

**TRAINING MANUAL FOR
TREATMENT ADVOCATES**

**HEPATITIS C VIRUS
& COINFECTION
WITH HIV**

TAG
Treatment Action Group

TAG

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

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/mm³).

The person needs a viral load test to confirm.

HCV Screening Tests and What the Results Mean

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.

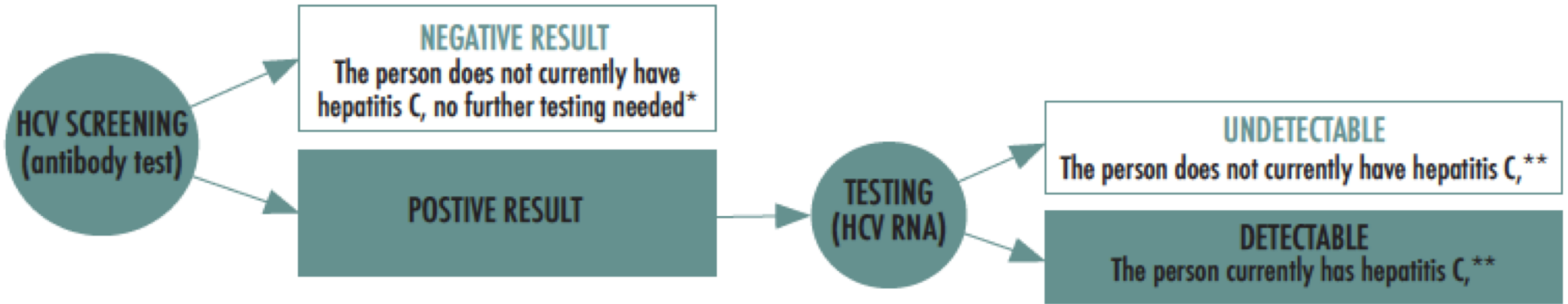
The person should be assessed for follow up testing.

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 whether 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 person 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 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.
 - 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

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 coinfecting 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.

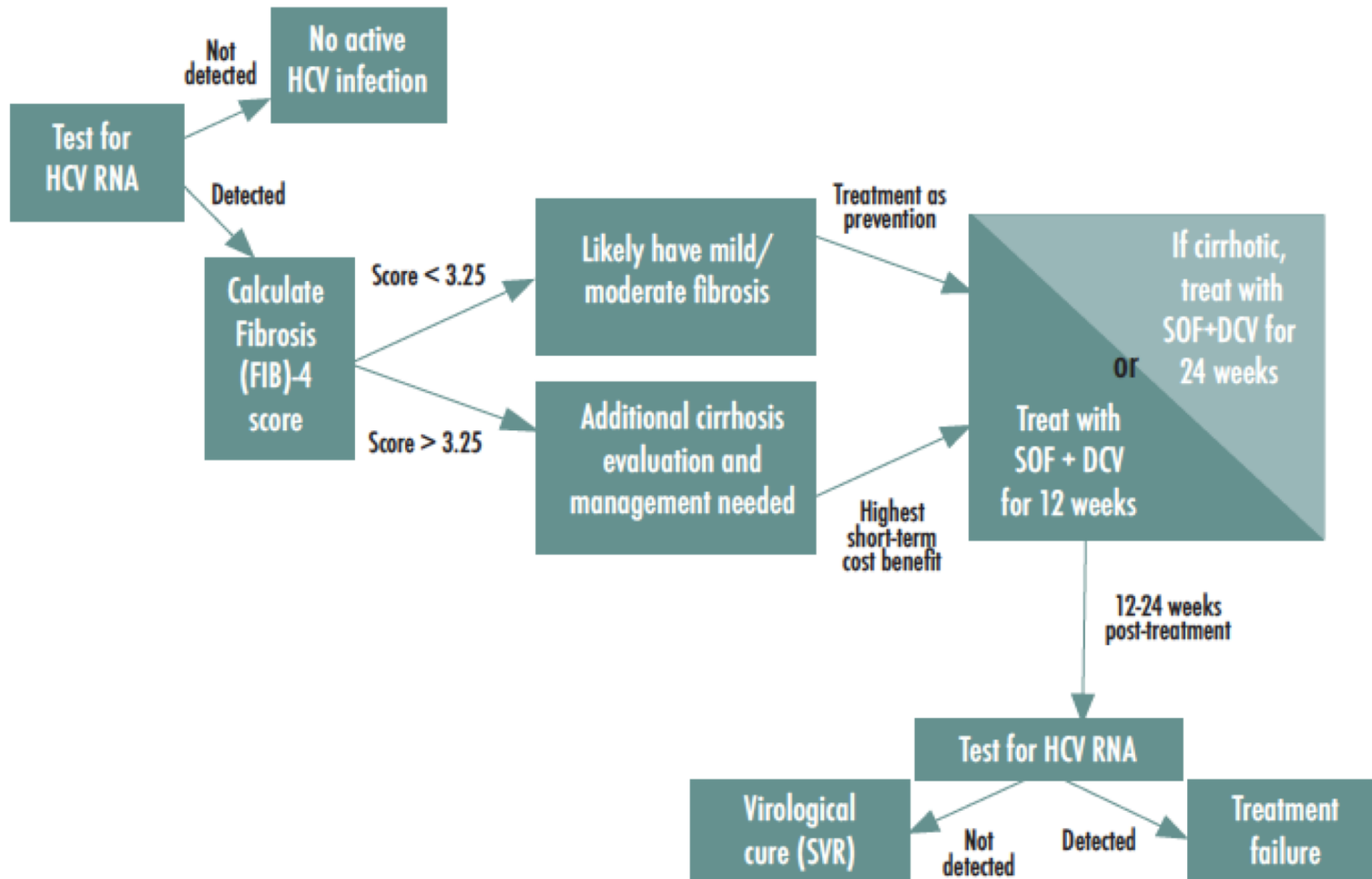
Need for simpler, cheaper tests

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?