	No hepatitis C virus was found in the bloodstream (this means that a persion either spontaneously cleared HCV or that they were cured)	Hepatitis C was found in the bloodstream, but the amount of the virus was too small for the test to measure	Hepatitis C was found in the bloodstream; the amount of virus is reported in international units per millileter (IU/mL). A person with a positive antibody test result and detectable HCV RNA has chronic hepatitis C (unless they were recently infected)

*Unit of measurement (international units per milliliter).

If no HCV is found in a person's bloodstream (undetectable) it means the person does not have HCV. The person should get tested regularly if they are at risk. If the second test result is also undetectable, it means that HCV has been cleared.

In cases of reinfection, RNA testing is recommended for people with ongoing risk behaviors or abnormal liver function tests.

In cases of reinfection, RNA testing is recommended for people with ongoing risk behaviors or abnormal liver function tests.[1]

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.

HCV Core Antigen Testing

The hepatitis C core antigen is a viral protein, so it is part of the hepatitis C virus itself. Since the core antigen is part of the hepatitis C virus, it can usually be found in the bloodstream two weeks after infection.

HCV core antigen testing is simpler and less expensive than viral load testing, but less specific, meaning it might miss some infections. Point-of-care (PoC) core antigen tests are still under development and will not be available in resource-limited settings for several years. Core antigen testing can be used with HCV antibody testing to detect acute HCV or to confirm chronic HCV infection. HCV core antigen testing can also be used to measure treatment outcome. Although it does not detect low levels of HCV (1,000 to 3,000 IU/mL depending on genotype),[2] usually the hepatitis C viral load is much higher in people who relapse after HCV treatment.

HCV Genotyping

There are at least seven known hepatitis C genotypes, numbered 1 through 7 in the order that they were discovered. Each genotype has many subtypes, and each given a letter in the order that they were discovered. People can be infected with more than one HCV genotype (called ***mixed infection***). This is most likely to happen to people who received blood products or blood transfusions many years ago or in a place where the blood supply is not checked for HCV; people receiving kidney dialysis in a facility with inadequate infection control; or people who inject drugs with shared, unsterilized equipment.

Worldwide, most people with HCV have not been diagnosed. Laboratory tests are often expensive and not covered by public health insurance in most low- and middle-income countries.

People who already have HCV can get infected again (***reinfected***) with the same or a different genotype.

Now, with DAAs that treat all genotypes (called ***pangenotypic***), HCV genotyping is becoming unnecessary.

Ensuring Accurate Results in the Laboratory

Worldwide, most people with HCV have not been diagnosed. Laboratory tests are often expensive and not covered by public health insurance in most low- and middle-income countries. Here are the key points to know about the process for getting your test results:

HCV tests require ***reagents***, or chemical ingredients added to test a reaction, which require refrigeration. The testing device used is a ***reagent cartridge***. Many laboratories conduct multi-disease testing, meaning they use a machine that tests for more than one infection at the same time, such as HIV, HBV, and HCV. Like in the HIV field, researchers aim to find a simple ***point-of-care*** rapid diagnostic test. This would not require centralized laboratory facilities; rather, they could be easily used in pharmacy or community settings, such as in harm reduction programs.

The validation of a test's quality is important. The WHO conducts pre-qualification (WHO PQ) assessment to examine the performance and quality of tests. WHO PQ assesses ***specificity*** (how accurate a test is) to ensure there are no or few false positives to avoid misinforming a person about being infected. WHO PQ also assesses the ***sensitivity*** (the smallest amount the test can detect). Therefore, in choosing an optimal test, high sensitivity and high specificity would be qualities to note.

Getting More Information About the Health of Your Liver

Liver Disease Staging

The type and length of HCV treatment sometimes depend on how much a person's liver has been damaged by the infection. DAAs can cure HCV infection in more than 95 percent of people without cirrhosis. However, people with cirrhosis are more difficult to cure. They sometimes need RBV and often need to be treated longer than people who have less liver damage.

If people with HCV infection and cirrhosis go untreated, their cirrhosis may become ***decompensated***, meaning their liver is beginning to fail. People with decompensated cirrhosis have symptoms such as the build up of fluid and toxins, kidney disease, and possibly internal bleeding. Some DAAs don't work in people who have decompensated cirrhosis and their cure rates are significantly lower. This shows how important it is to treat HCV early, before it has time to damage the liver. A person with decompensated cirrhosis has a lower rate of survival overall and should be considered for a liver transplant.

There are different methods that determine how much liver damage a person has, called ***staging***. Staging can be done by an invasive test, which takes blood or tissue samples with a needle (biopsies), or by noninvasive tests, which only take images. Noninvasive imaging tests are safer, less expensive, and easier to perform and undergo than biopsies. Biopsies should not be used to assess liver damage anymore. It is becoming more common to use routine blood tests or ultrasound imaging to see whether a person has cirrhosis.

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 directly measure liver function, and the results cannot predict or tell someone how much liver disease they have.

Alanine aminotransferase or serum glutamic-pyruvic transaminase (ALT; SGPT) and ***aspartate aminotransferase or serum glutamic oxaloacetic transaminase*** (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 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 such as St. John's wort, vitamins and supplements; exposure to toxic fumes; heavy alcohol consumption; acute or chronic viral hepatitis and certain other infections; and detoxing from drugs or alcohol. It is important to tell your doctor about the alcohol, substances, medications, and supplements you take to note the factors contributing to your liver enzyme levels.

Some HIV medications are broken down by the liver, and can cause abnormally high liver enzyme levels. People who are taking ART or tuberculosis (TB) treatments–whether or not they are coinfected with HBV or HCV–should have their liver enzyme levels checked regularly, as some HIV, TB, and other treatments can be hard for the liver to break down. Checking liver enzyme levels is a good way for everyone to check their liver health.

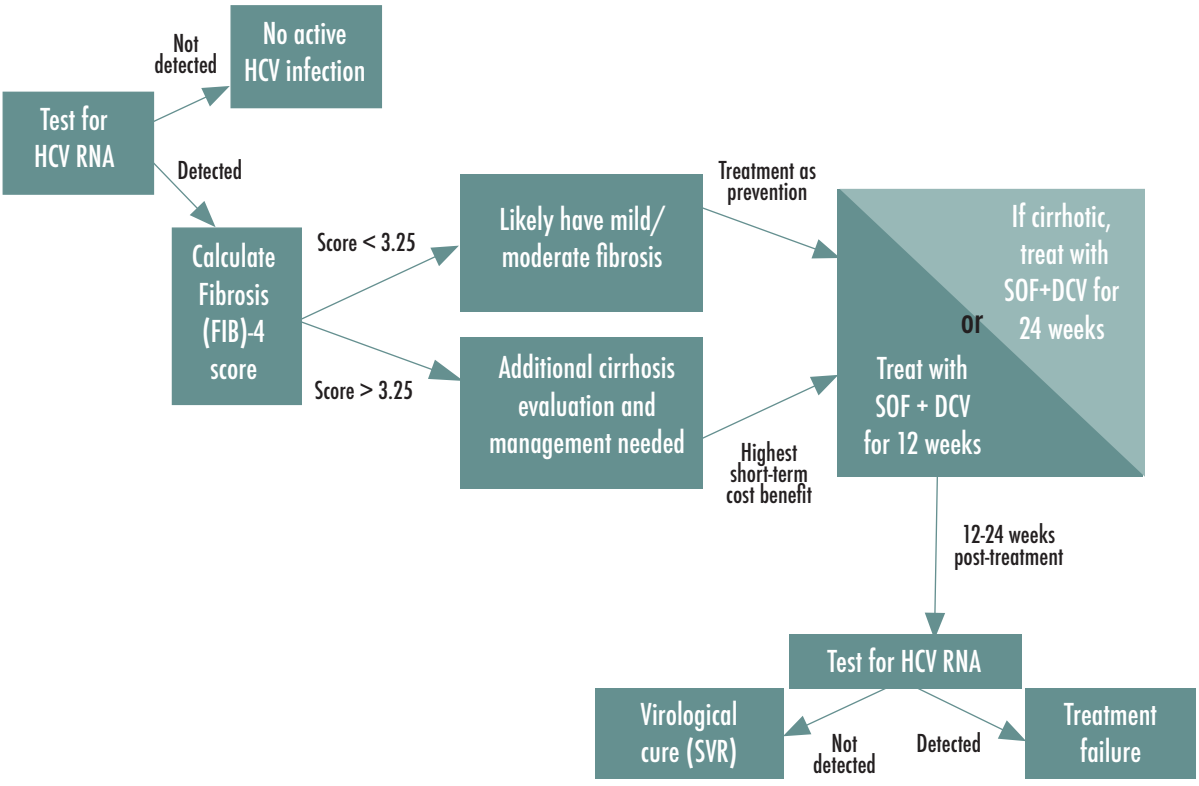
When liver enzyme levels are higher than normal for several months, it can be a signal that the liver is inflamed or damaged. Normal liver enzyme levels do not mean that a person's liver is healthy—some people may have normal liver enzyme levels for years although they have serious liver damage. It is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

New HCV Diagnostics

Now that HCV treatment is simpler, safer, and more effective, not all these steps may be required. Diagnostics need to become simpler and less expensive. HCV could soon be diagnosed with a single rapid point-of-care test and cured with a pangenotypic regimen. Until these kinds of tests are available everywhere, the aim should be to confirm diagnosis and start treatment on the same day. That means:

1. Every positive antibody test should be tested for RNA automatically (known as reflexive testing);
2. A FibroScan®, APRI Score (a formula that calculates the aspartate aminotransferase [AST] to platelet ratio index), or other test should be done to determine the level of cirrhosis; and
3. The appropriate DAA regime should be provided.

Figure 4. Minimum Steps to Managing HCV



Source: Adapted from Graham CS and Swan T. A path to eradication of hepatitis C in low- and middle-income countries; Antiviral Res. 2015 Jul;119:89-96. doi: 10.1016/j.antiviral.2015.01.004. Epub 2015 Jan 20; Dr. Saeed Hamid's real-world protocol in Pakistan in Luhman N. The rocky road to viral hepatitis elimination: Approach-es for simplified HCV diagnostics and screening algorithms: Thoughts about a public health approach for LMICs; 2017 July 22-23; Presented at: 4th International HIV/Viral Hepatitis Co-infection Meeting. Paris, France. Available from: http://www.iasociety.org/Web/WebContent/File/3_D_1150-1215_Niklas_Luhmann.pdf (Accessed 2017 November 22).

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 health care 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?
2. What are some good examples of places where people can be tested outside a central hospital or laboratory?

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SECTION 6:
HCV DIAGNOSTICS FOR MAKING TREATMENT DECISIONS

HCV Testing

Direct-acting antivirals can achieve a sustained virological response (SVR) in over 95 percent of people. An SVR means that a person has no detectable HCV after the treatment has been completed. Sometimes HCV genotype tests are required before starting HCV treatment, especially for people with cirrhosis, who may need longer treatment. However, as effective DAA combinations, such as sofosbuvir/daclatasvir and sofosbuvir/velpatasvir, are becoming accessible for more people, genotyping is becoming less relevant.

Health care providers can order a blood test to see which HCV genotype—or genotypes—a person has. Seven hepatitis C genotypes (subtypes of the virus), numbered 1 through 7, have been discovered.

Genotype 1 is most common in the United States. People with genotype 1 are more likely to have high hepatitis C viral loads. Genotyping may still be relevant if you have cirrhosis. These tests are still used in high-income countries, where they are more widely available and covered by insurance.

Genotype 3 is most common in India, Myanmar, Thailand, and other parts of Asia, the Middle East, and North Africa. People who have genotype 3 and cirrhosis are more likely to have ***steatosis*** (fat in the liver); this can make treatment less effective.

Newer treatments have been shown to be effective for multiple (***multigenotypic***) or all (***pangenotypic)*** genotypes (**see HCV Treatment and Side Effects in Section 7**).

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, operate a machine called FibroScan® that looks at liver stiffness using sound waves. FibroScans® can also determine the level of liver damage and degeneration of liver cells. It is difficult to diagnose mild or moderate liver disease without doing a biopsy, however, and FibroScan® is not widely available in most countries.

There are a number of blood tests that can look for cirrhosis that are noninvasive. An APRI, or aspartate aminotransferase (AST) to platelet ratio index, is a formula used to determine the level of cirrhosis. A group of blood tests, or ***liver function tests***, do not actually measure liver function, nor do they predict or tell someone how much liver disease they have. Instead, they check the level of liver enzymes and indicate other aspects of the health of the liver ***(see HCV Diagnostics in Section 5 and "Track Your Labs" Sheet in Appendix)***.

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 OPTIONS

Treating HCV is never an emergency, but early treatment prevents further liver damage. DAAs are easier to take, and better tolerated than PEG-IFN and RBV, therefore, treatment is recommended for all people with HCV, even those without liver damage. Treating HCV is important for HIV-coinfected people because they may get liver damage more quickly than people with HCV alone.

DAAs are easier to take and better tolerated, therefore, treatment is recommended for all people with HCV, even those without liver damage.

Despite treatment guidelines recommending treatment for all, many national health systems, private and public payers currently limit treatment to only those people with advanced fibrosis.

People with very advanced liver damage can be treated for HCV, but they may require treatment for up to 24 weeks and/or ribavirin, and treatment is less effective. Patients with advanced liver disease or liver cancer (hepatocellular carcinoma, or HCC) should discuss treatment options with their doctors, including liver transplant. In these cases, people will need close monitoring to check whether cancer develops or returns.

DAAs are:

- Easier to take. DAAs are oral medications, taken either once or twice a day. Some medications are combined in single-tablet formulations (called fixed-dose combinations, or FDCs). Some need to be taken with food;
- Highly effective. Cure rates have reached over 95 percent with some DAA combinations;
- Effective against many or all HCV genotypes; and
- Safe and tolerable. Unlike PEG-IFN and RBV, DAAs have fewer side effects—and they are usually mild.

The duration of treatment depends on whether or not a person has cirrhosis.

HCV treatments:

Pegylated interferon (PEG-IFN) is no longer recommended by WHO and American Association for the Study of the Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA), and is only recommended by the European Association for the Study of the Liver (EASL) when there are no other options. It may still be used in countries without access to DAAs or in prisons. (**See TAG's 2013 Training Manual that includes PEG-IFN and older regimes of protease inhibitors for more information.**)

Ribavirin (RBV) is from the same family as some of the treatments used to treat HIV, called ***nucleoside analogues***, but it does not work as an HIV treatment. RBV is taken as pills or capsules twice a day. The dose depends on a person's weight. RBV can increase cure rates in people with cirrhosis and is sometimes added to DAAs, although it causes several unpleasant side effects, such as anemia, insomnia, fatigue, irritability, and depression. RBV is not recommended for men and women who are planning a pregnancy, since it causes birth defects. Male partners of women who become pregnant or who breastfeed should use condoms for six months after completing HCV treatment. **(See Ribavirin Fact Sheet in Appendix for more information.)**

Sofosbuvir (Sovaldi®, or SOF) is an HCV-fighting treatment that must be used with other DAAs. In the United States, it is used to treat genotypes 1, 2, 3, and 4 for people over the age of 12. SOF is taken once daily, with or without food, for 12 to 24 weeks.

Daclatasvir (Daklinza™, or DCV) is taken with SOF, once daily with or without food for 12 or 24 weeks. In the United States, DCV is approved for people over 18 years old who have HCV genotype 1 or genotype 3 (although it has been used in other genotypes).

Sofosbuvir/daclatasvir (Darvoni, or SOF/DCV) treats all genotypes and must be taken once daily for 12 weeks. It can be used to treat people before or after liver transplant, with cirrhosis and/or HIV.

Simeprevir (Olysio®, or SMP), approved for genotype 1, must be taken with another HCV treatment and taken once daily, with food, for 12 or 24 weeks. It is rarely used in high-income countries.

Sofosbuvir/ledipasvir (Harvoni®, or SOF/LED) is two medications in one pill, taken daily, with or without food, for 8 to 24 weeks. In the United States, it is used to treat hepatitis C genotypes 1, 4, 5, and 6 in people who are over 12 years old. Harvoni® is also approved for people with HCV genotype 1 who have advanced (decompensated) cirrhosis, and for liver transplant recipients who have HCV genotype 1 or 4. It can be used to treat people with HIV. Studies have shown it to be effective at 8 weeks in people with genotype 1 and without cirrhosis who have not previously been treated with DAAs.

Paritaprevir/ritonavir/ombitasvir and dasabuvir (Viekira XR™) is a combination of HCV medications. In the United States, Viekira XR™ is approved for people with hepatitis C genotype 1 who are over 18 years old. Viekira XR™ was previously approved and prescribed as a twice-daily formula known as Viekira Pak®. The latest XR regimen contains the same medicines, in the same amounts, as Viekira Pak®, now in a once-daily package.

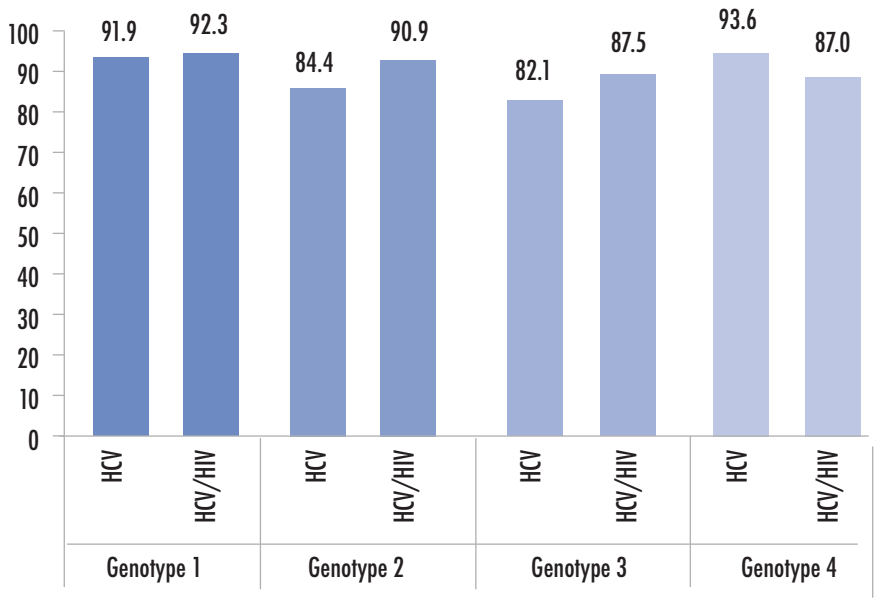
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®, or SOF/VEL/VOX) is a fixed-dose combination taken once daily for 12 weeks. It does not require RBV. It can effectively treat all genotypes, including difficult-to-treat genotype 3, people with or without cirrhosis, and people with chronic kidney disease. In the United States, it is marketed as a salvage treatment regimen for people who previously failed DAA treatment, but it is approved as a first-line treatment, taken for 12 weeks, in the European Union.

Glecaprevir/pibrentasvir (Mavyret™, or G/P) is a fixed-dose combination, taken once daily with food for 8, 12, or 16 weeks. It can effectively treat all genotypes, including difficult-to-treat genotype 3, people with or without cirrhosis, and people with chronic kidney disease. It shows a high SVR of 95 percent with eight weeks of treatment in people without cirrhosis who have never been treated with DAAs before, making it the shortest treatment course currently available.

Sofosbuvir/ravidasvir (SOF/RVD) is a generic regimen currently under study in clinical trials, which may be used to treat all genotypes. It is taken once daily for 12 weeks, or 24 weeks for people with compensated cirrhosis.

Figure 5 shows the SVR rates using DAAs (SOF/LED, SOF/DCV with and without RBV), according to genotypes, among people who are HCV mono-infected and people who are HIV/HCV coinfected. Most mono-infected people achieved over 90 percent SVR rates for 12 weeks of treatment; this includes people with cirrhosis. HIV/HCV cure rates at week 12 actually have higher results than in mono-infected people, except for genotype 4.

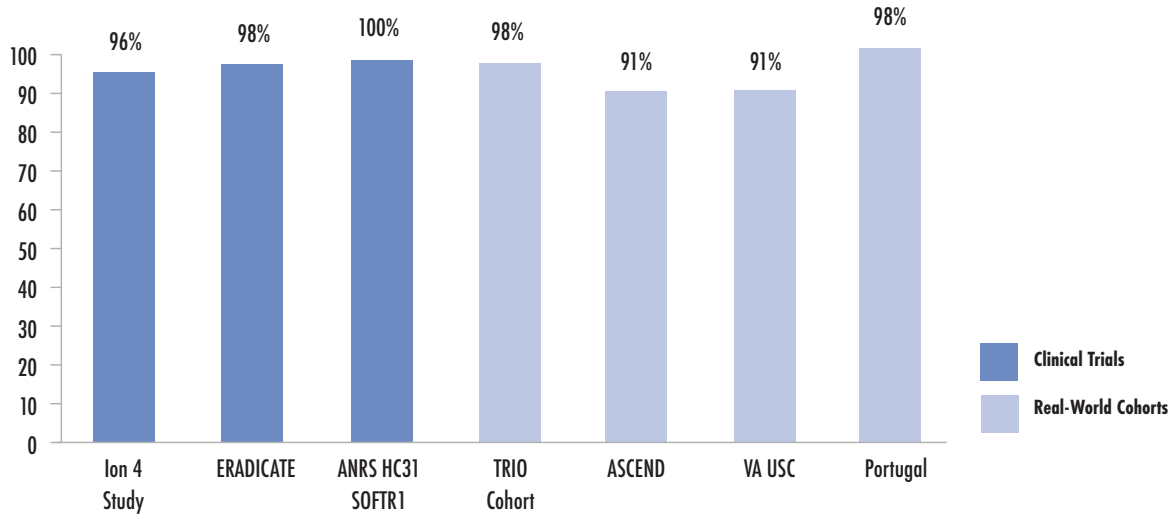
Figure 5. SVR12 Rates by HCV Genotype and Treatment Group



Source: Jurgen R. "Summary for AASLD 2016 for Hepatitis C: New HCV two and three drug regimens on their way: What do they promise? And what do clinicians need to look out for under DAA combination therapy and beyond SVR?" Reported from 67th Annual Meeting of the American Association for the Study of Liver Diseases; 2016 November 11-15; Boston, MA.

Furthermore, the DAAs show comparative rates for HIV/HCV coinfected people in clinical trials as in real-world studies (see Figure 6 below). For example, 12- to 24-week treatment of SOF/LED for genotype 1 in HIV/HCV coinfected people had over 90 percent SVR.

Figure 6. Clinical Trials Compared to Real-World Cohorts



Source: Naggie S et al. Real World Effectiveness of Ledipasvir/Sofosbuvir (LDV/SOF) in Patients Coinfected With HCV and HIV-1: A Comparative Analysis of Clinical Trials with Four Real World Cohorts. Poster presented at: 67th Annual Meeting of the American Association for the Study of Liver Diseases; 2016 November; Boston, MA; Abstract 898.

DAA treatment among people on OST and who are active or former people who inject drugs achieves similar outcomes as in non-drug using groups (see Figures 7 and 8). There is no scientific evidence for denying treatment to people who use drugs.

As with HIV treatments, the newer HCV medicines need to be taken regularly—missing doses can lead to drug resistance.

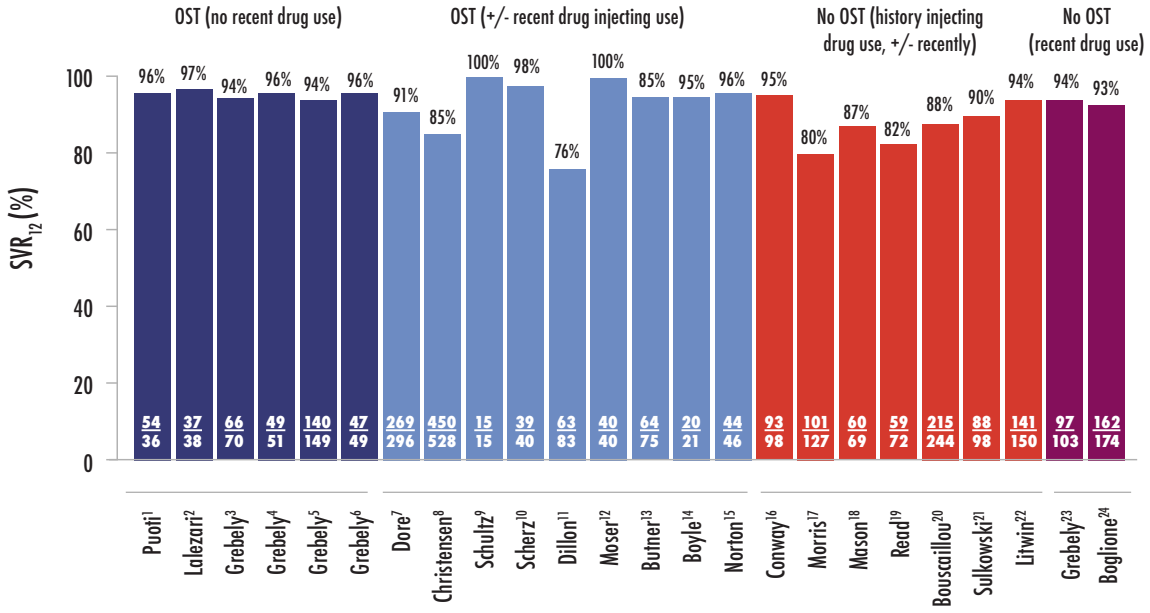
See Treatment Fact Sheets in the Appendix for more information.

Real-World Data in People Who Use Drugs

HCV transmission among people who inject drugs continues to be the main driver of the global epidemic. Stigmatization, discrimination, and myths that active drug users cannot adhere to daily treatment regimens have resulted in treatment restrictions and other policies that further marginalize those we need to engage the most. However, trials of DAA treatment in active drug users and people receiving opioid substitution therapy show HCV cure rates comparable to those in clinical trials can be achieved among people who continue to use and/or inject drugs during treatment.

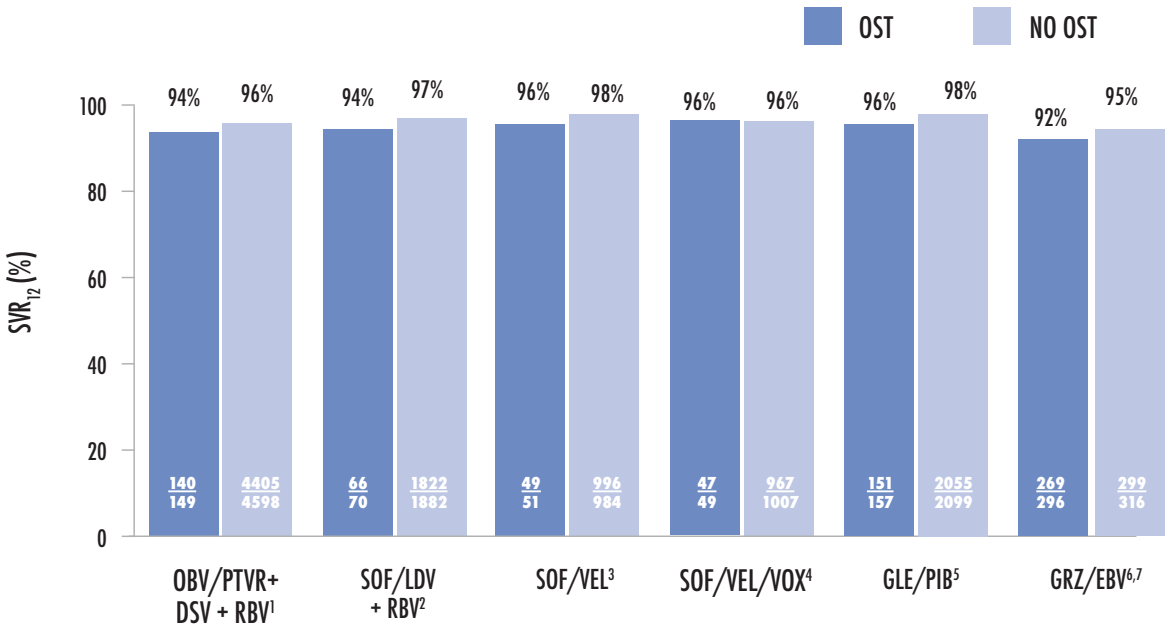
DAA treatment among people on OST and who are active or former people who inject drugs achieves similar outcomes as in non-drug using groups (see Figures 7 and 8). There is no scientific evidence for denying treatment to people who use drugs.

Figure 7. SVR12 among people on OST and former/recent PWID[1]



Source: See Figure 7 Notes.

Figure 8. People Receiving OST – Phase II/III Trials



Source: See Figure 8 Notes.

Adherence to HCV treatment regimens is shown to be good among people who use drugs or other substances.

Adherence to HCV treatment regimens is shown to be good among people who use drugs or other substances. The PREVAIL study[2] compared no treatment intervention vs. direct observed therapy using blister packs (pre-packaged tablets) to administer treatment for people. Results showed that drug use did not associate with poor adherence.

Is a Vaccine for HCV Still Necessary?

With the highly effective DAAs, questions arise on whether a vaccine for HCV is necessary. Vaccines for HAV and HBV exist, but a ***prophylactic*** (preventative) HCV vaccine has eluded researchers. HCV is considered to be a master virus, with the ability to mutate rapidly and to adapt quickly so as to stay ahead of detection and response by the human immune system.

A vaccine would be beneficial to prevent transmission among networks of people who inject drugs, sexual networks, or other groups such as prisoners, who may be repeatedly exposed to the virus. With this rationale, preventative vaccine trials are underway to prove efficacy and safety, and results in the coming years will determine the role of vaccines in ending the HCV epidemic.

ADVOCACY EXERCISE

Discussion Questions:

1. Do you know which HCV treatments 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?
3. What efforts can be made to ensure people who inject or use drugs can access DAAs?

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FIGURE 8 NOTES

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SECTION 8:

HOW TO TELL IF HCV TREATMENT IS WORKING AND SIDE EFFECTS

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.

Evidence suggests the viral load test at week 4 is not necessary, and provides an opportunity to reduce the number of lab tests, which can be costly.

Regular monitoring for liver cancer 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.

DAA regimens do not require extensive monitoring; however, a viral load test is usually performed 4 weeks after starting treatment, even though a detectable HCV viral load at week 4 is not predictive of HCV treatment outcome. There is no evidence showing that a week 4 viral load test actually improves treatment outcomes. AASLD recommends testing after four weeks of therapy. WHO suggests that viral load testing at week 4 of treatment can be bypassed (see Table 1). EASL recommends viral load testing only to confirm infection and after treatment to confirm cure.

Breakthroughs—when a person's HCV viral load first becomes undetectable on treatment and then becomes detectable again at a later point in treatment—do not occur frequently among people taking present-day DAA regimens. In fact, most people treated with DAAs have undetectable HCV viral loads by the fourth week of treatment. This evidence suggests the viral load test at week 4 is not necessary, and provides an opportunity to reduce the number of lab tests, which can be costly.

Testing HCV viral load 12 weeks after finishing treatment is the best measure for a sustained virologic response. An SVR12 means that a person has no detectable HCV after 12 weeks of treatment has been completed. An SVR12 is considered a cure. AASLD, EASL, and WHO guidelines all recommend HCV viral load testing at week 12 after treatment has ended.

Table 1. WHO Framework for Frequency of Monitoring of People Undergoing HCV Treatment, Based on Regimen Type

Time	DAAs alone			DAA + ribavirin			DAA + pegylated interferon + ribavirin			
	FBC, renal, liver function	Adherence, side effects	HCV viral load	FBC, renal, liver function	Adherence, side effects	HCV viral load	FBC, creatine, ALT	Thyroid function	Adherence, side effects	HCV viral load
Baseline	✔		✔	✔		✔	✔	✔		✔
Week 1				✔	✔		✔		✔	
Week 2	✔	✔		✔	✔		✔		✔	
Week 4	✔	✔		✔	✔		✔		✔	
Week 8				✔	✔		✔		✔	
Week 12				✔	✔		✔	✔	✔	✔
Week 12 after end of treatment			✔	✔		✔	✔	✔		✔
Week 24 after end of treatment										✔

ALT: alanine aminotransferase (a liver enzyme); FBC: full blood count

Source: World Health Organization. Guidelines for the Screening, Care and Treatment of Persons with Chronic Hepatitis C Infection; 2016 April.

Side Effects of HCV Treatment

Newer DAA regimens are much better tolerated than previous regimens containing interferon. In fact, present-day DAA regimens have been well tolerated by people living with HCV, as well as those living with both HCV and HIV, in clinical trials and real-world studies.

The most common side effects, or "adverse reactions," of DAAs include:

Daclatasvir (Daklinza™, or DCV): Fatigue, headache, and nausea in regimens with or without RBV.

Elbasvir/grazoprevir (Zepatier®, or EBR/GZR): Headache, nausea, insomnia, and diarrhea.

Ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak®): Itchy skin (pruritus); fatigue, nausea, and trouble sleeping (insomnia) more common when combined with RBV; increases in ALT (a liver enzyme, most frequently in people also using estrogen therapy), and bilirubin (most frequently in people using RBV).

Simeprevir (Olysio®, or SMP): Rash and sun sensitivity (photosensitivity), which may be more severe in people of East Asian ancestry; fatigue, headache, nausea, insomnia, and pruritus.

Sofosbuvir (Sovaldi®, or SOF) with or without ledipasvir (Harvoni®, or SOF/LED): fatigue, headache, insomnia, and nausea; abnormal heart rhythm (bradyarrhythmias) in people taking SOF at the same time as the medicine amiodarone (used to treat abnormal heart rhythms), so these medications should not be used together.

Sofosbuvir/velpatasvir (Epclusa®, or SOF/VEL): Headache and fatigue; additional side effects, which are more common in people with decompensated cirrhosis, include anemia, headache, insomnia, and diarrhea.

Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®, or SOF/VEL/VOX): Headache, tiredness, diarrhea, and nausea. This combination should not be taken with amiodarone, used to treat certain heart problems, as it may cause slow heart rate. In some cases the slow heart rate has led to death or the need for a pacemaker when amiodarone is taken with medicines containing SOF.

Glecaprevir/pibrentasvir (Mavyret™, or G/P): Headache, fatigue, and nausea. People with severe hepatic impairment (Child-Pugh C), or who take atazanavir or rifampin should not use this treatment. People who take carbamazepine, efavirenz-containing regimens, or St. John's wort are not recommended to take this treatment as it could be harmful and have reduced therapeutic benefits.

Regimens containing RBV are more likely to cause anemia, shortness of breath, rash, itching, depression, irritability, and achy joints.

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 OST, supervised injection facilities, safe consumption spaces, and mental health programs?
3. Does your country have HCV treatment guidelines? Are they following the WHO treatment guidelines?

Action Steps:

1. What are our most important arguments for increasing access to HCV treatment to policy makers?
2. What are some of the problems with organizing stakeholders in your country or particular setting?
3. What strategies have been used to overcome these problems?
4. What are some initiatives to include the newer DAAs on national treatment lists?

SECTION 9:
TREATMENT FOR PEOPLE WHO USE DRUGS OR ALCOHOL USERS AND TREATMENT ISSUES FOR HIV/HCV COINFECTED PEOPLE

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. Older 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. These studies were conducted during PEG-IFN treatment trials, and high cure rates among people who use drugs have been seen with DAAs using different levels of support. Access to clean injection equipment and safe drug consumption spaces are also critical to help prevent reinfection.

Access to clean injection equipment and safe drug consumption spaces are also critical to help prevent reinfection.

Alcohol Use

Although older studies reported that both lifetime and recent alcohol use among people undergoing HCV treatment reduced the chance of being cured, many of them were performed in the era of non-pegylated interferon, which is significantly less effective than DAAs. Plus, the studies didn't measure adherence.

Marijuana

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

Daily marijuana use may or may not affect fat buildup in liver cells ***(steatosis)***[1], which can worsen fibrosis. 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 in the pegylated interferon era—and be cured of the virus—compared with those who didn't.

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.

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

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

HIV treatment is now recommended for all people living with HIV. As a result, many people who are coinfected receive HCV treatment while continuing their HIV therapy. In fact, it is advisable that people coinfected with both viruses begin treatment for HIV, and get an undetectable HIV viral load before beginning HCV treatment.

People living with HIV and HCV are just as likely to be cured by DAAs as people living with HCV alone. SVR rates of 95 percent and higher have been reported by researchers who have conducted clinical trials of DAA regimens in people coinfected with both viruses—even for those who were not successfully cured by previous regimens or those who have advanced fibrosis.

Antiretrovirals (ARVs) and Liver Toxicity

Many ARVs are broken down by the liver. In turn, prescription drug-induced liver toxicity is more common in people coinfected with HIV and HCV. Liver toxicity is more likely for coinfected people with serious liver scarring. Having liver enzyme levels checked regularly is very important for coinfected people who are taking ARVs, because these can pick up liver problems caused by HIV treatments or other causes.

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

HIV Treatment Selection and Prescription Drug Interactions

Some HIV medications can interact with HCV medications, which can decrease HIV or HCV treatment effectiveness or increase the risk of serious side effects. In turn, some HIV and HCV medications should not be used at the same time, or dose changes should be made.

Table 2. Select HIV and HCV Prescription Drug Interactions[2,3]

Selected HIV Treatments	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Velpatasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir/ Dasabuvir	Simeprevir
	Daklinza	Sovaldi	Harvoni	Epclusa	Vosevi	Mavyret	Zepatier	Viekira Pak/XR	Olysio
Nucleoside Reverse Transcriptase Inhibitors									
Abacavir	✓	✓	✓	✓	✓	✓	✓	✓	✓
Emtricitabine	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lamivudine	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tenofovir alafenamide fumarate (TAF)	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tenofovir disoproxil fumarate (TDF)	✓	✓	✓ Monitor for kidney or bone side effects.	✓ Monitor for kidney or bone side effects	✓ Monitor for kidney or bone side effects	✓	✓	✓	✓
HIV Protease Inhibitors									
Atazanavir (unboosted)	✓	✓	✓	✓	X	X	X	✓ Reduce atazanavir dose to 300 mg & take in the morning at same time as Viekira Pak/XR	X

Selected HIV Treatments	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Velpatasvir/ Sofosbuvir	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir	Ombitasvir/ Paritaprevir/ Ritonavir/ Dasabuvir	Simeprevir
	Daklinza	Sovaldi	Harvoni	Epclusa	Vosevi	Mavyret	Zepatier	Viekira Pak/XR	Olysio
HIV Protease Inhibitors									
Atazanavir/ Ritonavir or Atazanavir/ Cobicistat	✓ Lower daclatasvir dose to 30 mg/day	✓	✓ If used with TDF, monitor for kidney or bone side effects	✓ If used with TDF, monitor for kidney or bone side effects d	X	X	X	✓ Discontinue ritonavir (or the combination tablet Evotaz) and switch to unboosted atazanavir (300 mg), taken in the morning at the same time as Viekira Pak/XR.	X
Darunavir/ Ritonavir or Darunavir/ Cobicistat	✓	✓			✓ If used with TDF, monitor for kidney or bone side effects; also monitor for liver toxicity	X	X	X	X
Lopinavir/ Ritonavir	✓	✓			X	X	X	X	X
Tipranavir/ Ritonavir	?	X	X	X	X	X	X	X	X
Non-Nucleoside Reverse Transcriptase Inhibitors									
Efavirenz	✓ Increase daclatasvir dose to 90 mg/day	✓	✓ If used with TDF, monitor for kidney or bone side effects	X	X	X	X	X	X
Etravirine	✓ Increase daclatasvir dose DCV dose to 90 mg/day	✓		X	X	X	X	X	X
Nevirapine	✓ Increase daclatasvir dose DCV dose to 90 mg/day	✓		X	X	?	X	X	X
Rilpivirine	✓	✓		✓	✓	✓	✓	X	✓

Selected HIV Treatments	Daclatasvir Daklinza	Sofosbuvir Sovaldi	Ledipasvir/ Sofosbuvir Harvoni	Velpatasvir/ Sofosbuvir Epclusa	Sofosbuvir/ Velpatasvir/ Voxilaprevir Vosevi	Glecaprevir/ Pibrentasvir Mavyret	Elbasvir/ Grazoprevir Zepatier	Ombitasvir/ Paritaprevir/ Ritonavir/ Dasabuvir Viekira Pak/XR	Simeprevir Olysio
Integrase Strand Transfer Inhibitors									
Dolutegravir	✔	✔	✔ If used with TDF, monitor for kidney or bone side effects	✔	✔	✔	✔	✔	✔
Elvitegravir/ Cobicistat/TDF/ Emtricitabine	✔ Decrease daclatasvir dose to 30 mg/day	✔	X	✔ If used with TDF, monitor for kidney or bone side effects	✔ If used with TDF, monitor for kidney or bone side effects; also monitor for liver toxicity	✔ If used with TDF, monitor for kidney or bone side effects; also monitor for liver toxicity	X	X	X
Elvitegravir/ Cobicistat/TAF/ Emtricitabine	✔ Decrease daclatasvir dose to 30 mg/day	✔	✔	✔	✔ Monitor for liver toxicity	✔ Monitor for liver toxicity	X	X	X
Raltegravir	✔	✔	✔	✔	✔	✔	✔	✔	✔
CCR5 Antagonist									
Maraviroc	✔	✔	✔	✔	✔	✔	?	X	✔

✔ = Can be used together

X = Not recommended for use together

? = Not enough information available to recommend use together

ADVOCACY EXERCISE

Discussion Questions:

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

Action Steps:

1. How can we increase access to HCV care and treatment for people living with HIV 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?
3. What additional support, programs, or resources are needed to overcome the stigmatization and discrimination towards people who use drugs to ensure they can access HCV treatment?
4. What are some harm reduction approaches aimed to reduce alcohol or drug use? What are some ways to protect liver health for someone with a history of drug and alcohol use?

NOTES

1. Nordmann S, Vilotitch A, Roux P, et al. Daily cannabis and reduced risk of steatosis in human immunodeficiency virus and hepatitis C virus co-infected patients (ANRS CO13-HEPAVIH). J Viral Hepat. 2017 Oct 6. doi: 10.1111/jvh.12797.
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services (U.S.). Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf (Accessed 2017 November 20); pp. J9-12; Table 12.
3. HIV Drug Interaction Checker [Internet]. University of Liverpool: HIV Drug Interactions. [cited 2017 November 20]. Available at: https://www.hiv-druginteractions.org/

SECTION 10:

FIGHTING FOR NEW HCV DRUGS IN THE ERA OF PANGENOTYPIC GENERICS

Nobody should be treated with older, more toxic medicines now that we have safe and highly effective direct-acting antivirals. Treatment advocates must fight for affordable, widely available DAAs for everyone infected with hepatitis C!

Nobody should be treated with older, more toxic medicines now that we have safe and highly effective direct-acting antivirals. Treatment advocates must fight for affordable, widely available DAAs for everyone infected with hepatitis C!

DAAs attack 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 DAA regimens are used with RBV (but for a shorter time)—especially in people with cirrhosis.

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

- People may need to switch their ARVs to avoid prescription 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;
- Multiple medical visits are needed, which could result in losing people to follow up and unnecessary costs to the healthcare system;
- While DAAs have few side effects, they do still occur for some people, making it difficult for some people to complete treatment (**How to Tell if HCV Treatment Is Working and Side Effects in Section 8**); 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 health care providers, who need to put aside sufficient time to provide care.

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, HCV DAAs can be used with 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; while others work against multiple genotypes or all genotypes. Some regimens are simple—fixed-dose combinations—that require less monitoring during treatment.

Some countries may not have access to the newer pangenotypic regimens due to intellectual property (IP) barriers. Originator companies (also referred to as the patent holders) can offer ***voluntary licenses***, or an arrangement to permit generic companies to produce or market a medicine in return for royalty payments. Originator companies can choose to exclude countries from their voluntary licenses, so they cannot produce or market the medicines at lower costs. To date, the only DAAs available through voluntary licensing are daclatasvir and those by Gilead

(SOF/LED, SOF/VEL and SOF/VEL/VOX). Several dozen middle-income countries have been left out of the license by Gilead; therefore, countries face enormous prices for SOF/LED, SOF/VEL, and SOF/VEL/VOX.

Furthermore, national drug regulatory authorities must approve the medicines when they are registered in the country. Originator companies often delay registration in countries, and under-resourced regulatory agencies and local clinical trial requirements can delay the time it takes to approve a medicine.

HCV treatment advocates have learned lessons from the HIV/AIDS movement and have been pushing for faster, wider, more affordable access to generic DAAs. Generic competition often reduces prices dramatically. In addition to opposing the patents on certain DAAs or active pharmaceutical ingredients used to produce them, advocates have raised awareness and pressured governments to make use of international intellectual property provisions, such as issuing a compulsory license (CL) on a DAA. A ***compulsory license*** enables a government to procure an affordable generic version of a medicine for use in the national health program.

While advocates work to expand access through legal and regulatory channels, other strategies, such as procuring generic DAAs for personal use, have emerged. Hepatitis C buyers' clubs, using vast networks of patients, liver doctors, and activists, and a quality assured supply chain have been created around the world, which enable generics to be imported (under personal importation provisions) at a significantly reduced price than the list price in high-income countries (HICs)

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?
3. Why do you think it is important to get access to DAA treatment?
4. What is the price of DAAs in your country? Do you know the prices in other countries in the region?

Action Steps:

1. How can we create or improve access to the high-quality, generic DAAs that are right for us?
2. Are generic HCV treatments available through buyers' clubs in your country?

Section 11:

PUSHING FOR SIMPLER, MORE AFFORDABLE HCV TESTS

HCV can effectively be cured for 95 percent of people with the new DAAs, yet less than 2 percent of individuals have been diagnosed. The path to similar coverage of HCV diagnosis will require a significant increase in political and financial commitments. HCV diagnosis will need to be streamlined and implemented across a range of settings outside hospitals, or even primary care and community health clinics, in order to screen and diagnose hundreds of millions of people at risk of infection.

HCV can effectively be cured for 95 percent of people with the new DAAs, yet less than 2 percent of individuals have been diagnosed.

HCV diagnosis is a two-step process. After screening with an antibody test, an RNA test is required to confirm chronic HCV infection, making diagnosis more costly and time consuming. As it can be difficult for people to take time off work or commute to health care sites for the series of tests, often people are lost to follow up. Individuals and health care workers also are not sufficiently aware of HCV risks and HCV treatment, and few health systems cover viral load tests through public insurance plans. In many low- and middle-income countries (LMICs), HCV viral load tests are nearly double the cost of HIV viral load tests. In the private sector, HCV viral load tests are frequently twice as costly as these tests in the public sector.

Genotyping tests are particularly expensive, and generally the most costly step of the diagnostic process. These high prices are exacerbated by the fact that many individuals must pay for the tests out of pocket.

Each national health system and service delivery program at the community level are unique, therefore, the most optimal screening and testing steps will remain specific to local contexts. To increase the number of people on treatment, expansion of screening programs are required. Significantly more antibody tests would be needed to identify one person for a confirmatory RNA test. For example, in a screening program within a population with a 2 percent prevalence rate, one out of 50 people would test positive for HCV and require confirmatory testing. The antibody tests are quoted at US$1 per test, but this can be cost-prohibitive for resource-limited countries. The development of additional, reliable antibody tests is needed to promote competition and reduce prices.[1]

Making the process to diagnose a person simpler is an important part of linking more people to treatment and care.

Most health systems rely on a highly centralized process for confirming HCV through viral load tests. Instead, an ideal confirmatory test would use capillary (fingerstick) blood samples, provide results in less than 15 minutes, and cost less than US$5 per test. This technology could be targeted for use by community health workers and thereby allow for a scale-up of testing approaches outside hospitals or primary care clinics.[2]

The large numbers of tests needed in countries with high disease burdens require large machines that can run confirmatory tests for many diseases like HIV, HCV, and TB at the same time. To date, Cepheid's GeneXpert® machine is the most flexible, commercially available platform, yet it requires a disease-specific cartridge to run the tests. It has been difficult to increase the number of people tested in national HCV programs in order to see prices fall at a rate similar to HIV tests, especially given the monopoly on Cepheid's GeneXpert®.

For this to happen, advocacy is needed to push for better integration of HCV testing into existing laboratory systems that test for many diseases at the same time. This might require planning and negotiating for the purchase of tests needed for multiple diseases like HIV, HCV, and TB (or ***bundled procurement***) to get cheaper pricing and discounts. In addition, price markups on HCV tests applied by local distributors need to be controlled. Activists can call on companies to impose price caps to gain control over their products, or demand that the government lift customs fees or value-added taxes on these essential diagnostics.

With the availability of high quality generics, HCV diagnostics need to catch up. Greater access to diagnostics will be essential to generating the volume of procurement necessary to see the biggest generic price reductions. Making the process to diagnose a person simpler is an important part of linking more people to treatment and care.

ADVOCACY EXERCISE

Discussion Questions:

1. What are some of the barriers to getting tested for HCV in your country or area?
2. Does your insurance cover the test costs? Which ones?
3. Do you know how much you need to pay out-of-pocket for the tests?

Action Steps:

1. How can we make the process and sequence of tests easier and more accessible for more people?
2. What are some additional programs and supports needed for people seeking the necessary follow up tests?
3. What are some campaign ideas to convince government officials to scale up testing?

NOTES

1. Forging a Path to HCV Elimination: Simpler Tests and Affordable Generics. Report of the World Community Advisory Board on HCV Generics and Diagnostics. 2017 July 18-20; Bangkok, Thailand. Available from: http://www.hepcoalition.org/IMG/pdf/hcv_world_cab_report_2017_final.pdf (Accessed 2017 November 10).
2. Ibid.

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, sexual health clinic, or people living with HIV/AIDS (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 HCV 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 prescription 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 PLWHA to ask for help in negotiating this issue with your provider or in places where it is possible to gain access to pain and antianxiety medication.

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 HCV. 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 prescription 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 RBV or 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.

Track Your Lab Work[1]

Lab Tests	Date	Date	Date	Normal Ranges
CD4 count				From 0 to 1,600 cells/mm3
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)				Women: 19 IU/L Men: 30 IU/L Alanine aminotransferase (ALT) is made by the liver. When ALT is abnormally high, it may be a signal that the liver 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 treatments, including some ARVs, may increase ALT.
AST (or SGOT)				Women: 9 to 25 IU/L Men: 10 to 40 IU/L 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.
ALP				Women: 30 to 100 IU/L Men: 45 to 115 IU/L Alkaline phosphatase (ALP) 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.
APRI				The lab results are used to plug in to a formula to determine the AST to platelet ratio index to predict cirrhosis. An APRI score greater than 0.7 has a sensitivity of 77 percent and specificity of 72 percent for predicting significant liver fibrosis.
GGT				Women: <45 IU/L Men: <65 IU/L 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.

Lab Tests	Date	Date	Date	Normal Ranges
Bilirubin (direct)				0.0 to 0.4 mg/dL (U.S.) 0 to 7 umol/L (SI units) 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.
Bilirubin (total)				0.0 to 1.0 mg/dL (U.S.) 0 to 17 umol/L (SI units) 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.
Albumin				3.1 to 4.3 g/dL (U.S.) 31 to 43 g/L (SI units) Albumin carries medications, hormones, and waste products through the bloodstream and keeps fluid in the body. Abnormally low albumin levels are a sign of liver damage.
PT				11 to 13.5 seconds (1 to 2 times above this range is abnormal: INR 2 to 3) 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.

NOTES

Adapted from Collins S and Swan T. Guide to hepatitis C for people living with HIV. i-Base. 2013 November. Available from: http://i-base.info/guides/wp-content/uploads/2013/11/HIV-and-HCV-coinfection-Nov2013e.pdf. (Accessed 2017 November 20).

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 gets 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, WHO estimates that there are 1.4 million new infections every year. In the United States, the CDC estimates 3,000 new acute infections each year; in 2014 there were 1,239 reported new cases. Cases of HAV have been dropping in the United States 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 HBV or chronic HCV. The cost for the vaccine 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 to 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.

WHO estimates that 257 million people worldwide have been infected with chronic HBV and about 1.34 million people die every year from liver disease and cancer attributable to HBV and HCV infection. The CDC reported 2,791 in 2014 in the United States, and between 850,000 and 2.2 million people are living with chronic HBV. New HBV infections have dropped dramatically in many countries where the vaccine is widely available.

There are recommendations to get tested for HBV in countries with a high prevalence, such as in Central Africa and East Asia.

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. WHO recommends that all infants receive the HBV vaccine; the first dose should be given to infants as soon after birth as possible, preferably within 24 hours. The birth dose should be followed by 2 or 3 doses to complete the series.

Symptoms: Most children do not have symptoms; some adults (30 to 50 percent) 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 percent), and in HIV- positive people (30 to 90 percent).

You can find out if you have hepatitis B by: Blood tests; they can tell if you cleared hepatitis B without treat-

ment, if you just got it, or if you have chronic hepatitis B.

Treatment: Chronic HBV can be treated with the oral antiviral treatments entecavir, tenofovir, tenofovir alafenamide, or with older regimens of PEG-IFN. The U.S. brand-name combination pills containing tenofovir include Truvada®, Atripla®, and Stribild®.

Treatment can suppress HBV, but less than 10 percent of people will clear it. Since HBV 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 HBV 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. HBV is worse in people coinfected with HCV.

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 treatments are also active against HBV, but not strong enough to fully control HBV, HIV/HBV-coinfected people should only use HIV regimens that contain tenofovir to prevent developing HBV drug resistance.

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 HCV is a much smaller virus than HIV, there is more of it in a drop of blood. Bleach doesn't kill it. Depending on the country, up to 90 percent of current and former injection drug users have HCV;
- 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 HCV treatment.

Worldwide, at least 71 million people have been infected with chronic HCV. In the United States, roughly 3.2 million people are living with chronic HCV.

You can protect yourself against HCV 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 60 to 80 percent 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 HCV without treatment, if you just got it, or if you have chronic HCV.

Treatment: HCV can be treated—and cured—in all genotypes, but HCV treatment may not get rid of the virus for some people.

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. HCV is worse in people who are coinfected with HBV.

HIV Coinfection

- All people living with HIV 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.

SOVALDI

The goal of hepatitis C virus (HCV) treatment is a cure (when there is no HCV in a person's bloodstream at least 12 weeks after treatment is finished).

What is Sovaldi? Sovaldi (sofosbuvir) is an HCV-fighting drug that must be used with other drugs. In the United States, Sovaldi is approved for people with hepatitis C genotypes 1, 2, 3, or 4 who are over 18 years old.

How is Sovaldi used? Sovaldi is taken once daily, with or without food, for 12 to 24 weeks. Some people will use Sovaldi with a drug called ribavirin (RBV), which is taken twice daily with food. The type and length of treatment depends on HCV genotype, treatment history, whether a person has cirrhosis, and the other drugs used with it.

Harvoni is a combination of Sovaldi and ledipasvir (see TAG's **Harvoni** fact sheet for more information).

Sovaldi and Olysio—another HCV-fighting drug—have been approved for use in people over 18 years old who have HCV genotype 1 (see TAG's **Olysio** fact sheet for more information).

Sovaldi and Daklinza—another HCV-fighting drug—have been approved for use in people over 18 years old who have HCV genotype 3 (see TAG's **Daklinza** fact sheet for more information).

Hepatitis C treatment is changing quickly. Sovaldi is being studied with, and used in, interferon-free combinations that have not been approved yet.

Sovaldi-Based Treatment Regimens and Cure Rates in HCV Clinical Trials and Real-World Settings*

(Sovaldi has been used with pegylated interferon and ribavirin—or ribavirin alone—but these regimens are no longer recommended for genotype 1)

Genotype 1, never treated for HCV, no cirrhosis	+ Cirrhosis
Sovaldi + Olysio (with or without RBV), 12 weeks: **95%** to **97%** (in a small trial; real-world: 88% to 92%)	Sovaldi + Olysio (with or without RBV), 24 weeks: **100%** (real-world: 75% to 87%) Sovaldi + Olysio, 12 weeks: **88%**
Genotype 1, treatment-experienced, no cirrhosis	**+ Cirrhosis**
Sovaldi + Olysio (with or without RBV), 12 weeks: **95%** (real-world: 81% to 87%)	Olysio + Sovaldi, 12 weeks: **79%** Sovaldi + Olysio (with or without RBV), 24 weeks: **95%** (real-world: 76% to 79%)
Genotype 2, never treated or treatment-experienced (includes people with cirrhosis)	
Sovaldi + RBV, 12 weeks: **88%** to **100%** (real-world: in people with cirrhosis, 65% [never-treated] and 75% [treatment-experienced]) Sovaldi + RBV, 16 weeks: **87%** Sovaldi + RBV, 24 weeks: **100%**	
Genotype 3, never treated for HCV, no cirrhosis	**+ Cirrhosis**
Sovaldi + Daklinza, 12 weeks: **98%** Sovaldi + Daklinza + RBV, 12 weeks: **100%** Sovaldi + Daklinza + RBV, 18 weeks: **100%** Sovaldi + PEG-IFN and RBV, 12 weeks: **96%** Sovaldi + RBV, 16 weeks: **83%** Sovaldi + RBV, 24 weeks: **90%** to **94%**	Sovaldi + Daklinza, 12 weeks: **58%** Sovaldi + Daklinza + RBV, 12 weeks: **88%** Sovaldi + Daklinza + RBV, 16 weeks: **86%** Sovaldi + PEG-IFN and RBV, 12 weeks: **91%** Sovaldi + RBV, 24 weeks: **82%** to **92%**
Genotype 3, treatment-experienced, no cirrhosis	**+ Cirrhosis**
Sovaldi + Daklinza, 12 weeks: **92%** Sovaldi + Daklinza + RBV, 12 weeks: **100%** Sovaldi + Daklinza + RBV, 18 weeks: **100%** Sovaldi + PEG-IFN and RBV, 12 weeks: **94%** Sovaldi + RBV, 24 weeks: **87%**	Sovaldi + Daklinza, 12 weeks: **69%** Sovaldi + PEG-IFN and RBV, 12 weeks: **86%** Sovaldi + RBV, 24 weeks: **60%** to **77%**
Genotype 4, never treated for HCV, no cirrhosis (all information in genotype 4 is from small trials)	**+ Cirrhosis**
Sovaldi + PEG-IFN and RBV, 12 weeks: **96%** Sovaldi + RBV, 24 weeks: **100%**	Sovaldi + RBV, 24 weeks: **100%**
Genotype 4, treatment-experienced, no cirrhosis	**+ Cirrhosis**
Sovaldi + RBV, 24 weeks: **87%**	Sovaldi + RBV, 24 weeks: **67%**

*Cure rates in clinical trials are higher than in real life since people in them are usually healthier and get extra monitoring and support. Some trials were small (fewer than 200 people).

The most important thing a person can do to be cured is not to miss taking doses of HCV treatment—called *adherence*. Adherence lowers the risk for drug resistance.

What is drug resistance? Each day, HCV makes billions of copies of itself. Some of these copies are not the same as the original virus. They may have changes (called *mutations*) that can stop hepatitis C drugs from working. If people miss doses of their treatment, the virus gets a chance to reproduce—and some of these copies can be resistant to HCV treatment.

Some people have drug resistance even though they have never been on hepatitis C treatment—but many can be cured anyway. Most people who are not cured have resistance to one or more of the HCV drugs they've taken. Resistance to certain hepatitis C drugs can disappear within months. But resistance to other drugs can last for years and might prevent re-treatment from working. Some people who were treated with—but not cured by—Sovaldi have been re-treated with—and cured by—a combination of drugs including Sovaldi.

Sovaldi and age, gender, and race/ethnicity: In clinical trials, there was no difference in cure rates by age (over 65 vs. under 65). Women were slightly more likely to be cured than men. There is not much information about cure rates by race or ethnicity because most people in the trials were white. Sovaldi and RBV are slightly less effective for black and Hispanic people versus nonblack and non-Hispanic people.

Side effects from Sovaldi: Talk with your health care provider about possible side effects and how they will be managed. In clinical trials of Sovaldi and RBV, headache and fatigue were most common. At least 15 percent of trial participants had one or more of these side effects: nausea, insomnia, itching, anemia, weakness, rash, diarrhea, and irritability; usually, these were mild.

Does Sovaldi work for HIV-positive people? Yes. In clinical trials, cure rates were the same for HIV-positive people.

Sovaldi and other medications: Combining medications can increase or lower drug levels (called *drug-drug interactions*). Increasing drug levels can make side effects from each drug worse. If drug levels get too low, a drug can stop working, putting people at risk for drug resistance or not being cured.

Sovaldi should not be used with a medication called amiodarone because it can cause life-threatening heart problems.

Talk with your health care provider before starting or stopping medications, supplements, or herbal remedies.

There are other drugs that should be switched, stopped, or avoided while using Sovaldi. More information is available in Sovaldi's prescribing information (https://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf) and at: www.hep-druginteractions.org.

Sovaldi and HIV antiretrovirals: Sovaldi can be used with all HIV drugs ***except*** boosted Aptivus.

Storing Sovaldi: Keep Sovaldi below room temperature (86°F).

Sovaldi in people with kidney disease: Sovaldi can be used in people with mild or moderate kidney damage. People with severe kidney disease (eGFR<30 mL/min/1.73 m^2) and people on dialysis should consult a specialist.

Sovaldi in people with cirrhosis: HCV treatment guidelines recommend that people with serious liver damage (Child-Pugh Class B or C) be treated by a specialist. In clinical trials, Sovaldi and RBV have been used in people with Child-Pugh Class B or Class C cirrhosis or liver cancer.

Sovaldi during pregnancy, nursing, and in children: It is not known whether Sovaldi causes harm to unborn babies. If you are pregnant or planning pregnancy, talk with your health care provider about the risks and benefits of HCV treatment. It is not known whether Sovaldi passes into breast milk.

RBV causes birth defects and miscarriage. RBV should not be used by pregnant women or by male partners of pregnant women. RBV stays in a person's body for months, so women and their male partners should avoid pregnancy until six months ***after*** stopping RBV (for more information, see TAG's ribavirin fact sheet).

Sovaldi and RBV are under study in children (ages 3 to 17) with HCV genotypes 2 and 3. Harvoni (Sovaldi and another drug in one pill) is under study in children (ages 3 to 18).

Access to Sovaldi may be restricted by public and private payers. The criteria differ depending on the type of coverage and the state it is issued in. Support Path is Gilead's patient assistance program for Sovaldi. People with private insurance may be eligible for assistance with copayments. Uninsured people may be eligible for medication at no charge. Information about Support Path is available by phone at 1.855.769.7284, Monday through Friday between 9:00 a.m. and 8:00 p.m. (Eastern Time), or online at: http://www.gilead.com/responsibility/us-patient-access/support%20path%20for%20sovaldi%20and%20harvoni.

This fact sheet is current as of November 2015. Always check for updated information.

The goal of hepatitis C virus (HCV) treatment is a cure (when there is no hepatitis C virus in a person's bloodstream at least 12 weeks after treatment is finished).

What is Harvoni? Harvoni is two HCV-fighting drugs (sofosbuvir and ledipasvir) in one pill. In the United States, Harvoni is approved for HIV-negative and HIV-positive people with hepatitis C genotypes 1, 4, 5, and 6 who are over 18 years old. Harvoni is also approved for people with HCV genotype 1 who have advanced (called *decompensated*) cirrhosis, and for liver transplant recipients who have HCV genotype 1 or 4.

How is Harvoni used? Harvoni is taken once daily, with or without food, for 8 to 24 weeks. Treatment length depends on HCV treatment history, whether a person has cirrhosis, and the amount of hepatitis C virus in a person's bloodstream (called *HCV RNA* or *viral load*). Some people will need to add another drug, called **ribavirin (RBV)**, twice daily with Harvoni.

FDA Recommended Treatment Length and Cure Rates in Clinical Trials*

Genotype 1, never treated for HCV, no cirrhosis	+ Cirrhosis
12 weeks (recommended): **96%** to **99%** (if HCV RNA is less than 6 million copies IU/mL, consider 8 weeks) 8 weeks: **94%** (if HCV RNA is less than 6 million copies IU/mL: **97%**)	12 weeks: **94%**
Genotype 1, treatment-experienced, no cirrhosis	**+ Cirrhosis**
12 weeks + RBV: **95%**	If past treatment with an HCV protease inhibitor: 12 weeks + RBV If past treatment with Sovaldi: 24 weeks + RBV Treatment-experienced (PEG-IFN + RBV): **100%**
Genotype 1, never treated or treatment-experienced + decompensated cirrhosis (Child-Pugh Class B or Class C)	
12 weeks + RBV. **Class B: 87%** (45/52); **Class C: 88%** (35/40)	
Genotype 1, posttransplant, for all stages of cirrhosis	
12 weeks + RBV. **No cirrhosis: 95%** (94/99); **+ Child-Pugh Class A cirrhosis: 98%** (55/56); **+ Child-Pugh Class B cirrhosis: 89%** (41/46); **+ Child-Pugh Class C cirrhosis: 57%** (4/7)	
Genotype 4, 5, and 6, never treated or treatment-experienced, with or without cirrhosis	
12 weeks. **Genotype 4: 93%; Genotype 5: 93%; Genotype 6: 96%**	
Genotype 4, posttransplant, with or without compensated cirrhosis	
12 weeks + RBV. Cure rates are similar to those in genotype 1	

*Cure rates in clinical trials are higher than in real life since the people in them are usually healthier and get extra monitoring and support.

The most important thing a person can do to be cured is not to miss taking doses of HCV treatment—this is called *adherence*. Adherence lowers the risk for drug resistance.

What is drug resistance? Each day, HCV makes billions of copies of itself. Some of these copies are not exactly the same as the original virus. They may have changes (called *mutations*) that can stop hepatitis C drugs from working. If people miss doses of their treatment, HCV gets a chance to reproduce—and some of the copies it makes may not respond to HCV treatment.

Some people have drug resistance even though they have never been on hepatitis C treatment—but many can be cured anyway.

Most people who are not cured have resistance to one or more of the HCV drugs they've taken. Resistance to certain hepatitis C drugs can disappear within months. But resistance to certain drugs, including Harvoni, can last for years and may limit re-treatment options.

Harvoni and age, gender, and race/ethnicity: In clinical trials, cure rates did not differ by age (over 65 vs. under 65). Cure rates have been the same for women and men. There is not much information about how well Harvoni works by race or ethnicity because most of the people in the trials were white. With HCV alone, black (99%, or 89/90) versus nonblack (96%, or 431/448) people were just as likely to be cured by 12 weeks of Harvoni. In ION-4, a trial in HIV/HCV coinfection, the overall cure rate was higher (96%, or 321/335) than among black participants (90%, or 105/115).

Side effects from Harvoni: Talk with your health care provider about possible side effects and how they will be managed. In clinical trials of Harvoni, the most common side effects were fatigue, headache, nausea, diarrhea, and insomnia; usually, these were mild. Some people have reported skin swelling, rash, or blisters.

Does Harvoni work for HIV-positive people? Yes. In clinical trial of 335 HIV/HCV-coinfected people, 321 (96%) were cured after 12 weeks of Harvoni. Harvoni cannot be used with certain HIV drugs (see Harvoni and other medications, below).

Harvoni and other medications: Harvoni should not be used with certain drugs. Combining medications can increase or lower drug levels (called ***drug-drug interactions***). Increasing drug levels can make side effects from each drug worse. If drug levels get too low, a drug can stop working, putting people at risk for drug resistance or not being cured.

Harvoni should not be used with a medication called amiodarone because sofosbuvir can cause life-threatening heart problems. For people who must take amiodarone, intensive heart monitoring in a hospital is recommended for 48 hours after starting Harvoni and daily monitoring for at least two weeks afterward.

Talk with your health care provider before starting or stopping any medications, supplements, or herbal remedies.

Some drugs should be switched, stopped or avoided while using Harvoni. More information is available in Harvoni's prescribing information (www.accessdata.fda.gov/drugsatfda_docs/label/2015/205834s006lbl.pdf) and online at: www.hep-druginteractions.org.

Harvoni and HIV Antiretrovirals

HIV Integrase Inhibitors	
Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir DF)	Stribild is not recommended during treatment with Harvoni
HIV Non-Nucleoside Reverse Transcriptase Inhibitors	
Atripla (efavirenz/emtricitabine/tenofovir DF)	Harvoni can increase tenofovir concentration; renal monitoring for tenofovir-associated adverse events is recommended; efavirenz may lower the level of ledipasvir, one of the drugs in Harvoni
HIV Protease Inhibitors	
Boosted **Aptivus** (ritonavir/tipranavir)	Do not use boosted Aptivus with Harvoni
Kaletra (ritonavir/lopinavir), boosted **Prezista** (ritonavir/darunavir), boosted **Reyataz** (ritonavir/atazanavir), with **Viread** (tenofovir DF) or **Truvada** (emtricitabine/tenofovir DF)	Consider a different HCV or HIV regimen to avoid increased tenofovir concentration; renal monitoring for tenofovir-associated adverse events is recommended

Storing Harvoni: Keep Harvoni at room temperature (below 86°F).

Harvoni in people with kidney disease: Harvoni can be used in people with mild or moderate kidney disease. It is not recommended for people with severe kidney disease (eGFR<30 mL/min/1.73 m^2) or people on dialysis.

Harvoni in people with cirrhosis: HCV treatment guidelines recommend that people with serious liver damage (Child-Pugh Class B or C) be treated by a specialist. In clinical trials, people with Child-Pugh Class B or C cirrhosis have been treated with Harvoni and ribavirin.

Harvoni during pregnancy, nursing, and in children: It is not known whether Harvoni causes harm to unborn babies. If you are pregnant or planning pregnancy, talk with your health care provider about the risks and benefits of HCV treatment. It is not known whether Harvoni passes into breast milk. Harvoni is under study in children (ages 3 to 18).

Ribavirin causes birth defects, and it can be fatal to unborn babies. Ribavirin should not be used by pregnant women or by male partners of pregnant women. Ribavirin stays in a person's body for months. Women and their male partners should avoid pregnancy for six months after they have stopped taking ribavirin. Using two forms of birth control to prevent pregnancy while taking ribavirin—and for six months afterward—is recommended. Nursing during treatment with ribavirin is not recommended (see TAG's ribavirin fact sheet for more information).

There is a ribavirin pregnancy registry at: http://www.ribavirinpregnancyregistry.com.

Access to Harvoni may be restricted by public and private payers. The criteria differ depending on the type of coverage and the state it is issued in. Support Path is Gilead's patient assistance program for Harvoni. People with private insurance may be eligible for assistance with copayments. Uninsured people may be eligible for medication at no charge. Information about Support Path is available online at: http://www.gilead.com/responsibility/us-patient-access/support path for sovaldi and harvoni. Information about Support Path is also available by phone at 1.855.769.7284, Monday through Friday between 9:00 a.m. and 8:00 p.m. (Eastern Time), or online at: https://www.harvoni.com/support.

This fact sheet is current as of April 2016. Always check for updated information.

EPCLUSA

The goal of hepatitis C virus (HCV) treatment is a cure (when there is no HCV in a person's bloodstream 12 weeks after treatment is finished).

What is Epclusa? Epclusa is a fixed-dose combination of two HCV-fighting drugs (sofosbuvir and velpatasvir) in one pill. In the United States, Epclusa is approved for people with all hepatitis C genotypes (1–6) who are 18 years of age and older.

How is Epclusa used? Epclusa is taken once daily, with or without food, for 12 weeks. People who have advanced (called decompensated) cirrhosis will need to add another drug, called ribavirin, twice daily. The effectiveness of the treatment depends on whether a person has cirrhosis, their virus genotype, and previous HCV treatment history.

U.S. Food and Drug Administration–Recommended Treatment Length and Cure Rates in Clinical Trials*

Genotype 1, 2, 4, 5 and 6, no cirrhosis	+ Decompensated Cirrhosis
Epclusa, 12 weeks: **99%**	Epclusa + ribavirin, 12 weeks: **94%**
Genotype 3, no cirrhosis	**+ Decompensated Cirrhosis**
Epclusa, 12 weeks: **95%**	Epclusa + ribavirin, 12 weeks: **85%**

*Cure rates in clinical trials are higher than in the general population because the people in trials are usually healthier and receive extra monitoring and support.

TAG Treatment Action Group

The most important thing a person can do to be cured is never miss a dose of HCV treatment—this is called *adherence*. Adherence lowers the risk for drug resistance.

What is drug resistance? Each day, HCV makes billions of copies of itself. Some copies are not the same as the original virus. They may have changes (called *mutations*) that can stop hepatitis C drugs from working. If people miss doses of their treatment, HCV gets a chance to reproduce—and some of the copies may be resistant to HCV treatment.

Some people have drug resistance even though they have never been on hepatitis C treatment—but many can be cured anyway.

Most people who are not cured have resistance to one or more of the HCV drugs they've taken. Resistance to some hepatitis C drugs can disappear within months, but it can also last for years and may limit re-treatment options.

Epclusa and age, gender, and race/ethnicity: In clinical trials, cure rates did not differ by age (over 65 vs. under 65) or by gender. There is not much information about how well Epclusa works by race or ethnicity because most of the people in the trials were white. With HCV genotypes 1, 2, 4, 5, and 6 alone (no cirrhosis), black patients (98% or 51/52) were as likely as nonblack patients (99% or 564/569) to be cured with 12 weeks of Epclusa (results from the ASTRAL-1 clinical trial). Similar cure rates were also seen in black patients (3/3 or 100%) and nonblack patients (95% or 261/274) with the harder to treat genotype 3 (results from the ASTRAL-3 clinical trial).

Side effects from Epclusa: Talk with your health care provider about possible side effects and how they can be managed. In clinical trials of Epclusa, the most common side effects were headache and fatigue, usually mild. In patients with decompensated cirrhosis, who need to take ribavirin along with Epclusa, the most common side effects were mild to moderate fatigue, anemia, nausea, headache, insomnia, and diarrhea.

Does Epclusa work with HIV drugs? Epclusa cannot be taken with certain HIV drugs. See Epclusa and HIV Treatments (Antiretrovirals) below for more information.

Epclusa and other medications: Epclusa should not be used with certain drugs. Combining medications can increase or decrease drug levels (called *drug-drug interactions*). An increase can make side effects worse. A decrease can prevent a drug from working, putting people at risk for resistance or not being cured.

Epclusa should not be used in people taking the heart rhythm medication amiodarone because sofosbuvir, a key ingredient, can cause life-threatening heart problems. Do not take St. John's Wort herbal supplements with Epclusa, and tell your doctor if you are taking medications for cancer, seizures, bacterial infections, heartburn/acid reflux, or statins.

Talk with your health care provider before starting or stopping any medications, supplements, or herbal remedies.

More information is available in Epclusa's prescribing information (http://www.gilead.com/~/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.pdf).

Epclusa and HIV Treatments (Antiretrovirals)

HIV Protease Inhibitors	
Boosted **Aptivus** (ritonavir/tipranavir)	Do not use boosted Aptivus with Epclusa
HIV Non-Nucleoside Reverse Transcriptase Inhibitors	
Atripla (efavirenz/emtricitabine/tenofovir DF) **Sustiva** (efavirenz)	Do not use Epclusa with medications containing efavirenz
HIV Nucleotide Reverse Transcriptase Inhibitors	
Viread (tenofovir DF) **Truvada** (emtricitabine/tenofovir DF) **Atripla** (efavirenz/emtricitabine/tenofovir DF) **Stribild** (elvitegravir/cobicistat/emtricitabine/tenofovir DF) **Complera** (emtricitabine/rilpivirine/tenofovir DF)	Renal monitoring for tenofovir-associated adverse events is recommended

Storing Epclusa: Keep Epclusa at room temperature (below 86°F).

Epclusa in people with kidney disease: Epclusa can be used by people with mild or moderate kidney disease. No studies have been conducted in people with severe kidney disease (eGFR <30 mL/min/1.73 m2) or people on dialysis. Patients with severe kidney disease, or on dialysis, who also have cirrhosis should ask their doctor whether Epclusa and ribavirin are right for them.

Epclusa in people with cirrhosis: HCV treatment guidelines recommend that people with serious liver damage (Child-Pugh Class B or C) be treated by a specialist. People with Child-Pugh Class B or C can be treated with Epclusa and ribavirin.

Epclusa during pregnancy, nursing, and in children: It is not known whether Epclusa causes harm to unborn babies or passes into breast milk. If you are pregnant or breast feeding, or planning for either, talk with your health care provider about the risks and benefits of HCV treatment. Epclusa has not been tested in children younger than 18 years old.

Ribavirin causes birth defects and miscarriage. It should not be used by pregnant women or by male partners of pregnant women. The drug stays in a person's body for months. Women and their male partners should avoid pregnancy for six months ***after*** they have stopped taking ribavirin. Using two forms of birth control to prevent pregnancy while taking ribavirin—and for six months afterward—is recommended. Nursing during treatment is not recommended. For more information, visit the ribavirin pregnancy registry at: http://www.ribavirinpregnancyregistry.com/.

Access to Epclusa may be restricted by public and private payers. The criteria differ depending on the type of coverage and the state in which it is issued. Support Path is Gilead's patient assistance program for Epclusa. People with private insurance may be eligible for assistance with copayments. Uninsured people may be eligible for medication at no charge. Information about Support Path is available online at: http://www.mysupportpath.com/. Information about Support Path is also available by phone at 1-855-7-MYPATH or 1-855-769-7284.

This fact sheet is current as of August 2016. Always check for updated information.

DAKLINZA

What is Daklinza? Daklinza (daclatasvir) is an HCV-fighting drug that blocks different steps of the virus life cycle. In the United States, Daklinza is approved for people over 18 years old who have HCV genotype 1 or genotype 3 (although it has been used in other genotypes).

How is Daklinza used? Daklinza is taken once daily with another drug, called Sovaldi. These drugs can be taken with or without food, for 12 or 24 weeks. Daklinza and Sovaldi have been used in HCV genotypes 1, 2, 3, and 4 (including in people with HIV/HCV coinfection) and before and after liver transplantation.

People with cirrhosis may need longer treatment with Daklinza and Sovaldi, or a third drug called ribavirin (RBV), which is taken twice daily with food.

Pretreatment resistance testing is recommended for people with genotype 1a and cirrhosis to make sure that Daklinza and Sovaldi will be effective (see What is drug resistance?, below).

Resistance testing is also recommended for all people with HCV genotype 1 who were not cured by Daklinza (or other drugs from the same family, such as Harvoni or Zepatier); treatment should be tailored to the results.

Daklinza: Recommendations from the FDA, and Cure Rates*

(Recommendations from the AASLD/IDSA HCV Treatment Guidelines Panel for the use of Daklinza and Solvadi can be found at www.hcvguidelines.org)

Genotype 1, treatment-naive or -experienced, no cirrhosis or compensated (Child-Pugh Class A) cirrhosis
Daklinza + Sovaldi, 12 weeks. HCV: **100%;** HIV/HCV: G1a: **96.7%**; G1b: **100%;** Posttransplant: **95%** (39/41)
Genotype 1, decompensated† (Child-Pugh Class B or Class C) cirrhosis or posttransplant
Daklinza + Sovaldi + RBV, 12 weeks. HIV/HCV: G1a: **97%**; G1b: **100%**
Genotype 3, treatment-naive or -experienced, no cirrhosis
Daklinza + Sovaldi, 12 weeks. HCV: **98%** HIV/HCV: **100%**‡ Treatment-experienced: HCV: **92%** HIV/HCV: **100%**‡
Genotype 3, treatment-naive or -experienced, compensated (Child-Pugh Class A) or decompensated† (Child-Pugh Class B or C) cirrhosis or posttransplant
Daklinza + Sovaldi + RBV, 12 weeks. HCV: **58%** Treatment-experienced: HCV: **69%** HIV/HCV: **100%**‡

*In people with decompensated cirrhosis or transplant recipients, start RBV at 600 mg/day; increase to 1,000 mg/day as tolerated.
†Cure rates in clinical trials are higher than in real life since the people in them are usually healthier and get extra monitoring and support.
‡Studied in fewer than 10 people

The most important thing a person can do to be cured is to not miss taking doses of HCV treatment—this is called *adherence*. Adherence lowers the risk for drug resistance.

What is drug resistance? Each day, HCV makes billions of copies of itself. Some copies are not exactly the same as the original virus. They may have changes (called *mutations*) that can stop hepatitis C drugs from working. If people miss doses of their treatment, hepatitis C gets a chance to reproduce—and some of the copies it makes may be resistant to HCV treatment.

Some people have drug resistance even though they have never been on hepatitis C treatment—but many can be cured anyway. Certain mutations make Daklinza less effective, including one called Y93H.

Daklinza and Sovaldi in Genotype 3, with and without the Y93H Mutation

	With Y93H	Without Y93H
Overall	54%	92%
No cirrhosis	67%	98%
Cirrhosis	25%	68%

Most people who are not cured by HCV treatment have resistance to one or more of the drugs they've taken. Resistance to certain hepatitis C drugs can disappear within months. But resistance to certain drugs, including Daklinza, can last for years—and might limit re-treatment options.

Daklinza and age, gender, and race/ethnicity: In clinical trials, cure rates did not differ by age (over 65 vs. under 65). Cure rates have been the same for women and men. In ALLY-2, a trial of Daklinza and Sovaldi in people with HIV/HCV, the overall cure rate was the same regardless of race/ethnicity. Information about how well Daklinza works by race or ethnicity is limited since most people in the clinical trials were white.

DAKLINZA

Side effects from Daklinza: **Talk with your health care provider about possible side effects and how they will be managed.** In clinical trials of Daklinza and Sovaldi, the most common side effects were fatigue and headache; usually, these were mild.

Does Daklinza work for HIV-positive people? Yes. In ALLY-2, a clinical trial in 153 HIV/HCV-coinfected people, 149 (97%) were cured after 12 weeks of Daklinza and Sovaldi.

Daklinza and other medications: drug-drug interactions: Daklinza should not be used with certain drugs. Combining medications can increase or lower drug levels (called *drug-drug interactions*). Increasing drug levels can make side effects from each drug worse. If drug levels get too low, a drug can stop working, putting people at risk for drug resistance or not being cured.

Talk with your health care provider before starting or stopping any medications, supplements, or herbal remedies.

Some drugs should be switched, stopped, or avoided while using Daklinza.

Sovaldi—which is used with Daklinza—should not be used with a medication called amiodarone because it can cause life-threatening heart problems.

More information is available in Daklinza's prescribing information (www.accessdata.fda.gov/drugsatfda_docs/label/2015/206843Orig1s000lbl.pdf) and at: www.hep-druginteractions.org.

Daklinza and HIV antiretrovirals: Daklinza can be used with most HIV drugs. A lower or higher dose of Daklinza may be needed when it is used with certain antiretrovirals.

HIV Integrase Inhibitors	
Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir DF)	Lower Daklinza dose from 60 mg to 30 mg
HIV Non-Nucleoside Reverse Transcriptase Inhibitors	
Atripla (efavirenz/emtricitabine/tenofovir DF)	Increase Daklinza dose from 60 mg to 90 mg
Intelence (etravirine)	Increase Daklinza dose from 60 mg to 90 mg
Viramune (nevirapine)	Increase Daklinza dose from 60 mg to 90 mg
HIV Protease Inhibitors	
Boosted **Reyataz** (atazanavir/ritonavir or atazanavir/cobicistat)	Lower dose of Daklinza from 60 mg to 30 mg

Storing Daklinza: Keep Daklinza at room temperature (between 59°F and 86°F).

Daklinza in people with kidney disease: Daklinza can be used without dose adjustment in people with mild, moderate, or severe kidney disease.

Daklinza in people with cirrhosis: HCV treatment guidelines recommend that people with serious liver damage (Child-Pugh Class B or C cirrhosis) be treated by a specialist. Daklinza can be used in mild, moderate, or severe hepatic impairment without dose adjustment. In clinical trials, people with Child-Pugh Class B or Class C cirrhosis have been treated with Daklinza and Sovaldi, with or without RBV. Daklinza-based treatment is less effective for people with Child-Pugh Class C cirrhosis.

Daklinza and Sovaldi have also been used to treat people for hepatitis C after liver transplantation.

Daklinza during pregnancy, nursing, and in children: It is not known whether Daklinza causes harm to unborn babies. In animal studies of pregnant rats and rabbits, very high doses of Daklinza caused birth defects, miscarriage, and maternal death. No harm was seen at lower doses.

If you are pregnant or planning pregnancy, talk with your health care provider about the risks and benefits of HCV treatment. It is not known whether Daklinza passes into human breast milk (in animal studies using much higher doses, it was found in the breast milk of rats).

Daklinza has not been studied in children, and it is not approved for people under 18 years old.

Access to Daklinza: Access may be restricted by public and private payers. The criteria differ depending on the type of coverage and the state it is issued in. Patient Support Connect is BMS's patient assistance program for Daklinza. People with private insurance may be eligible for assistance with copayments. Uninsured people may be eligible for medication at no charge. Information and enrollment forms are available online at: https://bmsdm.secure.force.com/patientsupportconnect/patient and http://www.bmspaf.org/documents/bmspaf-enrollment-form.pdf or by phone at 1.800.736.0003.

This fact sheet is current as of April 2016. Always check for updated information.

The goal of hepatitis C virus (HCV) treatment is a cure (when there is no hepatitis C virus in a person's bloodstream at least 12 weeks after treatment is finished).

What is Zepatier? Zepatier is two hepatitis C virus-fighting drugs in one tablet. These drugs block different steps of the virus lifecycle. In the United States, Zepatier is approved for people who are over 18 years old with hepatitis C genotype 1 or genotype 4.

How is Zepatier used? Zepatier is a beige pill, taken once daily, with or without food, for 12 or 16 weeks. Some people will need to take another drug with Zepatier, called **ribavirin (RBV)**, twice daily.

Zepatier comes in a 14-pill blister pack; each pill is individually packaged to protect Zepatier from moisture. Keep Zepatier in the packaging until you take it.

Drug resistance testing is recommended for people who have hepatitis C genotype 1a before starting treatment with Zepatier. Some people with genotype 1a will need 16 weeks of treatment and RBV (see What is drug resistance?, below). It is important to make sure that you have gotten the right treatment (with or without RBV), for the recommended length of time (12 or 16 weeks).

FDA Recommendations and Cure Rates for Zepatier in HCV Genotypes 1 or 4

Hepatitis C Genotype and Subtype (with or without Cirrhosis)	Recommended Treatment and Cure Rates in Clinical Trials*
Genotype 1a, never treated or past treatment (with PEG-IFN and RBV), no ***NS5A resistance***	Zepatier for 12 weeks Never treated: **92%** (144/157); HIV/HCV: **94%** (136/144) Treatment-experienced: **90%** (55/61)
Genotype 1a, never treated or past treatment (PEG-IFN and RBV), with ***NS5A resistance***	Zepatier + RBV for 16 weeks: **100%** (6/6)
Genotype 1b, never treated or past treatment (with PEG-IFN and RBV)	Zepatier for 12 weeks Never treated: **98%** (129/131); HIV/HCV: **96%** (43/45) Treatment-experienced: **100%** (35/35)
Genotype 1a or 1b, never treated or past treatment (with PEG-IFN, RBV and Incivek or Olysio or Victrelis)	Zepatier + RBV for 12 weeks **100%** (55/55) if treatment-experienced, no resistance to HCV protease inhibitors **88%** (21/24) if treatment-experienced, with resistance to protease inhibitors
Genotype 4, never treated	Zepatier for 12 weeks **97%** (64/66) HIV/HCV: **96%** (27/28)
Genotype 4, past treatment (PEG-IFN and RBV)	Zepatier + RBV for 16 weeks: **100%** (8/8)

*Cure rates in clinical trials are higher than in real life since the people in them are usually healthier and get extra monitoring and support.

The most important thing a person can do to be cured is not to miss taking doses of HCV treatment—this is called ***adherence***. Adherence lowers the risk for drug resistance.

What is drug resistance? Each day, HCV makes billions of copies of itself. Some of these copies are not exactly the same as the original virus. They may have changes (called ***mutations***) that can stop hepatitis C drugs from working. If people miss doses of their treatment, HCV gets a chance to reproduce—and some of the copies it makes may not respond to HCV treatment.

Some people have drug resistance even though they have never been on hepatitis C treatment—but many can be cured anyway.

Pretreatment resistance testing is recommended for people with HCV genotype 1a because they may have certain mutations that make Zepatier less effective. This can be overcome by taking Zepatier for 16 weeks with RBV.

Cure Rates in HCV Genotype 1a

	Zepatier, 12 weeks	Zepatier + RBV, 16 weeks
No NS5A resistance	98% (441/450)	100% (49/49)
With NS5A resistance	70% (39/56)	100% (6/6)

Most people who are not cured have resistance to one or more of the HCV drugs they've taken. Resistance to certain hepatitis C drugs can disappear within months. But resistance to other drugs can last for years and might prevent re-treatment from working.

Side effects from Zepatier: Make sure to talk with your health care provider about possible side effects and how they will be managed. In clinical trials, the most common side effects from Zepatier were fatigue and headache, nausea, insomnia, and diarrhea. People taking RBV also experienced anemia, shortness of breath, rash, itching, depression, irritability, and achy joints (see TAG's **ribavirin (RBV)** fact sheet for more information). Most of these side effects were mild.

Liver enzyme levels may increase while taking Zepatier. Your health care provider should check your liver with blood tests before you start taking Zepatier and 8 weeks after starting treatment. For people taking Zepatier for 16 weeks, another blood test is recommended at 12 weeks after starting treatment.

In clinical trials, people over 65 years old, women, and people of Asian ancestry had higher levels of Zepatier in their bloodstream and were more likely to have liver enzyme elevations.

Zepatier and age, gender, and race/ethnicity: In clinical trials, cure rates did not differ by age (over 65 vs. under 65). Cure rates have been the same for women and men, and in all races. Information is limited because most of the people in the trials were white.

Does Zepatier work for HIV-positive people? Zepatier works just as well for coinfected people. In C-EDGE Coinfection, a 189-person trial, 95% (179/189) of people being treated for the first time were cured. In the C-EDGE Treatment-Experienced trial, cure rates among people with HIV/HCV were 100% (11/11) after 12 weeks of Zepatier (with or without RBV). Cure rates among people treated with 16 weeks of Zepatier were 83% (5/6) without RBV and 100% (4/4) with RBV.

Zepatier and other medications: Zepatier should not be used with certain drugs. Combining medications can increase or lower drug levels (called *drug-drug interactions*). Increasing drug levels can make side effects from each drug worse. If drug levels get too low, a drug can stop working, putting people at risk for drug resistance or not being cured. **Talk with your health care provider about starting or stopping any medications, supplements, or herbal remedies.**

Some drugs should be switched, stopped, or avoided while using Zepatier. More information is available in prescribing information for Zepatier online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208261Orig1s000lbl.pdf and www.hep-druginteractions.org.

Zepatier and HIV antiretrovirals: Zepatier can be used with these HIV drugs: Complera/Edurant, Emtriva, Epivir, Isentress, Tivicay, Triumeq, Truvada, Viread, and Ziagen.

Zepatier during pregnancy, nursing, and in children: It is not known whether Zepatier causes harm to unborn babies. If you are pregnant, or planning pregnancy, talk with your health care provider about the risks and benefits of HCV treatment.

It is not known whether Zepatier passes into breast milk or whether nursing during treatment with Zepatier causes harm to infants and children.

Zepatier has not been studied in children and is not approved for people under 18 years old.

Ribavirin causes birth defects, and it can be fatal to unborn babies. Ribavirin should not be used by pregnant women or by male partners of pregnant women. Ribavirin stays in a person's body for months. Women and their male partners should avoid pregnancy for six months ***after*** they have stopped taking ribavirin. Using two forms of birth control to prevent pregnancy while taking ribavirin—and for six months afterward—is recommended. Nursing during treatment with ribavirin is not recommended. There is a ribavirin pregnancy registry at: http://www.ribavirinpregnancyregistry.com.

Storing Zepatier: Keep Zepatier at room temperature (below 68°F to 77°F).

Zepatier in people with kidney disease: Zepatier can be used without dose adjustment in mild, moderate, or severe kidney disease, including people on dialysis. In C-SURFER, a clinical trial of people with stage 4 and stage 5 kidney disease, 94% (115/122) were cured by 12 weeks of Zepatier.

Zepatier in people with cirrhosis: Hepatitis C treatment guidelines recommend that people with serious liver damage (Child-Pugh Class B or C cirrhosis) be treated by a specialist. People with Class B and Class C cirrhosis **should not use Zepatier**.

Zepatier can be used by people with mild liver impairment (Child-Pugh Class A cirrhosis).

Access to Zepatier may be restricted by public and private payers. The criteria differ by type of coverage and the state it was issued in. Merck's Access Program may help people who have private insurance. Information is available at: http://www.merckhelps.com/ZEPATIER. Enrollment forms are available online at: http://www.merckhelps.com/docs/MAP_Enrollment_Form_INFC-1161739_English.pdf or by phone at 1.866.251.6013, Monday through Friday, from 8 a.m. to 8 p.m. (Eastern Time).

Some uninsured people may be eligible for free medication through the Merck Patient Assistance Program; information is available online at: http://www.merckhelps.com/programs.aspx?tab=MAP and by phone at 1.800.727.5400, Monday through Friday from 8 a.m. to 8 p.m. (Eastern Time).

This fact sheet is current as of April 2016. Always check for updated information.

The goal of hepatitis C virus (HCV) treatment is a cure (when there is no HCV in a person's bloodstream at least 12 weeks after treatment is finished).

What is Viekira XR? Viekira XR is a combination of hepatitis C virus–fighting drugs (paritaprevir/ritonavir/ombitasvir and dasabuvir) that block different steps of the virus life cycle. In the United States, Viekira XR is approved for people with hepatitis C genotype 1 who are over 18 years old. Viekira XR was previously approved and prescribed as a twice a day formula known as Viekira Pak. XR contains the same drugs, in the same amounts, as Viekira Pak, now in a once daily package.

What is Technivie? Technivie is a combination of paritaprevir/ritonavir and ombitasvir. Technivie is approved for people over 18 years of age who have hepatitis C genotype 4 without cirrhosis.

How is Viekira XR used? Viekira XR is taken once daily, with food, for 12 or 24 weeks. Viekira XR comes in a box of 4 (weekly) cartons of daily-dose packs with three beige tablets in each pack. The tablets should be swallowed whole (they should not be split, chewed or crushed). Some people will need to take another drug, called **ribavirin (RBV)**, twice daily when taking Viekira XR.

How is Technivie used? Technivie is taken once daily, with food, for 12 weeks. Technivie comes in a box of 28 daily-dose packs with two pink tablets. Both pink tablets are taken in the morning. It should be used with another drug, called **ribavirin (RBV)**, which is taken twice daily. Using Technivie by itself can be considered for people who cannot take RBV if they are being treated for the first time.

It is important to make sure that you have gotten the right treatment (with or without RBV) for the recommended length of time (12 or 24 weeks).

Viekira XR and Technivie with Cure Rates*

Genotype 1a (including mixed or unknown subtypes), never treated or treatment-experienced, no cirrhosis	+ Cirrhosis
Viekira XR + RBV, 12 weeks: **94%** to **97%****	Viekira XR + RBV, 24 weeks: **95%** Viekira XR + RBV, 12 weeks: **89%** (consider 12 weeks of treatment according to HCV treatment history)
Genotype 1b, never treated or treatment-experienced, no cirrhosis	**+ Cirrhosis**
Viekira XR, 12 weeks: **100%**	Viekira XR, 12 weeks: **99%**
Genotype 4, never treated, no cirrhosis	**+ Cirrhosis**
Technivie + RBV, 12 weeks: **100%** (**90.9%** without RBV)	N/A
Genotype 4, treatment-experienced, no cirrhosis	**+ Cirrhosis**
Technivie + RBV, 12 weeks: **100%**	N/A

*Cure rates in clinical trials are higher than in real life since the people in them are usually healthier and get extra monitoring and support. **Cure rates are from clinical trials of the components of Viekira XR (administered as Viekira Pak).

The most important thing a person can do to be cured is not to miss taking doses of HCV treatment—called ***adherence***. Adherence lowers the risk for drug resistance.

What is drug resistance? Each day, HCV makes billions of copies of itself. Some of these copies are not the same as the original virus. They may have changes (called ***mutations***) that can stop hepatitis C drugs from working. If people miss doses of their treatment, the virus gets a chance to reproduce—and some of these copies can be resistant to HCV treatment. Some people have drug resistance even though they have never been on hepatitis C treatment—but many can be cured anyway.

Most people who are not cured have resistance to one or more of the HCV drugs they've taken. Resistance to certain hepatitis C drugs can disappear within months. But resistance to other drugs can last for years and might prevent re-treatment from working.

Viekira XR or Technivie and age, gender, and race/ethnicity: In clinical trials, cure rates did not differ by age (over 65 vs. under 65). Cure rates were the same for women and men. There is not much information about how well Viekira XR or Technivie work by race or ethnicity because most people in the trials were white. But researchers noticed two things: adding RBV to Viekira XR increased cure rates for African Americans with HCV genotype 1a (100% vs. 84%), and people with a common genetic factor among African Americans (called the IL28B TT genotype) were less likely to be cured by Viekira XR (see TAG's **Hepatitis C and the IL28B Gene** fact sheet).

Side effects from Viekira XR and Technivie: Talk with your health care provider about possible side effects and how they will be managed. In clinical trials, the most common side effects from Viekira XR or Technivie were nausea, itching, and insomnia. People taking RBV also experienced fatigue, weakness, rash, and other skin reactions (see TAG's RBV fact sheet for more information). Most of these side effects were mild.

Liver enzyme levels may increase while taking Viekira XR or Technivie. Your health care provider should check your liver with blood tests during the first four weeks of treatment—and afterward as needed.

Do Viekira XR and Technivie work for HIV-positive people? Yes, but Viekira XR or Technivie should not be used by coinfected people unless they are also being treated for HIV. This is because one of the drugs in Viekira XR and Technivie can cause resistance to some HIV drugs. In a clinical trial of 63 people with HIV and hepatitis C genotype 1, 93.5% were cured after 12 weeks of Viekira Pak plus RBV. Technivie has not been studied in people coinfected with HIV and hepatitis C genotype 4.

Viekira XR or Technivie can be used with these HIV drugs: Isentress or Reyataz (300 mg), which should be taken in the morning, ***without ritonavir (Norvir)***, plus Truvada or Viread with Epivir or Emtriva.

Viekira XR or Technivie and other medications: Viekira XR or Technivie should not be used with certain drugs. Combining medications can increase or lower drug levels (called *drug-drug interactions*). Increasing drug levels can make side effects from each drug worse. If drug levels get too low, a drug can stop working, putting a person at risk for drug resistance or not being cured. **Talk with your health care provider about starting or stopping any medications, supplements, or herbal remedies.**

Some drugs should be switched, stopped, or avoided while using Viekira XR or Technivie. More information is available in the prescribing information for Viekira XR and Technivie (http://www.rxabbvie.com/pdf/viekiraxr_pi.pdf and http://www.rxabbvie.com/htm/technivie/technivie_pi.htm) and at: www.hep-druginteractions.org.

Viekira XR or Technivie and hormonal contraception (birth control): Viekira XR and Technivie cannot be used with medications containing ethinyl estradiol (women can use progestin-only birth control). Medications containing ethinyl estradiol can be restarted two weeks after stopping Viekira XR or Technivie.

Viekira XR or Technivie during pregnancy, nursing, and in children: It is not known whether Viekira XR or Technivie cause harm to unborn babies. If you are pregnant or planning pregnancy, talk with your health care provider about the risks and benefits of HCV treatment. It is not known whether Viekira XR or Technivie pass into breast milk.

Viekira XR and Technivie have not been studied in children and are not approved for people under 18 years old.

Ribavirin causes birth defects and miscarriage. Ribavirin should not be used by pregnant women or by male partners of pregnant women. Ribavirin stays in a person's body for months. Women and their male partners should avoid pregnancy for six months ***after*** they have stopped taking ribavirin. Using two forms of birth control to prevent pregnancy while taking ribavirin—and for six months afterward—is recommended. Nursing during treatment with ribavirin is not recommended. There is a ribavirin pregnancy registry at: http://www.ribavirinpregnancyregistry.com.

Storing Viekira XR: Keep Viekira XR or Technivie at room temperature (below 86°F).

Viekira XR or Technivie in people with kidney disease: Viekira XR or Technivie can be used by people with mild or moderate kidney disease. People with severe kidney disease should consult with a specialist before using Viekira XR or Technivie. They have not been studied in people on dialysis.

Viekira XR or Technivie in people with cirrhosis: Hepatitis C treatment guidelines recommend that people with serious liver damage (Child-Pugh Class B or C cirrhosis) be treated by a specialist. Technivie has not been studied in people with HCV genotype 4 and cirrhosis. Viekira XR and Technivie should ***not*** be used in people with Child-Pugh Class B or Class C cirrhosis.

Access to Viekira XR and Technivie may be restricted by public and private payers. The criteria differ by type of coverage and the state it is issued in. ProCeed is AbbVie's Viekira XR patient assistance program. ProCeed may help people with private insurance with copayments. Uninsured people may be eligible for free medication through proCeed.

Information about proCeed is available by phone at 1.844.2PROCEED (1.844.277.6233), Monday through Friday between 8:00 a.m. and 5:00 p.m. (Eastern Time), or online at: https://www.viekira.com/patient-support/financial-resources.

Information about the Technivie patient assistance program is also available by phone at 1.844.2PROCEED (1.844.277.6233), Monday through Friday between 8:00 a.m. and 5:00 p.m. (Eastern Time.

This fact sheet is current as of January 2017. Always check for updated information.

RIBAVIRIN

The goal of hepatitis C virus (HCV) treatment is a cure (when there is no hepatitis C virus in a person's bloodstream at least 12 weeks after treatment is finished).

What is ribavirin? Ribavirin (RBV) is an HCV-fighting drug. RBV does not work by itself. Adding RBV to other drugs can increase the chance of being cured from HCV. In the United States, ribavirin is approved for children (3 to 18 years of age) and adults.

RBV is made by Merck (sold as Rebetol), Genentech (sold as Copegus), and Kadmon Pharmaceuticals (sold as Ribasphere).

How is ribavirin used? RBV is taken twice a day with food; the dose is based on weight.

Is there anyone who cannot use ribavirin? People with sickle cell disease or thalassemia cannot use RBV. People who have serious heart disease cannot use RBV since it increases the risk for heart attacks.

Ribavirin and pregnancy: RBV causes birth defects and miscarriage. RBV should not be used by pregnant women or by male partners of pregnant women. RBV stays in a person's body for months, so women and their male partners should avoid pregnancy until six months ***after*** stopping it. Using two forms of birth control to prevent pregnancy while taking RBV—and for six months afterward—is recommended. There is an RBV pregnancy registry at: http://www.ribavirinpregnancyregistry.com.

Ribavirin and nursing: It is not clear whether RBV passes into breast milk. Nursing is not recommended while taking RBV.

Side effects from RBV: Talk with your health care provider about possible side effects and how they will be managed. Some people develop *anemia* (low red blood cell count) from RBV, usually within the first few weeks of treatment. It is important to have blood tests before and during RBV treatment to check for anemia and other side effects. Anemia is usually treated by lowering RBV dose.

When RBV was used without interferon in clinical trials, side effects included: aching muscles, anxiety, back pain, colds, constipation, coughing, diarrhea, dizziness, fever, headaches, insomnia, irregular periods, irritability, itchy skin, nausea, night sweats, rash, stomach pain and swelling, stuffy nose, tiredness, vomiting, and weakness.

Ribavirin and bilirubin levels: *Bilirubin* is left over from the breakdown of red blood cells. RBV can increase the amount of bilirubin in the bloodstream. *Jaundice* (yellow skin and eyes), dark urine, and pale stool are common signs of increased bilirubin.

TAG
Treatment Action Group

Does ribavirin work for HIV-positive people? Yes. RBV can temporarily lower CD4 cell count (but not the percentage of CD4 cells)—even for people on HIV drugs. This usually returns to normal after finishing HCV treatment.

HIV-positive people should not use RBV with Retrovir, Videx, or Zerit. Using Reyataz and RBV may cause jaundice.

Ribavirin and other medications: RBV should not be used with certain drugs. Combining medications can increase or lower drug levels (called *drug-drug interactions*). Increasing drug levels can worsen side effects. Decreasing drug levels may cause a drug to stop working; this can lead to drug resistance or treatment failure.

Talk with your health care provider about starting or stopping any new medications, supplements, or herbal remedies.

More information about drug-drug interactions is available in ribavirin's prescribing information (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021511s023lbl.pdf or http://kadmon.com/files/ribasphere-tablets-pi.pdf or http://www.merck.com/product/usa/pi_circulars/r/rebetol/rebetol_pi.pdf) and at: www.hep-druginteractions.org.

Storing ribavirin: Keep RBV at room temperature (between 59°F and 86°F).

Ribavirin and age, gender, and race/ethnicity: RBV is always used with other drugs, so it is not known whether there are differences in how well it works by age, gender, or race/ethnicity. The risk for anemia from RBV is higher for people over 65 and women. There is no information on ribavirin side effects according to race/ethnicity.

Ribavirin and kidney disease: RBV is filtered out through the kidneys. People with moderate or severe kidney disease, and people on dialysis, are treated with lower RBV doses. People with severe kidney disease should consult with a specialist before using RBV.

Ribavirin and advanced liver disease: Hepatitis C treatment guidelines recommend that people with serious liver damage (Child-Pugh Class B or C cirrhosis) be treated by a specialist.

Access to ribavirin: Kadmon's Keys Program provides patient assistance. People with private insurance may be eligible for assistance with copayments. Uninsured people may be eligible for medication at no charge. Information about the Keys Program is available by phone, at 1.888.668.3393, Monday through Friday between 9:00 a.m. and 5:00 p.m. (Eastern Time), or online at: https://www.pparx.org/prescription_assistance_programs/kadmon_patient_assistance_program.

This fact sheet is current as of November 2015. Always check for updated information.

OLYSIO

TAG
Treatment Action Group

The goal of hepatitis C virus (HCV) treatment is a cure (when there is no hepatitis C virus in a person's bloodstream at least 12 weeks after treatment is finished).

What is Olysio? Olysio (simeprevir) is an HCV-fighting drug. It must be used with other drugs to treat hepatitis C. In the United States, Olysio is approved for people with hepatitis C genotype 1 who are over 18 years old.

How is Olysio used? Olysio is taken once daily, with food, for 12 or 24 weeks. The type and length of treatment depends on HCV treatment history, whether a person has cirrhosis, and the other HCV drugs used with Olysio.

Hepatitis C treatment is changing quickly. Although Olysio was approved for use with pegylated interferon (PEG-IFN) and ribavirin (RBV), it is being studied and used with other drugs in interferon-free combinations.

U.S. HCV treatment guidelines list Olysio and PEG-IFN, or Olysio and Sovaldi, with or without RBV, as alternative treatments for genotype 4 in people being treated for the first time.

Olysio: Treatment Length and Cure Rates from Clinical Trials and Real-World Settings*

Genotype 1, never treated for HCV, no cirrhosis	+ Cirrhosis
Olysio + Sovaldi (with or without RBV), 12 weeks: **95%** (in a small trial; real-world: 88% to 92%)	Olysio + Sovaldi (with or without RBV), 24 weeks: **100%** (real-world: 75% to 87%)
Genotype 1, treatment-experienced, no cirrhosis	**+ Cirrhosis**
Olysio + Sovaldi (with or without RBV), 12 weeks: **95%** (real-world: 81% to 87%)	Olysio + Sovaldi (with or without RBV), 24 weeks: **95%** (real-world: 76% to 79%)

*Cure rates in clinical trials are higher than in real life since the people in them are usually healthier and get extra monitoring and support. These results came from a small trial (fewer than 200 people); Olysio and Sovaldi are being studied in larger trials.

The most important thing a person can do to be cured is not to miss taking doses of HCV treatment—called *adherence*. Adherence lowers the risk for drug resistance.

What is drug resistance? Each day, HCV makes billions of copies of itself. Some of these copies are not the same as the original virus. They may have changes that can stop hepatitis C drugs from working (called *drug resistance*). If people miss doses of their treatment, the virus gets a chance to reproduce—and some of these copies can be resistant to HCV treatment.

Some people have drug resistance even though they have never been on hepatitis C treatment—but many can be cured anyway.

Most people who are not cured have resistance to one or more of the HCV drugs they've taken. Sometimes, resistance disappears within months. Resistance may pop back up if hepatitis C is re-treated with the same drug—or another drug from the same family. No one is sure how long HCV drug resistance lasts, or whether it will make it harder to re-treat hepatitis C.

Olysio and age, gender, and race/ethnicity: In real-world settings, cure rates did not differ by age (over 65 vs. under 65) in people treated with Olysio and Sovaldi (with or without RBV). Real-world cure rates were slightly higher in women than men. There is not much information from clinical trials of Olysio and Sovaldi by race or ethnicity because most people in the trials were white. In real-world reports, there was no difference in cure rates between black people and nonblack people. Drug levels of Olysio are higher in people of Asian ancestry; this may worsen their side effects.

Side effects from Olysio: Olysio can cause photosensitivity (severe sunburn, blistering). Limit exposure to sunlight, tanning beds, and sunlamps while using Olysio, and wear a hat, sunglasses, sunscreen, and protective clothing. If sunburn or rash occur, consult your health care provider immediately. In a clinical trial of Olysio and Sovaldi, the most common side effects were fatigue, headache, nausea, dizziness, diarrhea, insomnia, rash, and sensitivity to light. **Olysio can cause rash**, especially during the first four weeks of treatment. Consult your health care provider immediately if you have mouth sores or red and swollen eyes.

Does Olysio work for HIV-positive people? With PEG-IFN and RBV, Olysio was just as effective for people with HIV. There are no clinical trials of Olysio and Sovaldi (with or without RBV) in HIV/HCV, but cure rates have been the same among coinfected people treated in real-world settings.

Olysio can be used with these HIV drugs: Isentress (raltegravir), Selzentry (maraviroc), Fuzeon (enfuvirtide), Edurant (rilpivirine), Epivir (lamivudine), Ziagen (abacavir), Viread (tenofovir), Emtriva (emtricitabine), and Truvada (emtricitabine and tenofovir disoproxil fumarate).

Olysio and other medications: drug-drug interactions: Olysio should not be used with certain drugs. Combining medications can increase or lower drug levels (called *drug-drug interactions*). Increasing drug levels can make side effects from each drug worse. If drug levels get too low, a drug can stop working, putting people at risk for drug resistance or not being cured. **Talk with your health care provider about starting or stopping any medications, supplements, or herbal remedies.**

Some drugs should be switched, stopped, or avoided while using Olysio. More information is available in Olysio's prescribing information (https://www.olysio.com/shared/product/olysio/prescribing-information.pdf) and at: www.hep-druginteractions.org.

Storing Olysio: Store Olysio at room temperature (under 86°F). Keep Olysio in the same bottle it came in to protect it from light.

Olysio in people with kidney disease: Olysio can be used by people with mild or moderate kidney disease. People with severe kidney disease should consult with a specialist before using Olysio. It has not been studied in people on dialysis.

Olysio in people with cirrhosis: Hepatitis C treatment guidelines recommend that people with serious liver damage (Child-Pugh Class B or C cirrhosis) be treated by a specialist. Olysio is ***not recommended*** for people with Child-Pugh Class C cirrhosis.

Olysio during pregnancy, nursing, and in children: In animal studies, high doses of Olysio caused birth defects. Since it is not known whether Olysio will harm unborn babies, it should be used during pregnancy only if the potential benefits of HCV treatment outweigh the risks.

In animal studies, Olysio was found in breast milk—and it harmed breast-fed baby rats. It is not known whether Olysio passes into human breast milk, but nursing mothers should decide whether to stop breast-feeding or discontinue treatment with Olysio to avoid potential risk to their infants.

RBV causes birth defects and miscarriage. RBV should not be used by pregnant women or by male partners of pregnant women. RBV stays in a person's body for months, so women and their male partners should avoid pregnancy until six months ***after*** stopping it. Using two forms of birth control to prevent pregnancy while taking RBV—and for six months afterward—is recommended (for more information, see TAG's ribavirin fact sheet).

It is not clear whether RBV passes into breast milk. Nursing is not recommended while taking RBV.

Olysio has not been studied in children, and it is not approved for people under 18 years old.

Access to Olysio may be restricted by public and private payers. The criteria differ depending on the type of coverage and the state it is issued in. People with private insurance may be eligible for assistance with copayments. Uninsured people may be eligible for medication at no charge.

Janssen's patient assistance program is called Olysio Support. Information is available by phone, at 1.855.565.9746, Monday through Friday between 8:00 a.m. and 8:00 p.m. (Eastern Time), or online at: http://www.janssenprescriptionassistance.com/olysio-cost-assistance.

This fact sheet is current as of November 2015. Always check for updated information.

HCV GENOTYPES

What are genotypes? A genotype is a way to put the hepatitis C virus (HCV) into categories based on similar genes. It's important to know and understand HCV genotypes because different genotypes respond differently to medicines that treat and cure HCV.

HCV has six genotypes, labeled 1 through **7.** There are also subtypes labeled with letters, for example, genotypes 1a and 1b. Most people are infected by a single, dominant genotype, but it is possible to have more than one at the same time (called a ***mixed infection***).

Why do genotypes matter for treatment? Knowing your HCV genotype is important information that can help patients and doctors find the most effective treatment.

All HCV genotypes cause the same amount of liver damage. However, people infected with genotype 1, particularly subtype 1b, may have a greater chance of developing ***cirrhosis***, or severe liver scarring, than other genotypes. Genotypes 1b and 3 may increase the risk of liver cancer.

HCV can now be cured by all oral, direct-acting antivirals (DAAs), medications that prevent the hepatitis C virus from make copies of itself. DAAs do this by sticking to proteins in the virus and blocking steps in the virus' life cycle. This allows your immune system to clear the virus out of your body. How well a DAA works depends on where it sticks to the target proteins in the virus.

Some of the latest DAA treatments are ***pangenotypic***, which means they can cure all genotypes at nearly the same rates.

Why do people have different genotypes? A person of any racial or ethnic group can carry any genotype or subtype. However, some may be more prevalent in some racial or ethnic groups than others. In the United States, over 90% of African Americans, compared to 67% of Caucasians, carry genotype 1.

People who travel between regions where different genotypes are more common can be exposed to different HCV genotypes, leading to a ***mixed infection***. HCV is transmitted through contact with blood, such as through contaminated blood products or medical equipment, blood transfusions, kidney dialysis, or the sharing of drug injection equipment, such as syringes, or non-injection equipment, such as pipes, spoons, cotton balls, or straws for snorting drugs.

Do genotypes change over time? A virus's genotype usually stays the same. Genetic changes, or ***mutations***, can occur at random or in response to the environment. Some mutations are harmless, but others can affect how well a patient responds to treatment. New HCV treatments include more than one drug to prevent drug resistance from happening by targeting more than one step in the virus' life cycle. However, if patients miss treatment doses, this can lead to genetic mutations, which cause resistance to HCV treatment (see TAG's Adherence fact sheet).

HARDER TO TREAT GENOTYPE 3

Genotype 3 is the second most common HCV subtype in the world, particularly in Northern Europe, South Asia, and Southeast Asia. It can pose more difficult health problems for people with HCV, including more rapid progression of liver disease, increased rates of steatosis (non-alcoholic fatty liver disease), and a higher risk for cancer (hepatocellular carcinoma). Genotype 3 has been associated with unique characteristics, such as how it creates resistance to insulin and how it causes the liver to break down fats, which make it harder to treat with DAAs.

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People infected with genotype 3 are the most challenging to treat if they:

- have previously tried treatment (are treatment-experienced)
- have cirrhosis, and
- have decompensated liver disease, which is a life-threatening condition leading to liver failure.

Genotype 3 often requires longer treatment and does not achieve strong cure rates. There are lower cure rates in patients with cirrhosis.

What tests are needed for knowing my genotype? When screening for HCV, a patient takes several tests to make a diagnosis (see HCV Diagnostics fact sheet).

Once a patient has been diagnosed with HCV, the doctor will run viral load level and genotype tests before starting treatment. Knowing a patient's genotype determines the best treatment regimen.

Genotype tests use blood taken from fingersticks or simple blood draws. A patient might need to return to the doctor's office to confirm whether the infection is chronic or to confirm whether they have been cured of the virus.

Genotypes 1a and 1b may require a patient to take additional blood tests to determine whether the virus has any resistance (see Adherence fact sheet).

HCV treatment is now simpler, safer, and more effective, and diagnostics, including HCV genotyping, need to become simpler and less expensive.

The medications are available depending on the payer or what is available in a country or region.

Which treatment works for each genotype?

- All Genotypes: see Epclusa fact sheet
- Genotypes 1 through 4: see Sovaldi, Viekira XR & Technivie, Harvoni, Olysio fact sheets
- Genotypes 1 or 4: see Zepatier fact sheet
- Genotypes 2 or 3: see Sovaldi, Daklinza fact sheets
- Genotype 6: see Harvoni fact sheets
- **Genotype 7: This genotype is extremely rare; patients may be considered for pangenotypic regimens, including sofosbuvir/velpatasvir.**

Ribavirin (RBV) causes birth defects and miscarriage. HCV treatment regimens that include RBV should not be used by pregnant women or by male partners of pregnant women. RBV stays in a person's body for months, so women and their male partners should avoid pregnancy until six months after stopping it (see Ribavirin fact sheet).

This fact sheet is current as of December 2016. It is recommended to be read alongside the Adherence and HCV Diagnostics fact sheets. Always check for updated information.