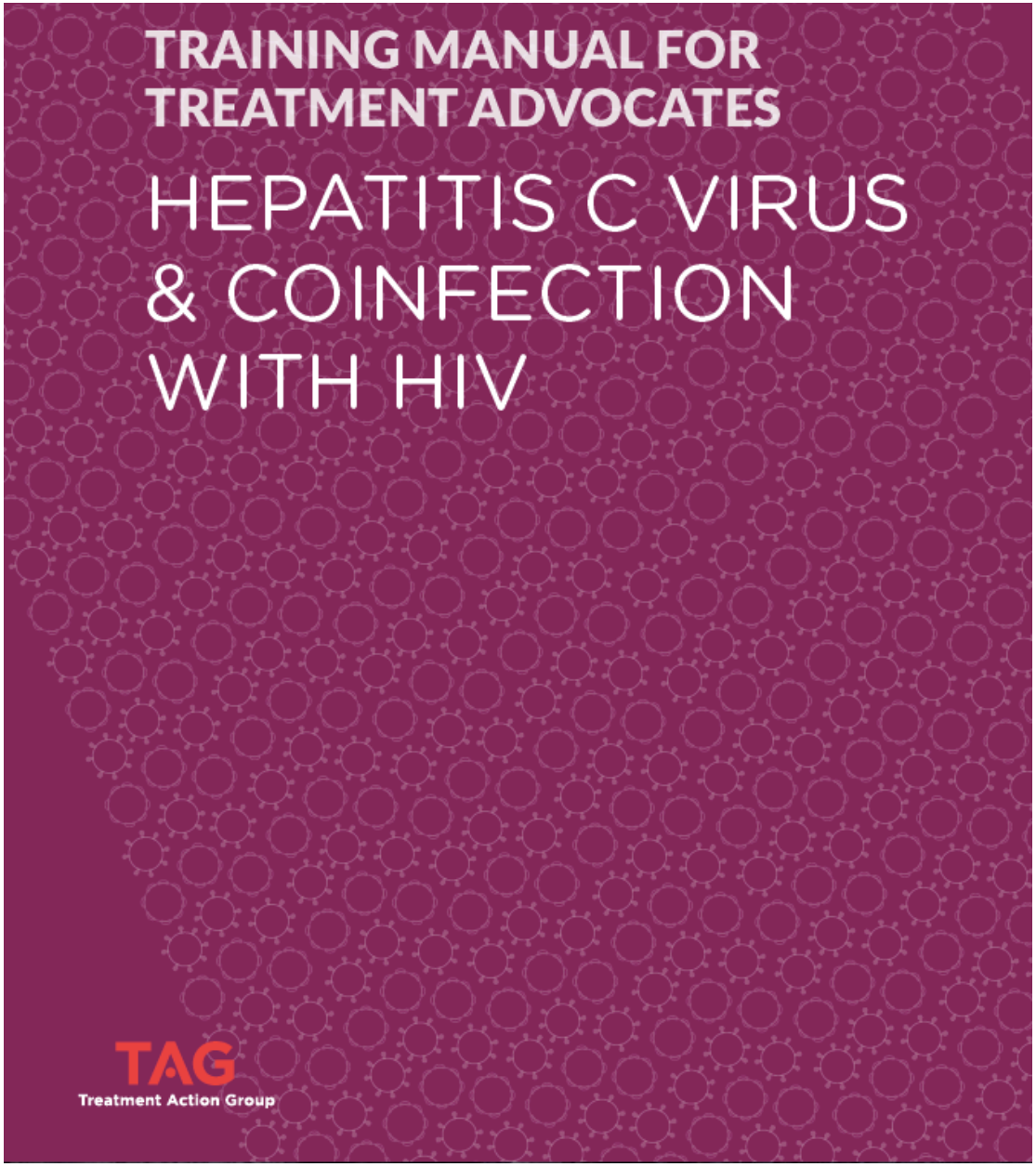

TRAINING MANUAL FOR
TREATMENT ADVOCATES
HEPATITIS C VIRUS
& COINFECTION
WITH HIV
TAG
Treatment Action Group

TAG

SECTION 1:
ABOUT HEPATITIS

Hepatitis means "**swollen liver**"

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 types: A, B, C, D, E, and G.

- Each of these viruses acts differently
- Most people who have viral hepatitis don't know it, most don't have any symptoms
- But some people do have jaundice (yellow skin and eyes), appetite loss, nausea, vomiting, dark urine and pale stool, fever, aches, fatigue, and liver or abdominal swelling

Hepatitis A (HAV)

- Usually not serious, but it can make some people feel very ill
- Transmitted through feces (stool, shit) from a person with HAV getting into your mouth
  - Contaminated water, eating raw fish, improperly washed fruit/ vegetables, mouth-to-anus play
- There is a preventative vaccine
- There are no treatments because the body usually clears the virus by itself
- Most people will recover without treatment
- It rarely causes liver damage
- HAV is very rarely fatal

Hepatitis B (HBV) and Hepatitis C (HCV)

- Two of the most serious hepatitis viruses
- Transmitted through blood, semen, and sometimes vaginal and rectal fluid
  - 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.
- There is a preventative vaccine for HBV, but not for HCV
- Some people can clear HBV and HCV without treatment
- But most will become chronic (lifelong) infections
- Treatments are available, and some people can even be cured
- **Not everyone with chronic HBV or HCV will need treatment due to spontaneously clearing the virus**
- Some people will develop serious liver damage, liver cancer, or liver failure if they go without treatment, although this takes many years
- Most deaths from liver disease are caused by chronic HBV and HCV

Hepatitis D (HDV)

- Only happens in people who already have HBV
- Some people may have been infected with both viruses at the same time
- A person cannot get HDV unless they already have HBV
- 20% of people will clear HDV without treatment
- 80% will develop chronic HDV infection
- HDV worsens HBV, and can lead to cirrhosis (serious liver scarring that can lead to liver failure) or sudden liver failure

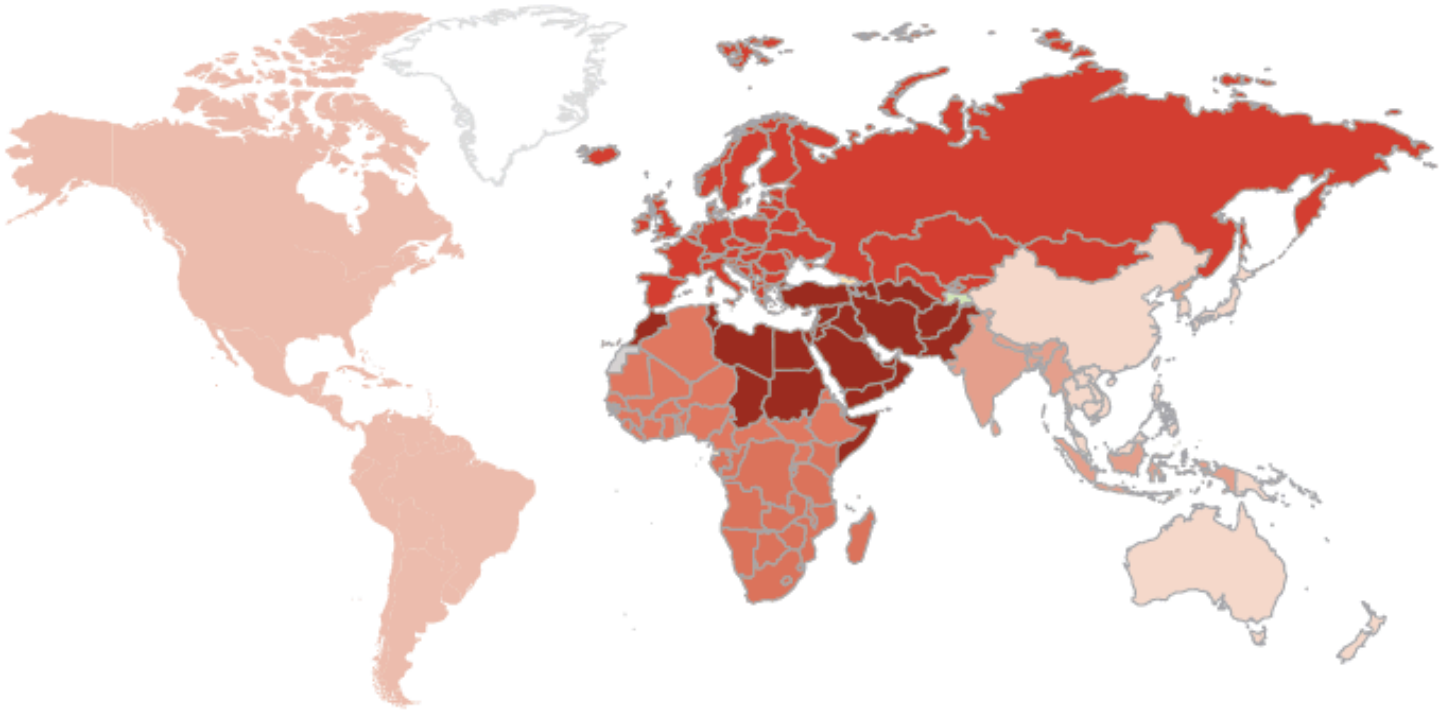
Hepatitis E (HEV) and Hepatitis G (HGV)

- HEV is transmitted through water contaminated by feces or through un-cooked or under-cooked meat
- HEV goes away without treatment, and often has no symptoms
- Usually not serious, but can become life-threatening during pregnancy, particularly in the third trimester
- HGV is transmitted through contaminated blood or blood products, unsterile drug use, injection or tattoo equipment
- HGV, often called GB virus C (GBV-C), does not make people sick or cause liver damage

Viral Hepatitis Can Cause Serious Liver Disease

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

GLOBAL HCV PREVALENCE: Who Has It?



Map 1. Global HCV Prevalence: Estimated **71 million people** living with chronic HCV

- **400,000 people die** each year from advanced liver disease & liver cancer

GLOBAL HCV PREVALENCE: Who Has It?

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

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

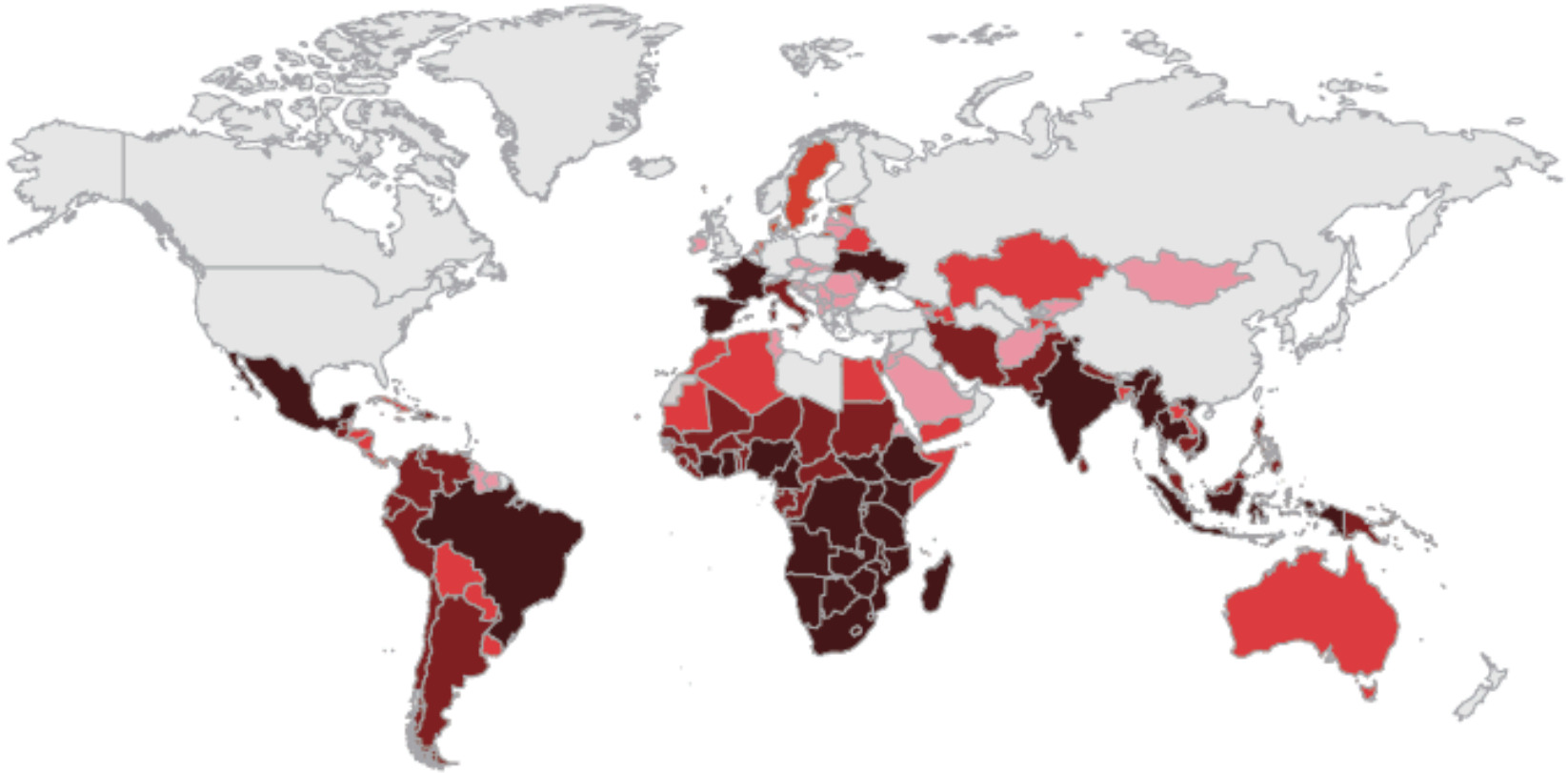
GLOBAL HCV PREVALENCE: Who Has It?

	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

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

GLOBAL HIV PREVALENCE: Who Has It?

Map 2. Global HIV Prevalence: Estimated **36.7 million people** 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

- 2.3 million (6.2%) of 36.7 million people living with HIV are coinfected with HCV
- 1.36 million people who inject drugs have become infected with HCV and/or HIV
- In countries where **injection drug use** is the biggest risk factor for HIV transmission, as many as **7 in 10** people living with HIV are coinfected with HCV
  - These include countries in Asia, Eastern Europe, and the Middle East
- HCV prevalence is 6.4% among men who have sex with men
- HCV prevalence is 2.4% in people living with HIV who do not engage in behaviors that involve transmission of HCV-infected blood

HCV IN THE UNITED STATES

- Not enough info on number of people have HCV in US
- Lack of reliable data & weak monitoring/surveillance system
- CDC estimate: 3.2 million people living with chronic HCV
- Prevalent among “baby boomers” (born between 1945-1965)
  - Infection likely occurred before blood screening & identification of virus
- 20,000 HCV-related deaths each year
- More common among people with less than 12 years of education, and who live below the poverty line, regardless of race or ethnicity

Young People Who Inject Drugs

- Sky-rocketing use of heroin and synthetic opioids in US
  - Stigma, risk of arrest, sharing of unsterilized needles and drug paraphernalia puts people at risk of HIV and HCV transmission
- Result = largest increases of new HCV infections among young people who inject drugs
- Leading cause of death for Americans under age 50 = **opioid-related overdoses**
- Expanded harm reduction programs, safe consumption spaces, access to clean syringes & other materials for individual use:
  - Prevent HCV transmission
  - Prevent overdoses
  - Provide medication-assisted treatment (opioid substitution [OST])
  - Increase access to HIV & HCV treatment and care

HCV and People of Color in the United States

- Overall, an estimated 1.8% of people in the United States have been infected with HCV
  - Other studies: 997,000 people tested positive for HCV antibodies
- Hepatitis C is more common among African-Americans than Mexican Americans or White Americans – both men & women
  - Homeless and incarcerated people, who have high rates of HCV, were not included in NHANES survey, nor was other information about race or ethnicity
  - Antibody prevalence: 32.1% among homeless people, 11.5% among Native Americans, 4.5% among nursing home residents, 0.48% among active military personnel
  - Rates were twice as high in African Americans versus whites (3.2% vs. 1.5%)
- The highest rates of HCV were found among African-American men between 40 and 49 years of age (13.4%), and Mexican American men between 50 and 59 (10%)

Source: Third National Health and Nutrition Examination Survey (NHANES)

HCV and Incarceration

- **10.2 million people** incarcerated worldwide
  - US has highest rate in the world: **2.3 million people** in prisons & jails (youth/juveniles not reflected in these figures)
- Lack of clean syringes, OST, condoms, limited testing & treatment, overcrowding contribute to transmission of HIV, HCV, TB
- Compulsory detention centers, inhumane conditions in some countries fuel substance use disorders & infectious diseases
- 15.1% (1.53 million) of prisoners living with HCV but no treatment
- **Treating substance use as public health issue, including ending war on drugs, shown to reduce incidence of HIV, possibly HCV**
- Prisons are potential sites for treatment and linkage to care

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:

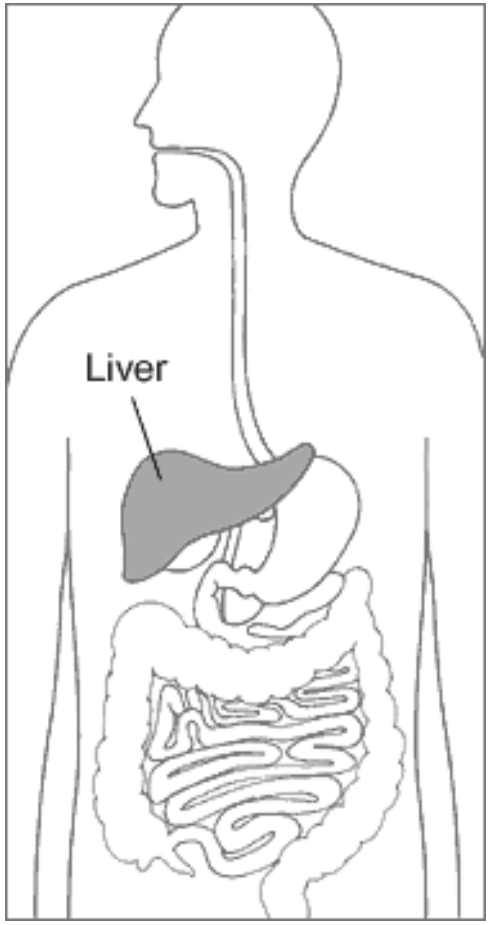
1. How can you use this training manual to share information about viral hepatitis with others in your community?
2. Do you know how to find more information about HCV in your country or region?
3. Have there been any campaigns to widen access to HCV treatment for key populations in your country?

TAG

SECTION 2:
ABOUT THE LIVER

- The liver is the largest organ inside the body that has many critical functions
- When the liver becomes very damaged (such as by chronic viral hepatitis), it cannot work properly
- Serious liver scarring is called ***cirrhosis***
- Cirrhosis can lead to life-threatening complications such as liver cancer and liver failure

The Liver Performs Many Important Functions



- The biggest organ inside the human body
- On the right side, underneath the rib cage
- Works as a filter and processing plant
- Anything you eat, drink, and inhale passes through the liver
- Also breaks down herbal remedies, vitamins, and drugs

Each day, your liver

- Filters waste from the blood;
- Stores vitamins, minerals, and iron;
- Changes food into energy;
- Makes bile (a liquid that your body uses to digest fat);
- Helps balance sugar and hormone levels;
- Makes cholesterol; and
- Creates the hormone that helps to produce platelets, which stop bleeding by clotting blood.

Immune Response to Viral Hepatitis Infection Causes Liver Damage

- The immune system tries to get rid of infected liver cells by surrounding them and walling them off
- Over time, this creates scarring in the liver
- Although the liver grows new cells, cells that are already scarred cannot become unscarred
- As the scarring worsens, the liver hardens, making it more difficult for blood and other important fluids to pass through it
- These fluids, which are usually filtered by the liver, can build up to toxic levels in the bloodstream when the liver is too damaged to function

Liver Damage from HCV Happens Slowly, Usually over Decades

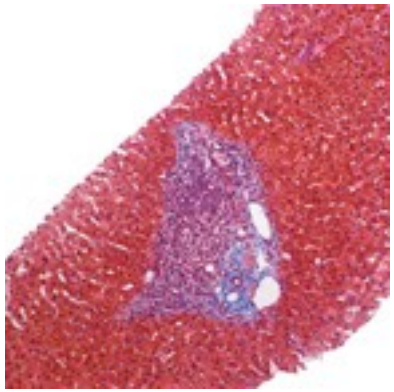
- It can take from 15 to 50 years for an HIV-negative person who has chronic hepatitis C to develop cirrhosis
- Having chronic HCV does not always mean that you will have serious liver damage, or that you need treatment
- Some people live with hepatitis C for many years and will never have liver damage

Some Things Cause Faster Liver Damage from Viral Hepatitis

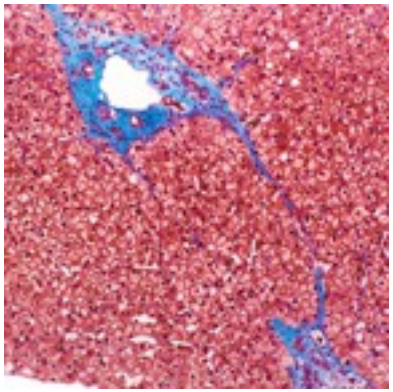
- Being HIV---positive—especially if you got HCV after HIV
- Being coinfected with HBV and HCV
- Drinking alcohol, especially heavily
- Age over 40
- Having fat in your liver (a condition called ***steatosis***), usually in overweight people, heavy drinkers, or people with metabolic disorders
- Being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

Stages of Liver Damage

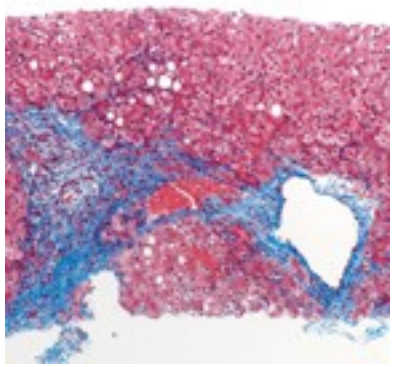
No Fibrosis (F0)



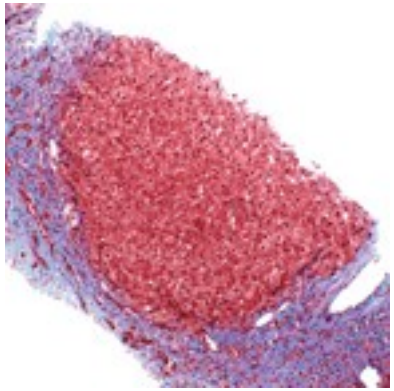
Mild Fibrosis (F1)



Mild–Moderate Fibrosis (F2)



Moderate–Severe Fibrosis (F3)



Cirrhosis (F4)

Source: Faria SC, Ganesan K, Mwangi I, et al. MR imaging of liver fibrosis: current state of the art. Radiographics. 2009;29:1615–35.

Stages of 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
- ***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

Stages of Liver Damage

- 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*** (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

Preventing Liver Disease

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

Alcohol: Harmful to the Liver

- Alcohol is hard for the liver to break down, even in people who don't have hepatitis C
- In people with HCV, alcohol hurts the liver by increasing inflammation and scarring, which leads to cirrhosis
- Heavy drinking increases the risk for cirrhosis in people with all types of viral hepatitis, including HCV
- Even though experts have not agreed on a safe amount of alcohol, many recommend complete abstinence from alcohol, or limiting it to a small amount on special occasions

Alcohol: Harmful to the Liver

- Some studies 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—may be the most important thing a person with hepatitis C can do to prevent liver damage**

Street Drugs

- People who regularly use heroin, cocaine, and crystal methamphetamine may not be getting enough sleep or eating well, and may be under a great deal of stress
- People who don't have access to clean injection equipment are at risk for infections such as HIV, HBV, and HCV (including reinfection after being cured of the virus)
- For these reasons, using street drugs (***illicit drugs***)—especially on a daily basis—can have a negative overall impact on a person's health

Street Drugs and the Liver

- **There is very little research or information on whether or not street drugs cause or worsen 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

Street Drugs and the Liver

- **Occasional use of marijuana has not been found to be harmful**
- One study done in the pegylated interferon-era found that smoking marijuana during HCV treatment helped people to deal with side effects and complete their treatment
- Some researchers have found that daily marijuana use (one joint or more per day over several years) reduced risk of ***nonalcoholic fatty liver disease***, or a build-up of fat in the liver, in HIV/HCV coinfected people
- Some researchers have found that daily marijuana use 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 drugs, including prescription opioids like oxycodone and hydromorphone, to get high
- This can be risky because they may interact with other medications, causing lowered or increased drug levels in a person's body
- If drug levels are too low, medications may stop working
- In some cases—such as with HIV medications and antibiotics—drug resistance can develop because there is not enough drug in a person's system to stop viruses and bacteria from reproducing
- Drug levels that are too high can also be dangerous, since they can increase drug toxicity and side effects, or cause an overdose

Prescription Drug Use

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

Drug Overdose

- The risk of overdosing on anti-anxiety and pain medications may be higher in people with hepatitis– induced cirrhosis, since they are broken down by the liver
- Include benzodiazepines, opioids, and anesthetics (alprazolam, diazepam, midazolam, triazolam, fentanyl, and lidocaine)
- 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 can be prevented with **naloxone**, which reverses an opioid overdose by blocking the effects in the body.
  - Nasal spray or muscle injection
  - Does not work for overdoses of benzodiazepines, cocaine, or amphetamines without opioids
- An overdose is a medical emergency and the person should receive medical care as soon as possible
- 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 (St. John's wort), and food supplements can be hard on the liver
- Some medications should not be taken at the same time as certain HCV drugs or will need to have their doses adjusted
- It is very important that your health care provider and pharmacist know about all of the medications and supplements you are taking, with or without a prescription, to help prevent serious drug interactions

ADVOCACY EXERCISE

Discussion Questions:

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

Action Steps:

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

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

- HCV is spread by direct blood-to-blood contact, when infected blood directly enters a person's bloodstream
- HCV is a very small virus, much smaller than HIV
- But—unlike HIV—the HCV 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 injecting equipment with heat kills HCV most effectively**
- HCV is common among people who inject drugs (PWID), since most don't have access to clean injection equipment

The most common ways to catch HCV are:

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

The most common ways to catch HCV are:

- Having condomless sex with a person who has HCV
  - HCV can be present in semen and rectal fluid (can be spread from receptive to insertive partner)
  - "Chemsex" or "party-n-play" culture among MSM, sex with multiple partners & more frequency can increase risk
- Sex during menstruation with a person who has HCV
- Sharing toothbrushes, razors, manicure equipment, personal care items that could have contact with blood

HCV **cannot** be spread by:

- Sharing eating utensils or eating food made by a person with HCV
- Drinking from the same glass as someone with HCV
- Casual contact (kissing, hugging, holding hands, etc.)

Sharing noninjection drug equipment (straws and pipes)

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

HCV reinfection

- A person who already has HCV can get infected again—this is called ***reinfection***
- **You can be reinfected with HCV even after being successfully cured**
- You can also be infected with more than one subtype of hepatitis C virus (called ***genotype***) at the same time
- Prevention is key! Not sharing your injection equipment or using clean/new equipment (needles, measuring syringes, cookers, cotton, water, and ties) every time protects you and the people that you are getting high with

Sexual transmission of HCV

- Sexual transmission of HCV isn't common, but can occur. HCV can be found in semen, rectal, and vaginal fluid, although it is mainly found in blood.
- **People have become infected from condomless sex**
- Sexual transmission of HCV appears to be highest among sex workers, and men who have sex with men (MSM) who are living with HIV
  - The ***incidence*** of HCV infection among HIV-positive MSM—the number of new infections that occur every year—has not been accurately determined:
    - Irregular HCV testing = insufficient useful data.
- The risk for sexually transmitted HCV is greater when blood is involved, even when the amount is too small to see
  - Rough, unprotected anal and 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
  - 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

Risk factors for transmitting HCV among MSM

- 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.

→Need to routinely test HIV-negative MSM using PrEP and engaging in anal sex without condoms for HCV

Mother-to-Child Transmission

- HCV can be passed in the womb, or during labor and delivery
  - If mother has HCV but not HIV: 4% risk baby also has HCV
  - If mother has HIV and not on ***antiretroviral therapy***, higher risk of transmission: Up to 20%
    - Pregnant women coinfected with HIV and HCV can reduce the risk of passing HIV and HCV to their infants by taking antiretroviral therapy.
- There is not enough info on HCV treatment during pregnancy and breastfeeding
    - Ribavirin cannot be taken by pregnant women or women trying to get pregnant: causes birth defects
- HCV has not been found in breast milk
- HIV-negative mothers who have HCV can safely breastfeed their infants as long as their nipples do not have any cuts or cracks

ADVOCACY EXERCISE

Discussion Questions:

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

Action Steps:

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

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

- HCV has two stages: ***acute*** and ***chronic*** (lifelong)
- Acute infection is a term for the first six months after a person gets HCV. Most people—80%—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

- Some people (20–40%) will get rid of the virus without treating it, usually during acute infection
- The medical term for this is ***spontaneous viral clearance***
- HIV-negative people, women, children and young adults, and people who have symptoms during acute HCV are more likely to spontaneously clear HCV
- HIV-positive people are less likely to clear HCV without treatment; experts think that up to 25% of HIV-positive people will get rid of their HCV without treatment

Most people with chronic HCV do not have any symptoms at all

- But the most common symptoms are being forgetful and feeling tired 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

- 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 severe liver damage (***cirrhosis***)
- People who get HCV when they are over 40 seem to progress more quickly, probably because a person's immune system tends to slow down as they age
- People who drink alcohol—especially heavy drinkers—are more likely to develop liver damage
- People with cirrhosis are at risk for very serious complications, such as ***liver cancer*** and ***liver failure***

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
- **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 gotten cirrhosis in less than 10 years
- HCV is curable, no matter what a person's HIV status is
- 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 can help to slow down liver damage from HCV
- HIV treatment, also called ***antiretroviral therapy*** (***ART***), may help keep the liver in good condition by keeping the immune system strong
- Coinfected people with less than 200 CD4 cells/mm^3 are at the highest risk for serious liver damage from HCV.

HIV/HCV Coinfection: Impact of HCV on HIV

- So far, no one is sure about the impact of HCV on HIV
- Being coinfected with HCV makes treating HIV more complicated
- HCV coinfection increases the risk for liver toxicity (also called ***hepatotoxicity***) from HIV meds
- It is important to know which medicines are easier on the liver
- However, many studies in HIV/HCV---coinfected people have shown that the benefits of HIV treatment outweigh the risks

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?

SECTION 5: HCV DIAGNOSTICS

- The first step in dealing with HCV is to get 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

TAG

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.

HCV Screening Tests and What the Results Mean

TAG

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.

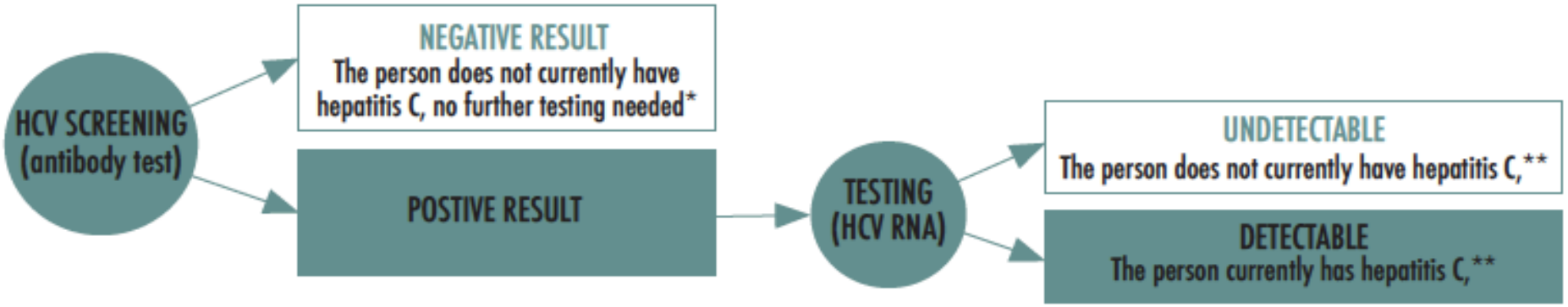
Two different blood tests are used to diagnose HCV

antibody test and ***viral load*** test

- Diagnosing HCV is different from diagnosing HIV

- ***Screening*** looks to see whether someone might have a disease by looking for ***antibodies*** instead of the virus
  - 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.

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.

Antibody tests

- A positive HCV-antibody test result does not always mean that someone has chronic HCV
- It simply means that a person was infected with HCV in the past, and may still be infected
- People who get rid of HCV without treatment (called ***spontaneous viral clearance***) usually stay HCV antibody-positive for years
  - 20-40% of people with HCV will spontaneously clear the virus
  - More likely to happen in young people, women, children, HIV-negative people
- 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.

Antibody tests

- 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/mm3, and people taking immunosuppressants.

HCV RNA (confirmatory) tests

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

Two types of viral load tests

- **Qualitative** testing checks <u>whether</u> there is hepatitis C virus in the bloodstream. Test result is either positive (virus is ***detectable***) or negative (virus is ***undetectable***).

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).

- **Quantitative** testing measures the <u>amount</u> 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.
  - DAAs are effective: quantitative tests are not required to tell whether a person is cured.
  - The test result is a number: the higher the number, the more virus was detected.

Viral load tests

- ***Undetectable*** 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.
- 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

- ***Core antigen*** is a viral protein, so it is part of the hepatitis C virus itself.
- Core antigen 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
  - to confirm chronic HCV infection, or
  - to measure treatment outcome.
- Although it does not detect low levels of HCV (1,000 to 3,000 IU/mL depending on genotype), usually the hepatitis C viral load is much higher in people who relapse after HCV treatment.

HCV Genotyping

- **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***). Likely for:
  - People who received blood products or blood transfusions 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.

- 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.**

Key aspects about laboratory process:

- 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.

Validating test quality

- The World Health Organization conducts ***pre-qualification*** (WHO PQ) assessment to examine the performance and quality of tests.
  - Assesses ***specificity*** (how accurate a test is) to ensure there are no or few false positives to avoid misinforming a person about being infected.
  - Assesses the ***sensitivity*** (the smallest amount the test can detect).
- In choosing an optimal test, high sensitivity and high specificity would be qualities to seek out.

Getting More Information About the Health of Your Liver

TAG

Liver Disease Staging

- Type and length of HCV treatment depends on liver damage
- DAAs can cure HCV infection in >95% of people without cirrhosis
- People with cirrhosis can be more difficult to cure: Might need RBV or to be treated longer
- People with HCV infection and cirrhosis go untreated, their cirrhosis may become ***decompensated***, meaning their liver is beginning to fail.
  - Symptoms: fluid and toxins build up, kidney disease, possibly internal bleeding
  - DAAs might not work for people with decompensated cirrhosis
  - Person should be considered for liver transplant
  - Importance of treating HCV early before liver becomes more damaged
- **Staging** assesses extent of liver damage
  - **Invasive** (biopsy: takes blood or tissue sample with needle) – should not be used
  - **Non-invasive test** (ultrasound imaging) – safer, less expensive, easier to perform

Liver Enzyme Tests (ALT)

- Liver enzymes are proteins in the body
- When a person's liver is injured, increased numbers of these enzymes leave the liver cells and enter the bloodstream
- Enzyme levels can be checked by a group of blood tests, sometimes called ***liver function tests*** (LFTs)
- The tests do not actually measure liver function
- Results cannot predict or tell someone how much liver disease they have

Liver Enzyme Tests (AST)

- ***Alanine aminotransferase*** (ALT; SGPT) and ***aspartate aminotransferase*** (AST; SGOT) are two liver enzymes
  - **ALT** is made in the liver. If 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 (PT) are other important liver enzymes
- Liver enzyme levels can be caused by:
  - Prescription and over-the-counter medications
  - Herbs (St. John's wort), vitamins and supplements
  - Exposure to toxic fumes
  - Heavy alcohol consumption
  - Acute or chronic viral hepatitis and other infections
  - Detoxing from drugs or alcohol

Liver enzyme tests

- People taking ART or TB treatments (whether or not coinfected with HBV or HCV) should have liver enzymes checked regularly as these medications might be hard for liver to break down
- When liver enzyme levels are higher than normal for several months, it can be a signal that the liver is inflamed or damaged.
- Normal liver enzyme levels **do not always 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.

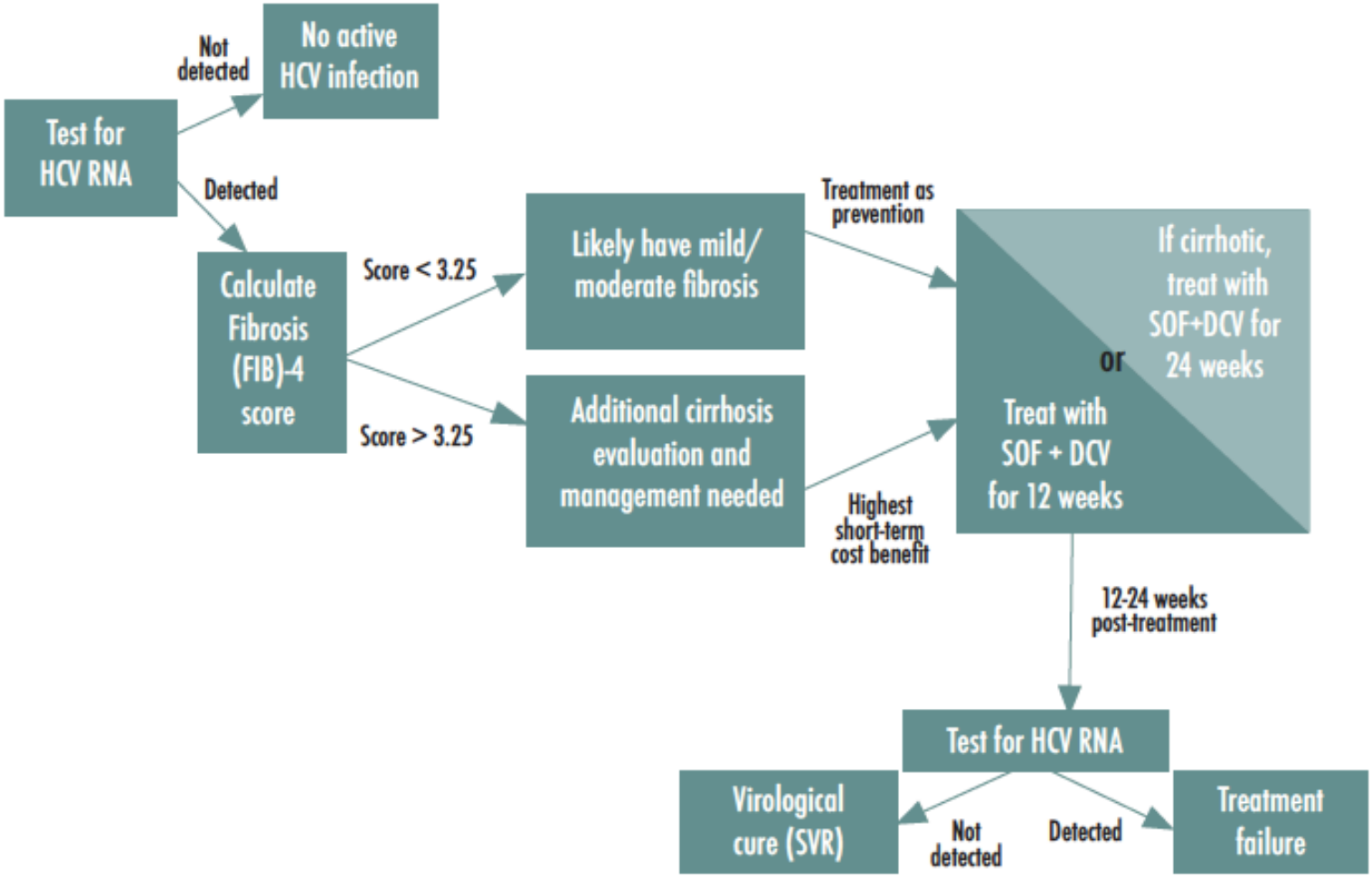
Need for simpler, cheaper tests

HCV could soon be diagnosed with a single, rapid point-of-care test and cured with a pangenotypic regimen

The aim should be to confirm diagnosis and start treatment the same day:

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.

Minimum steps to managing HCV



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?

SECTION 6:
HCV DIAGNOSTICS FOR MAKING TREATMENT DECISIONS

- DAAs can achieve a ***sustained virological response*** (SVR) in over 95% of people. An SVR means a person has no detectable HCV after completing the treatment.
- Effective DAA combinations, such as sofosbuvir/daclatasvir and sofosbuvir/velpatasvir, are becoming accessible for more people, genotyping is becoming less relevant.

HCV Genotyping and Treatment Decisions

- Seven hepatitis C genotypes (subtypes of the virus), numbered 1 through 7.
- 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; 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.

Cirrhosis Can Be Diagnosed Without a Liver Biopsy

- Liver specialists, particularly in Europe, operate a machine called ***FibroScan*** that looks at liver stiffness using sound waves. Also determine the level of liver damage and degeneration of liver cells.
- Difficult to diagnose mild or moderate liver disease without doing a biopsy, however, and FibroScan is not widely available in most countries.
- Non-invasive blood tests look for cirrhosis:
  - **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.
    - Check the level of liver enzymes and indicate other aspects of the health of the liver

Track Your Lab Work (1/2)

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.

TAG

Track Your Lab Work (2/2)

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.

TAG

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?

TAG

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.**
- 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.

- 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.
  - People will need close monitoring to check whether cancer develops or returns.

Direct-acting antivirals 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% 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.

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

HCV treatments (1/4)

- **Pegylated interferon (PEG-IFN)** - no longer recommended by WHO and AASLD/IDSA, and is only recommended EASL when there are no other options.
  - It may still be used in countries without access to DAAs or in prisons.
- **Ribavirin (RBV)** - 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.
  - Dose depends on a person's weight.
  - RBV can increase cure rates in people with cirrhosis and is sometimes added to DAAs
  - Causes several unpleasant side effects:
    - Anemia, insomnia, fatigue, irritability, and depression
  - 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**.

HCV treatments (2/4)

- **Sofosbuvir (Sovaldi®, or SOF)** - must be used with other DAAs.
  - In US, 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)** - taken with SOF, once daily with or without food for 12 or 24 weeks.
  - In US, 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 once daily, with food, for 12 or 24 weeks. It is rarely used in high-income countries.

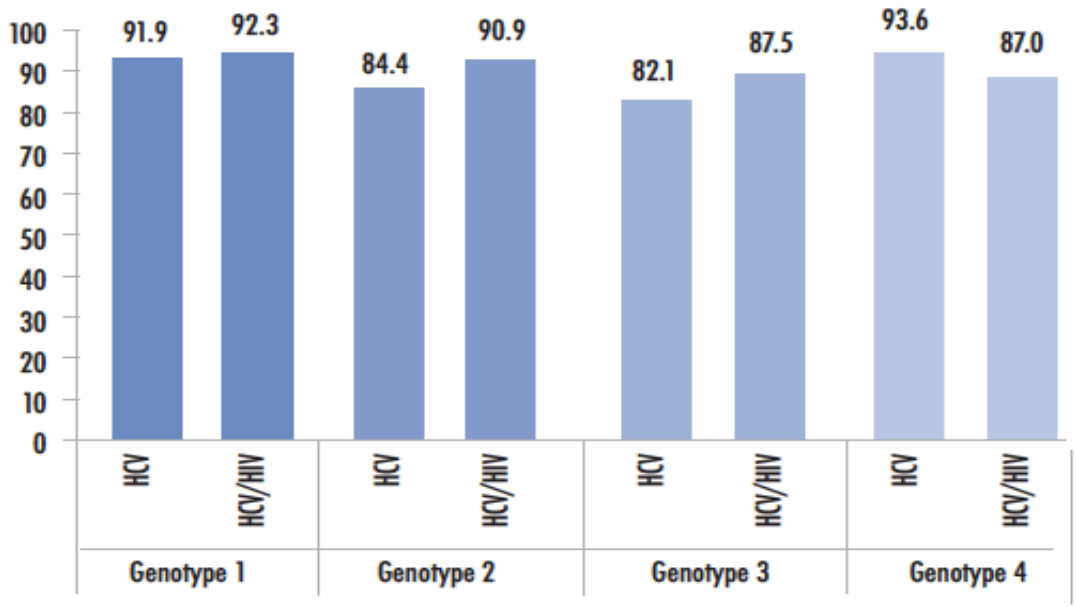
HCV treatments (3/4)

- **Sofosbuvir/ledipasvir (Harvoni®, or SOF/LED)** - two medications in one pill, taken daily, with or without food, for 8 to 24 weeks.
  - In US, it is used to treat hepatitis C genotypes 1, 4, 5, and 6 in people who are over 12 years old.
  - Harvoni approved for people with HCV genotype 1 who have advanced (decompensated) cirrhosis, and for liver transplant recipients who have HCV genotype 1 or 4.
  - 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™)** - combination of HCV medications.
  - In US, Viekira XR™ is approved for people with hepatitis C genotype 1 who are over 18 years old.
  - Viekira XR™ previously approved and prescribed as a twice-daily formula known as Viekira Pak.
  - Latest XR regimen contains the same medicines, in the same amounts, as Viekira Pak, now in a once-daily package.

HCV treatments (4/4)

- **Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®, or SOF/VEL/VOX)** - fixed-dose combination taken once daily for 12 weeks.
  - Does not require RBV.
  - Can effectively treat all genotypes, including difficult-to-treat genotype 3, people with or without cirrhosis, and people with chronic kidney disease.
  - In US, 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)** - fixed-dose combination, taken once daily with food for 8, 12, or 16 weeks.
  - Can effectively treat all genotypes, including difficult-to-treat genotype 3, people with or without cirrhosis, and people with chronic kidney disease.
  - 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) -** generic regimen currently under study in clinical trials, which may be used to treat all genotypes.
  - Taken once daily for 12 weeks, or 24 weeks for people with compensated cirrhosis.

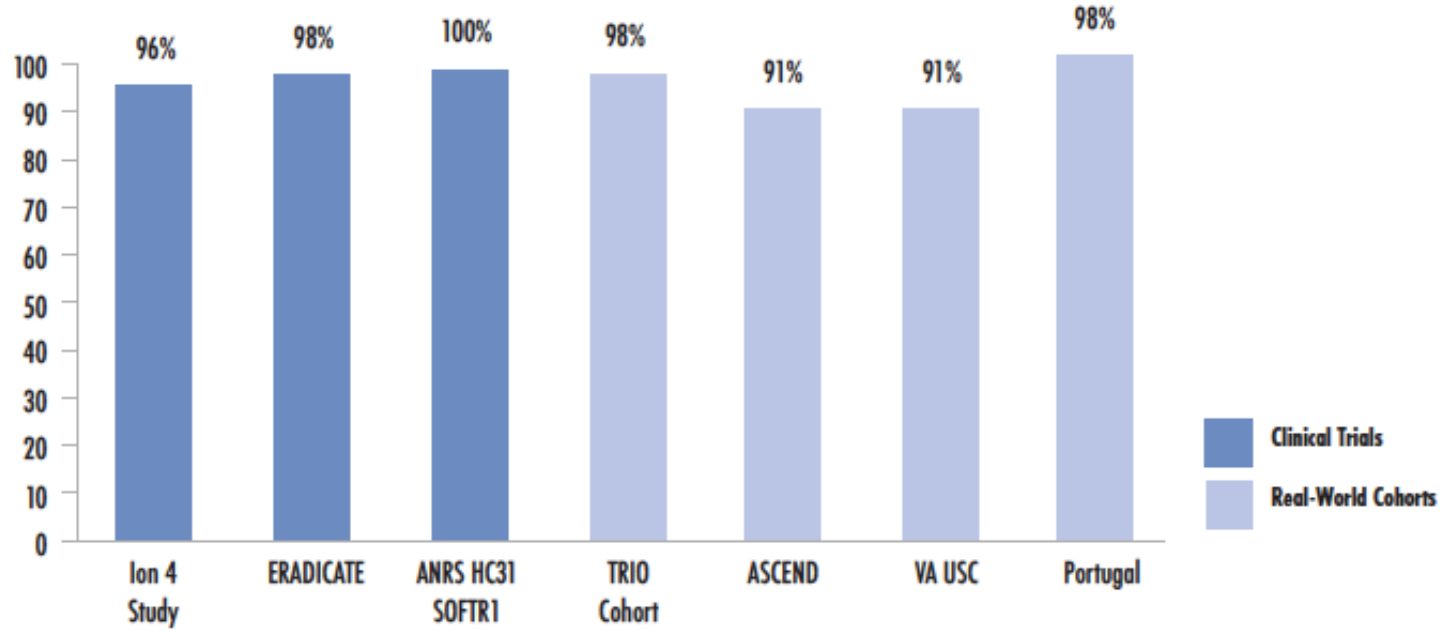
SVR12 Rates by HCV Genotype and Treatment Group



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.

- Using SOF/LED, SOF/DCV with and without RBV, according to genotypes, DAAs are effective among HCV mono-infected and HIV/HCV coinfected people.
- Most mono-infected people achieved **over 90% SVR rates for 12 weeks** of treatment, including people with cirrhosis.
- HIV/HCV cure rates at week 12 actually have higher results than in mono-infected people, except for genotype 4.

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.

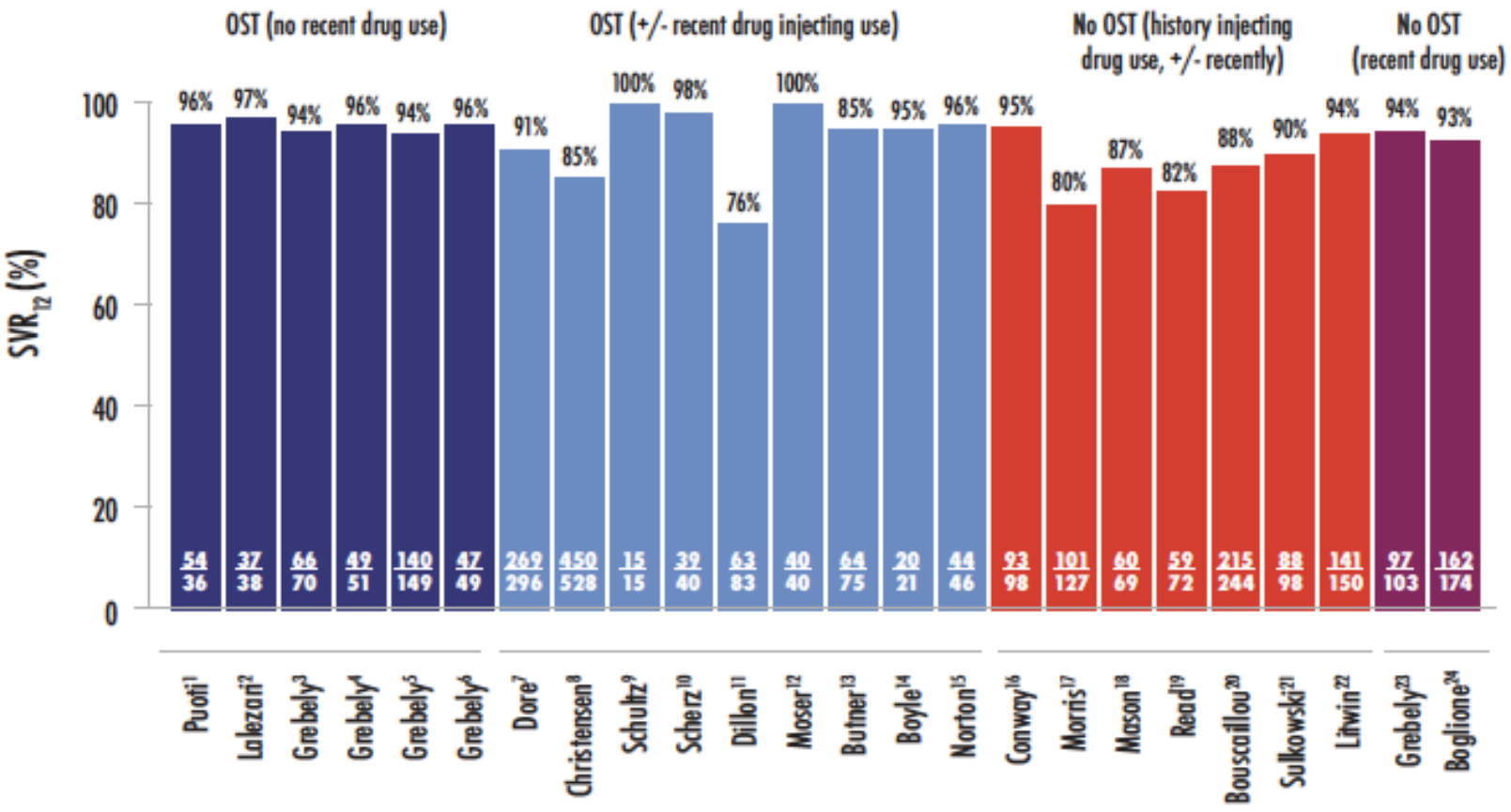
- DAAs show **comparative rates** for HIV/HCV coinfected people in clinical trials as in real-world studies.
- As with HIV treatments, the newer HCV medicines need to be taken regularl—missing doses can lead to **drug resistance**.

TAG

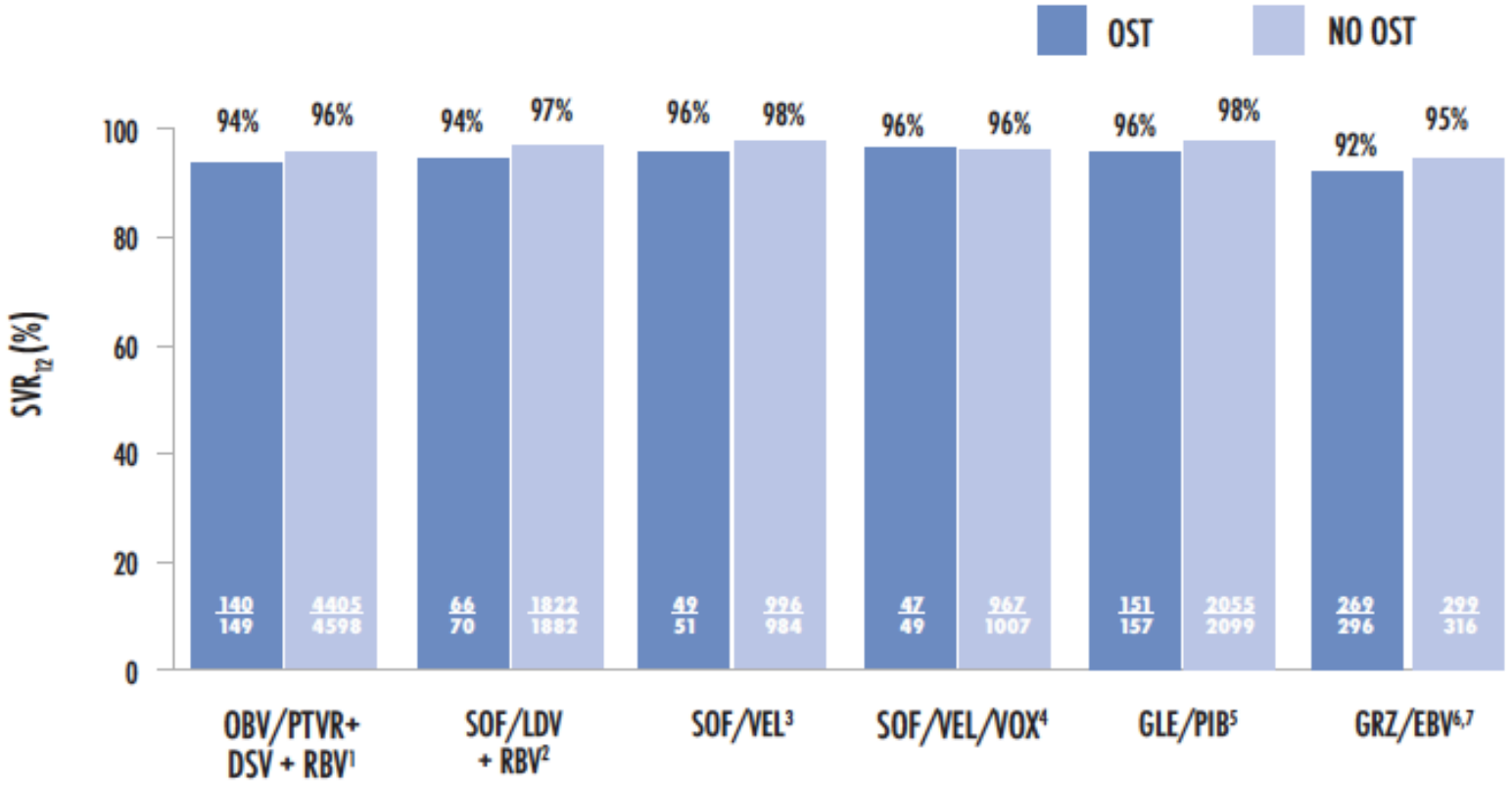
Real-World Data in People Who Use Drugs

- 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.
- **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.**
- **There is no scientific evidence for denying treatment to people who use drugs.**

SVR12 among people on OST and former/recent people who inject drugs



People Receiving OST: Phase II/III Trials



- Adherence to HCV treatment regimens is shown to be good among people who use drugs or other substances.
- **PREVAIL study** compared no treatment intervention vs. direct observed therapy using blister packs to give treatment to people.
- Results showed that **drug use did not associate with poor adherence**.

Is a Vaccine for HCV Still 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
- 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?

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.
- Regular monitoring for liver cancer after successful treatment is important, especially for people with cirrhosis—they are at risk of liver cancer.
- 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.
- **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.

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	Adher-ence, 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.

TAG

Side Effects of HCV Treatment (1/2)

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**.

Side Effects of HCV Treatment (2/2)

- **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?

TAG

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

- 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.**

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.
- The studies didn't measure adherence.
- People who drink alcohol, especially heavy drinkers, are more likely to develop liver damage.
- 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!**

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***), 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.
- HIV treatment is now recommended for all people living with HIV.
- Many people who are coinfected receive HCV treatment while continuing their HIV therapy.
- 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% 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

- ARVs are broken down by the liver
- 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.
- Some HIV and HCV medications should not be used at the same time, or dose changes should be made.
- Important to inform your doctor about the medications you are taking.

Select HIV and HCV Prescription Drug Interactions (1/4)

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
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

✓ = Can be used together

X = Not recommended for use together

? = Not enough information available to recommend use together

Select HIV and HCV Prescription Drug Interactions (2/4)

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

✓ = Can be used together

X = Not recommended for use together

? = Not enough information available to recommend use together

TAG

Select HIV and HCV Prescription Drug Interactions (3/4)

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
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	✓

✓ = Can be used together

X = Not recommended for use together

? = Not enough information available to recommend use together

Select HIV and HCV Prescription Drug Interactions (4/4)

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

TAG

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?

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!**
- 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.

- Some of these older 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; 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.

Tailoring advocacy efforts for DAAs

- HCV treatment advocates have learned lessons from the HIV/AIDS movement and have been pushing for faster, wider, more affordable access to generic DAAs.
- 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.
  - 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.

Tailoring advocacy efforts for DAAs

- Some countries may not have access to the newer pangenotypic regimens due to intellectual property 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
  - Choose to exclude countries from their voluntary licenses, so they cannot produce or market the medicines at lower costs
- 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.

Tailoring advocacy efforts for DAAs

- 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.
- Advocates can work to speed up registration in their country and push regulatory authorities to approve medicine faster.

Tailoring advocacy efforts for DAAs

- Generic competition often reduces prices dramatically. Ways to expand access to generics:
  - Patent oppositions on certain DAAs or active pharmaceutical ingredients used to produce them
  - Awareness building and pressuring governments to make use of international intellectual property provisions, such as issuing a ***compulsory license*** 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.
  - Procuring generic DAAs for personal use
  - 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

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% of people with the new DAAs, yet less than 2% 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.

- HCV diagnosis is a two-step process:
    1. Screening with an antibody test
    2. RNA test is required to confirm chronic HCV infection
- Makes diagnosis more costly and time consuming.
- 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.

Expensive diagnostics costs

- Few health systems cover viral load tests through public insurance plans.
- In many low- and middle-income countries, 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**.

Unique national health systems

- 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.
  - In a screening program within a population with a 2% prevalence rate, 1 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.**

Move away from centralized process for HCV confirmatory 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.
- Target this technology for use by community health workers and thereby allow for a scale-up of testing approaches **outside hospitals or primary care clinics**.
- 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.
- Cepheid's GeneXpert. machine is the most flexible, commercially available platform, yet it requires a disease-specific cartridge to run the tests.
- 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: Monopoly on Cepheid's GeneXpert.

Ramp up diagnostics advocacy

- Push for better integration of HCV testing into existing laboratory systems that test for many diseases at the same time.
- Requires governments to plan and negotiate for the purchase of tests needed for multiple diseases like HIV, HCV, and TB (or bundled procurement) to get cheaper pricing and discounts.
- Price markups on HCV tests applied by local distributors need to be controlled.
- Call on companies to impose price caps to gain control over their products.
- Demand government to lift customs fees or value-added taxes on essential diagnostics.
- **Greater access to diagnostics will be essential to generating the volume of procurement necessary to see the biggest generic price reductions.**
- Making 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?