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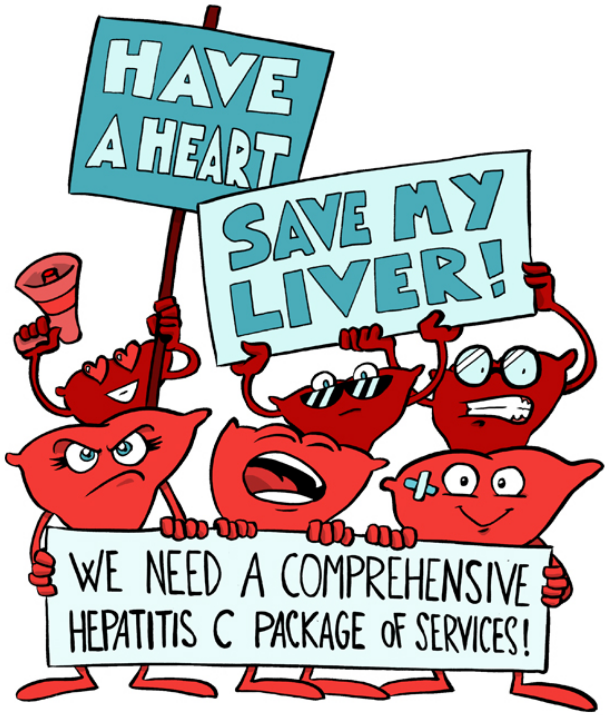
www.treatmentactiongroup.org

HCV Diagnostics Advocacy Training Curriculum

HEPATITIS C VIRUS PROJECT

TREATMENT ACTION GROUP



TOPICS

- Introduction: Diagnostic “Burnout”
- Diagnostics Basics
- Brief Introduction to the WHO Guidelines for People Diagnosed with Chronic HCV
- Determining Whom to Test
- Minimizing Steps to Diagnosis
- Diagnostics Access and Barriers
- Activist Lessons

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Starting Point of E M P O W E R M E N T

Denver Principles (1983) just as relevant today and for all key populations

We condemn attempts to label us as "victims," a term which implies defeat, and we are only occasionally "patients," a term which implies passivity, helplessness, and dependence upon the care of others. We are "People With AIDS."

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- We need to learn about the steps involved and technologies used to diagnose someone with hepatitis C.
- Diagnosis refers to detecting a disease or condition.
- **Access to affordable, quality healthcare, including diagnostic services, is a human right.**
- Everyone has the right to know their health status and receive quality treatment and care, including for infectious diseases like hepatitis C.

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Objectives of the Activist Guide and Training Curriculum:

- Translate the scientific research about HCV diagnostics to increase treatment activists' and community members' technical knowledge and the capacity that they need to mobilize communities and demand access to diagnostics;

- Strengthen activists' ability to participate in planning and policy processes related to national HCV elimination;

- Serve as a resource when activists engage in community monitoring and surveillance related to the quality, affordability, and accessibility of HCV testing and care services;

- Provide advocacy exercises to help activists' explore ways to overcome diagnostics barriers.

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How to Use the Activist Guide and Training Curriculum:

- Encourages participatory learning with interactive discussions.
- Organized into six sections.
- Each section can be presented and shared with a small group of people in 2-hour sessions.
- Advocacy exercises at end of each section that include **discussion points** and **action steps**.
- Discussion points are intended to start conversations about key issues raised in each section.
- Action steps are intended to start conversations about how to translate the key issues into advocacy in the community and to allow participants to find solutions together.

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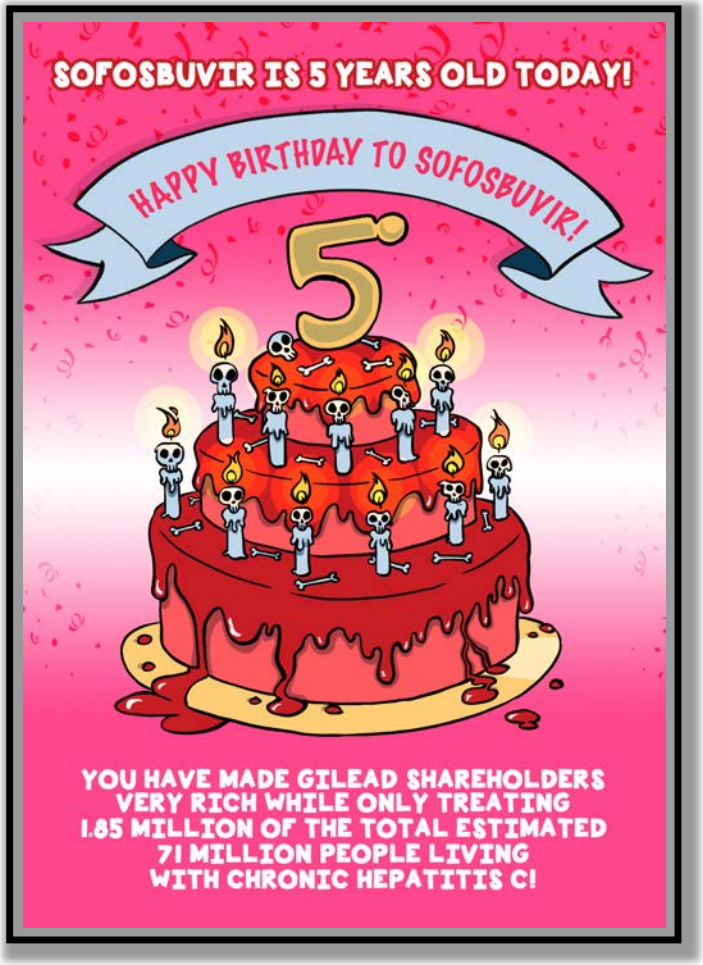
Introduction: Diagnostic "Burnout"



- All-oral direct-acting antivirals (DAAs) effectively cure all genotypes of the hepatitis C virus (HCV) in 2–3 months
- Monopolies, licensing, registration, and pricing barriers remain for some low- and middle-income countries (LMICs), where 2/3 of people living with hepatitis C and people who use drugs live
- Globally: estimated 71 million people are living with chronic HCV
- 2.3 million (6.2%) of 36.7 million people living with HIV are coinfected with HCV
- Since 2013, only an estimated 5 million people have been treated

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Introduction: Diagnostic "Burnout"

The World Health Organization (WHO) set global targets to eliminate viral hepatitis as a public health threat by 2030. Achieving elimination requires:

- 90 percent reduction in incidence;
- 65 percent reduction in mortality;
- 90 percent of people infected with hepatitis C to be diagnosed; and
- 80 percent of people diagnosed to be treated.[3]

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Introduction: Diagnostic "Burnout"

- '**Diagnostic burnout**' = phenomenon in which countries have failed to diagnose new infections and run out of diagnosed patients to treat
- We're treating all the 'warehoused patients' = not enough people being diagnosed every year to keep up with the treatment rates.
- **New infections continue to outpace annual cures**
- Governments will run out of people known to have HCV and who need to be treated
- Crux of an elimination strategy: people who are marginalized; don't have health insurance; obstructed to access health care

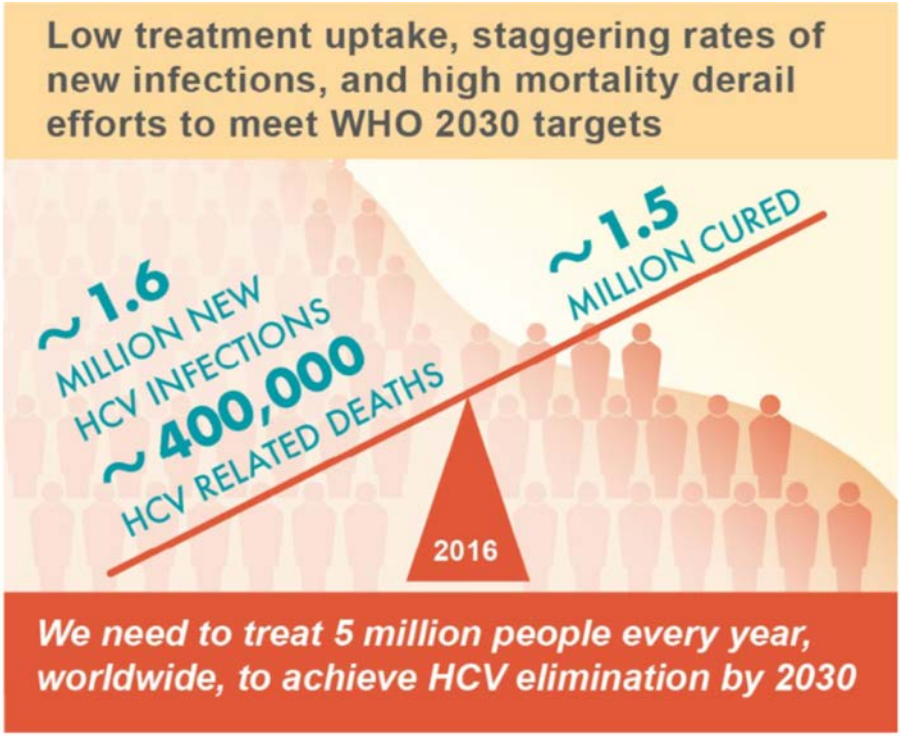

Figure 1. HCV infections, HCV-related deaths, and cures.

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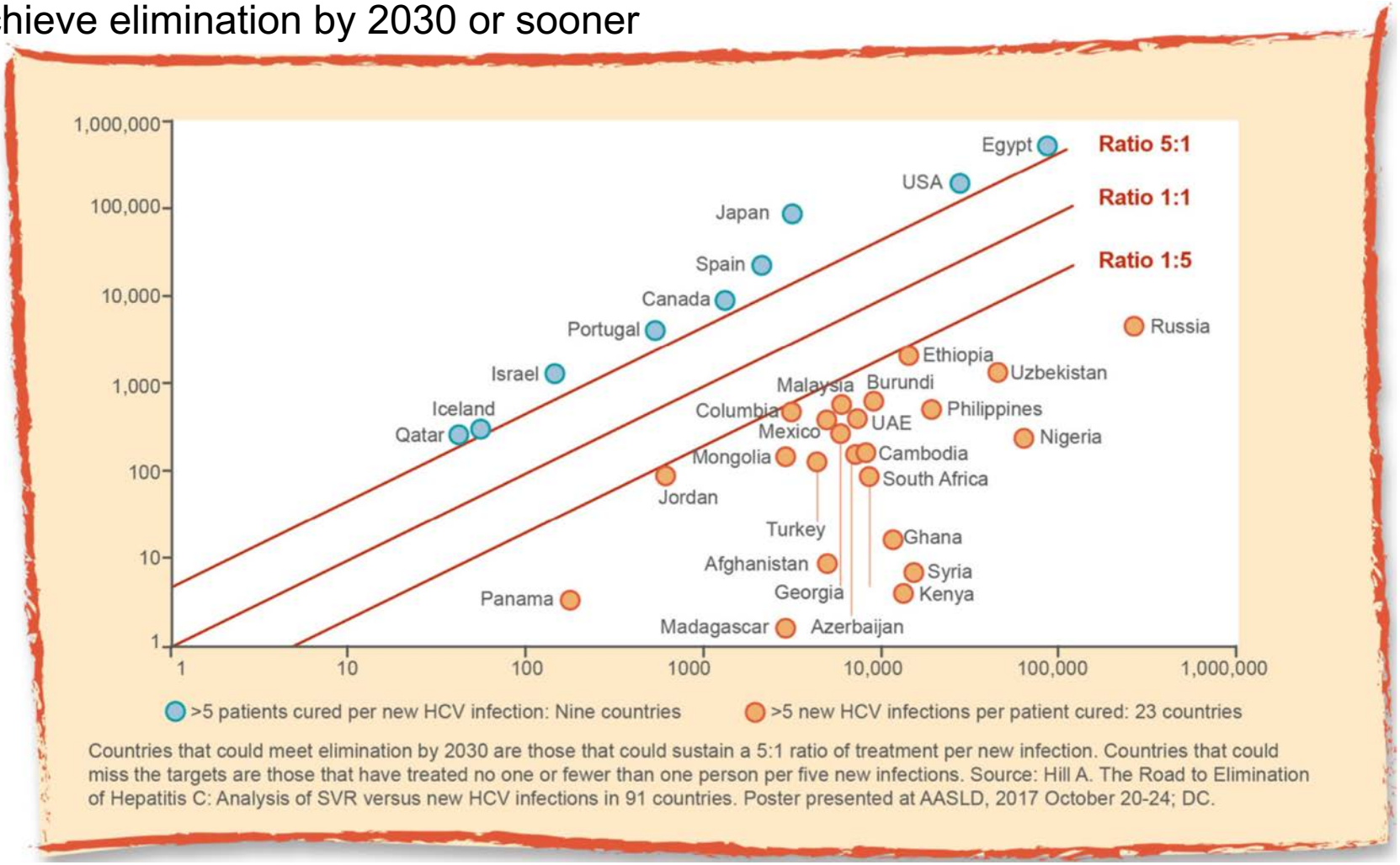
Introduction: Diagnostic "Burnout"

Countries with higher cure rates to new infections (5:1 or more) are projected to achieve elimination by 2030 or sooner



Countries that could meet elimination by 2030 are those that could sustain a 5:1 ratio of treatment per new infection. Countries that could miss the targets are those that have treated no one or fewer than one person per five new infections. Source: Hill A. The Road to Elimination of Hepatitis C: Analysis of SVR versus new HCV infections in 91 countries. Poster presented at AASLD, 2017 October 20-24; DC.

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Introduction: Diagnostic "Burnout"

- Annual cures must exceed annual new infections in order to bend the curve towards elimination
- Modeling forecasts: Brazil, Spain and Portugal could soon reach the stage where there are no more diagnosed patients available to treat
- At this stage, cure of HCV is limited by rates of new HCV diagnosis, which are currently low

Table 1. "Diagnostic burnout": Potential outcomes, based on 2016 data[6]

Country	HCV epidemic	Diagnosed before 2016[8]	New HCV diagnoses[9]	Cumulative Cures in 2016	Outcome
Brazil	1.8 million	235,000 (13%)	10,000 (0.6%)	43,000 (2.4%)	Dx burnout in 2025
Spain	328,000	140,000 (43%)	5500 (1.7%)	25,000 (8%)	Dx burnout in 2022
Portugal	96,000	37,000 (39%)	1300 (1.3%)	4400 (4.6%)	Dx burnout in 2026

Sources: Hill A et al. 2017; CDA Foundation database, POLARIS Observatory 2016

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Diagnostics Basics

The first step in finding out if you have HCV is to get laboratory tests from a medical provider. You may be asked to take laboratory tests that can tell:

- if you have been infected with HCV;
- if you are still infected with HCV;
- the amount of HCV in the bloodstream;
- the subtype of the virus (genotype) you have;
- if your liver has been damaged;
- if you have been infected with other viruses (such as HIV or hepatitis B virus);
- if you are infected with HCV and have underlying conditions (such as pregnancy, diabetes, kidney disorders, etc.).

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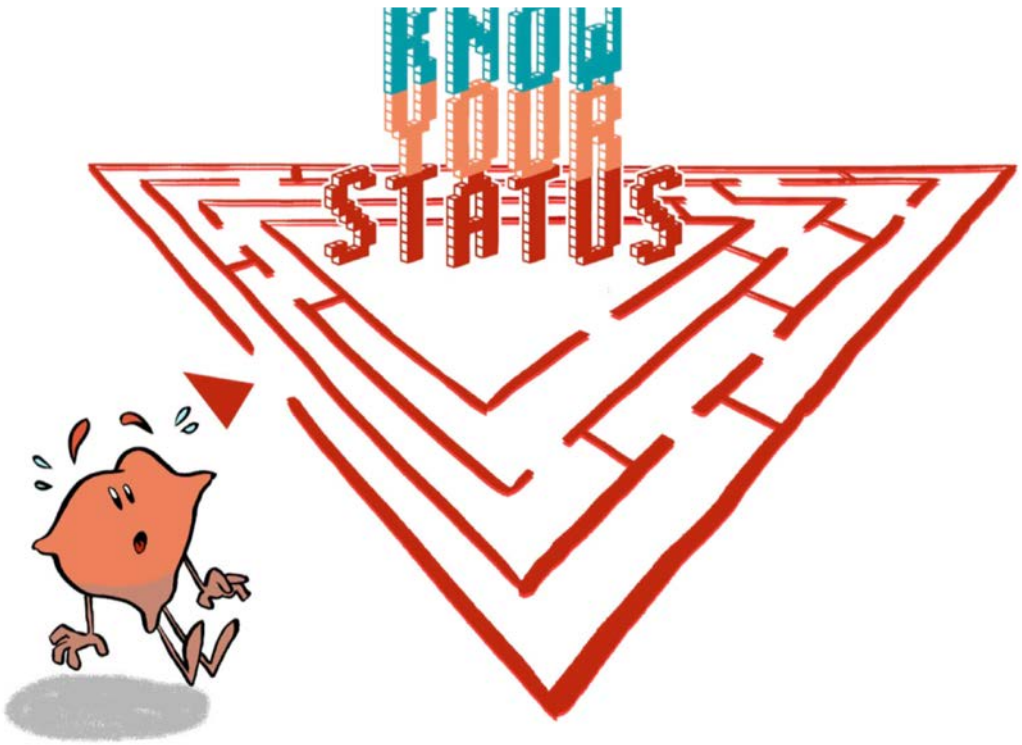
Diagnostics Basics

Diagnosing hepatitis C is a two-step process: screening and virological (also known as confirmatory) testing.



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Diagnostics Basics

- What is screening?

Screening looks to see whether someone who is apparently healthy and without any symptoms might have an infection or a disease. For hepatitis C virus (HCV), screening means looking for antibodies instead of the virus.

- What are antibodies?

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

- HCV triggers an immune response – makes HCV-fighting antibodies.
- Spontaneous viral clearance – likely in young people, women, HIV-, IL28B CC genotype
- 20-40% of people with HCV will spontaneously clear the virus
- HCV antibodies remain in blood for years. Screening looks to see whether someone who is apparently healthy and without any symptoms might have an infection or a disease

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Diagnostics Basics

List of different tests

- **Antibody screening** involves:
  - **Rapid diagnostic test (RDT)** that uses oral fluid (saliva) or blood from your veins or from a fingerstick, or
  - **Enzyme immunoassay (EIA)** that uses blood or plasma samples.
- When antibody screening uses blood, it is also known as **serological screening**.
- RDTs are designed for **point-of-care (PoC)** settings — conducted at the time and place of the patient seeking care (community clinics, harm reduction sites, prisons, etc).
- RDT results can take between 5 and 20 minutes
- EIAs — conducted in laboratory settings
- EIAs results become available usually in a few days. EIAs are conducted in batches of 96 tests

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Diagnostics Basics

- What does a negative HCV antibody test result mean?

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

- It takes **6 to 24 weeks** (sometimes up to 9 months) for a person to make antibodies to HCV (often called the ***window period***).

- One in four people will spontaneously clear the virus within six months of becoming infected.

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Diagnostics Basics

- What does a positive HCV antibody test result mean?

  A positive antibody test result means that a person has been infected with hepatitis C. A different test (confirmatory test), to look for the actual hepatitis C virus, is needed to make a diagnosis.

- Even when a person has cleared HCV or has been cured by treatment, HCV antibodies remain in a person's blood for years, possibly for the rest of the person's life.

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Diagnostics Basics

Step 1. HCV Antibody Test	
Positive Result	**Negative Result**
There are three potential meanings: 1 The person was recently infected with HCV; or 2 The person may have chronic HCV; or 3 The person was infected in the past, but has cleared HCV and is no longer infected. ***This person needs a viral load test to confirm.***	There are three potential meanings: 1 The person has never been infected with HCV. ***This person does not need a viral load test to confirm.*** 2 The person may have been recently exposed to HCV within the last 2 weeks; or 3 If the person is HIV positive, with a CD4 count <200 cells/mm3, or has a weakended immune system. The person may have chronic HCV. ***This person needs a viral load test to confirm.***

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Diagnostics Basics

- What is virological (also called confirmatory) testing?

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

- How is a person tested for hepatitis C?

  2 tests to diagnose someone with HCV:

  - A **viral load test** (called HCV RNA or NAT—nucleic acid testing) is used to check for HCV in the bloodstream.
  - HCV **core antigen** test detects the viral protein of hepatitis C—found in the bloodstream within 2 weeks.
    - Only available in large laboratory settings, such as a central hospital.

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Diagnostics Basics

Step 2. Confirm Diagnosis	
Detectable Result	**Undetectable Result**
There are two potential meanings: 1 The person may be recently infected with HCV; or 2 The person may have chronic HCV. ***This person should be assessed for HCV treatment.***	There are two potential meanings: 1 The person has never been infected; or 2 The person was once infected in the past, but has now cleared HCV. ***This person should be assessed for follow up testing.***

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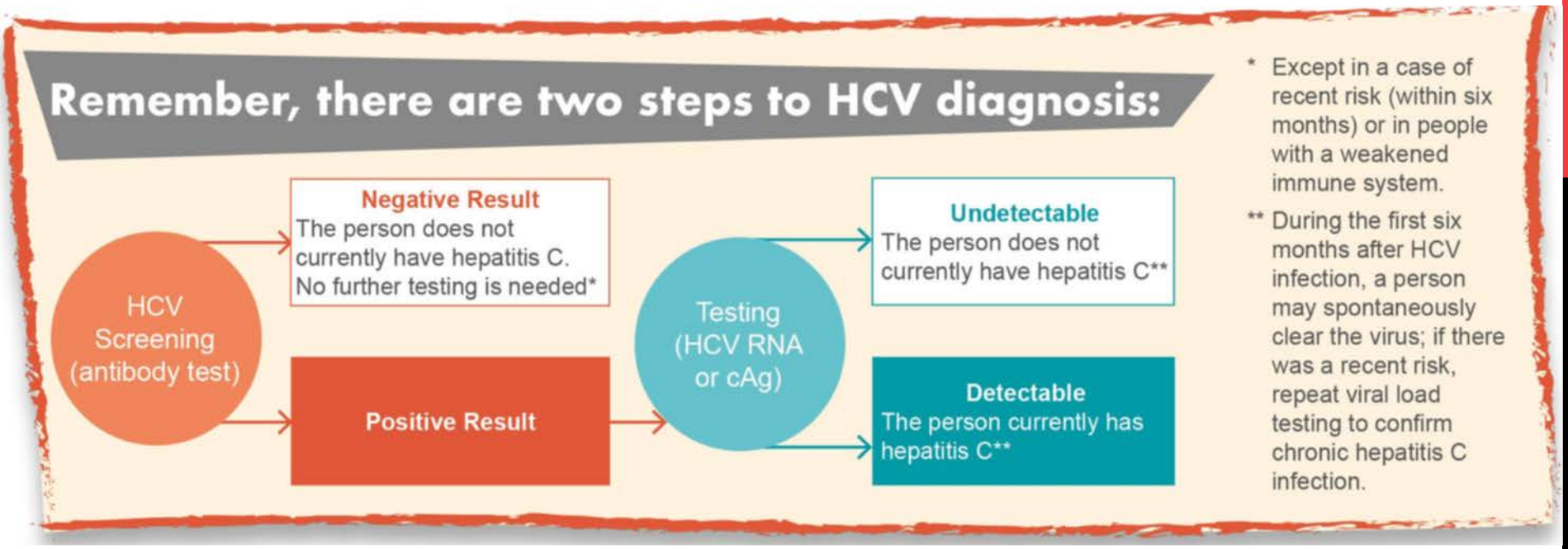
Diagnostics Basics



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Diagnostics Basics

List of different tests

- **Viral load tests** — also known as RNA tests, molecular tests, or nucleic acid tests.
- A person should get tested regularly if they are at risk.
- If a viral load test result is also undetectable, it means that HCV has been cleared.
- To diagnose 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.
- Viral load tests are more likely to be used than core antigen tests.

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Diagnostics Basics

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***).
- **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.
- New research on guidance to manufacturers of point-of-care HCV diagnostics: **optimal limit of viremic detection should be close to 1300 IU/mL**.
  - This threshold would detect 97% of active HCV infections and minimize false negatives.

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Diagnostics Basics

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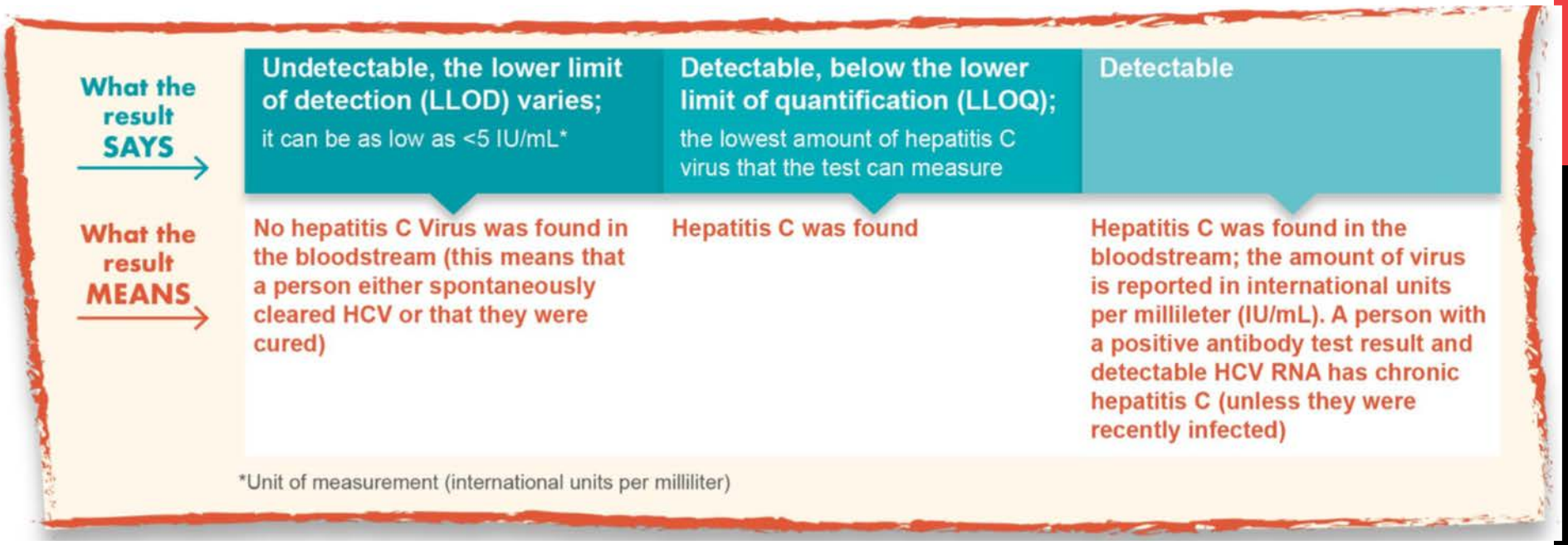

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Diagnostics Basics

List of different tests

- ***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 should be less expensive** than viral load testing, **but less sensitive**, meaning it might miss some infections.
  - Not used in high-income countries – could market in LMICs and bundle HBV, HPV antibody tests
  - Need price transparency; countries need to be more aggressive in negotiations

- ***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 has the following characteristics:
  - Can be used with HCV antibody testing to detect acute HCV
  - Confirms chronic HCV infection
  - Less sensitive—does not detect low levels of HCV (threshold: 3000 IU/mL depending on the genotype)
- May be possible to use core antigen to confirm cure at week 12 (or SVR12), but there are currently not enough data to know.

Diagnostics Basics

List of different tests

HCV Genotyping

- **Six** known hepatitis C genotypes; also subtypes
- People can be infected with more than one HCV genotype (called ***mixed infection***).
- 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**.
- **WHO 2018 Guidelines recommend eliminating genotype tests if pangenotypic are used.**

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Diagnostics Basics

List of different tests

Liver Disease Staging

- Type and length of HCV treatment depends on liver damage
- **Treating HCV early is critical before the liver becomes more damaged.**
- 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.

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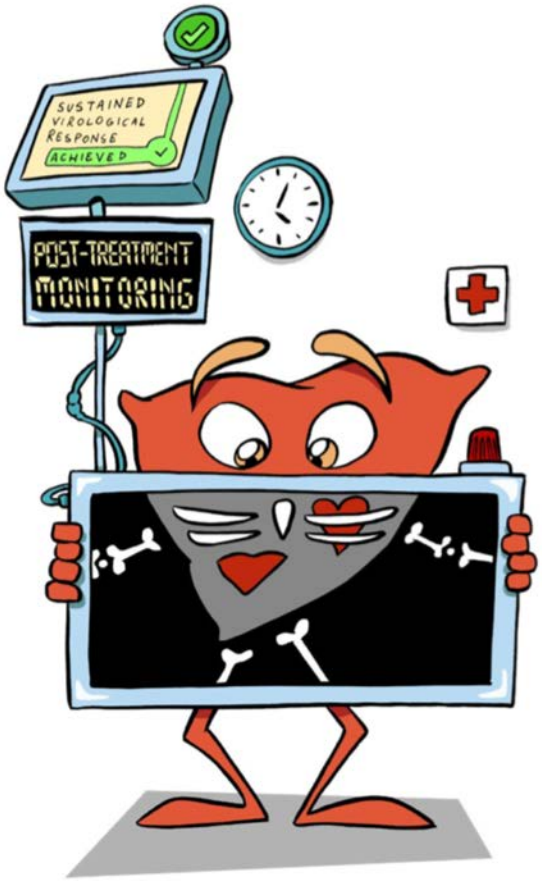
- Pangenotypic DAAs = genotype testing less relevant
- Note: People with genotype 3 and cirrhosis more likely to have ***steatosis*** (fat in the liver); this can make treatment less effective.



Staging assesses extent of liver damage before starting treatment

- **Invasive** (biopsy: takes blood or tissue sample with needle) — should not be used
- **Non-invasive test** (ultrasound imaging) — safer, less expensive, easier to perform

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Diagnostics Basics

- Cirrhosis can be assessed without a liver biopsy
  - **In resource limited settings, WHO recommends FIB-4 or APRI lab-based tests (<u>less expensive</u>) for liver function tests.**
  - Liver specialists 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.
  - Examinations are conducted within 5 minutes and patients can receive results immediately.
  - FibroScan has been used as a prevention and noninvasive assessment tool to engage people who are often excluded from the healthcare system (e.g., in harm reduction settings)
  - Difficult to diagnose mild or moderate liver disease without doing a biopsy, however, and FibroScan is not widely available in most countries.
  - ***FibroScan + Fibrotest/ActiTest*** more accurate for people with cirrhosis/advanced liver disease.
  - FibroScan + FibroTest/ActiTest both publicly funded in France; under patent/exclusive licensing

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Table 2. Comparison of FibroScan and FibroTest.[16]

Features	Fibroscan	Fibrotest
Pricing	Platform price: **US$300,000** Mini platform price: **US$70,000** Minimum **US$50**, generally **US$60–80** per test	**US$59 to over US$100** per test, depending on the country, to analyze results with BioPredictive's technology
Setting	Generally for clinics or PoC settings. For large numbers of patients, multiple devices would be needed To consider for rural patients Can be used in community settings and to engage patients and peers, and link patients to services	Hospital laboratory settings
Obtaining results	Provides detailed imaging	Not an imaging platform; works with blood tests results to be shipped to BioPredictive company for interpretation Seen as better than FIB-4 or APRI for accuracy/reading the results, especially for people with cirrhosis or advanced liver disease Requires reliable shipping/transport infrastructure
Patient care	Patients need referral or follow up in hospital, especially for HCC diagnosis	Patients need referral or follow up in hospital
Inputs and maintenance	No reagents required, but plan for maintenance every 6 months	Company has monopoly on reagents

Source: Londeix P. 2018 May.

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Diagnostics Basics

Liver Function Tests (LFT) – check enzyme levels in the liver

- People taking ARVs or TB treatments (whether or not coinfected with HBV or HCV) should have liver enzymes checked regularly as these medications might be hard for the liver to break down.

There are several types of enzymes:

- **ALT** is made in the liver. If ALT keeps increasing over time, it may be a sign of hepatitis C progression
  - Results cannot predict or tell someone how much liver disease they have
- **AST; SGOT**
  - **AST** is made in the heart, intestines, and muscles
- **ALP, GGT**, bilirubin, albumin, and prothrombin (PT) are other important liver enzymes used to measure liver health.

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Diagnostics Basics

One liver function test is an **APRI**, or aspartate aminotransferase to platelet ratio index, which is a formula used to determine level of cirrhosis.

$$\text{APRI} = \frac{\frac{\text{AST LEVEL}}{\text{AST (UPPER LIMIT OF NORMAL)}}}{\text{PLATELET COUNT } (10^9/\text{L})} \times 100$$

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Diagnostics Basics

The **FIB-4** is another test that is inexpensive and noninvasive. FIB-4 is a calculation to determine the amount of liver scarring by using patient's age, platelet count, AST, and ALT.

$$\text{FIB-4} = \frac{\text{AGE (YEARS)} \times \text{AST (U/L)}}{\text{PLATELET COUNT } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

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Diagnostics Basics

Other important parts of the 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***.
- Some machines can save time by running several different tests using the same sample at the same time (known as ***multiplexing***)
- Many laboratories conduct multi-disease testing (***polyvalency***), meaning they use a machine that tests for more than one infection at the same time, such as HIV, HBV, and HCV.
- 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.

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Diagnostics Basics

Challenges and gaps in diagnostics: How far are we from the ideal test?

"Ideal" HCV test:

- Uses either HCV ribonucleic acid (RNA) or HCV core antigen (cAg) – performed using fingerstick or DBS
- accurate, with high sensitivity and specificity (both are closer to 100 percent)
- Confirms diagnosis in 20 minutes
- Costs less than US$5 per test (including the reagent cost)
- Enables a person to initiate a pangenotypic treatment immediately (after conducting the liver disease staging + checking for any other complications), then return for test of cure at 12 or 24 weeks (SVR12 or SVR24) after completion of DAA treatment.

But, still several years away.

Lack of simple, affordable tests in LMICs.

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Screening tests: rapid diagnostic antibody tests[18]

Advantages

- Easy to use (minimal training which allows task-shifting)
- Oral fluid (saliva), whole blood, serum or plasma (fingerprick and oral fluid allow decentralization of testing)
- Equipment free (can be used at PoC settings with limited lab infrastructure/electricity)
- Good sensitivity and specificity
- Qualitative (yes/no) results
- Fast delivery of results (less than 20 minutes)
- 1–2 years of shelf life (if stored correctly at room temperature)

Limitations

- Low throughput (rate/performance for processing results; amount of tests that can be processed at a given time)
- Subjective interpretation (operator dependent), inadequate for people with a low amount of antibodies or compromised immune system (such as PLHIV)
- Possible higher cost (compared with lab-based tests) depending on volume
- Difficult for quality-control activities

Screening tests: enzyme immunoassay antibody tests[19]

Advantages

- High sensitivity
- High specificity (~100%)
- High sample throughput (good for processing large volumes of samples)
- Possible lower cost based on high volumes
- Data-processing filing of results
- Cost-effective in large numbers of samples
- Allows easier oversight of quality-control activities
- The same equipment can used for serological screening of other diseases e.g. HIV, HBV, etc.

Limitations

- Requires an effective specimen transport system
- Cold chain, in which temperature is controlled generally between 2 °C and 8 °C (36 °F to 46°F), is needed for reagents (not always possible in some LMIC settings)
- Requires additional equipment (high precision pipettes, centrifuges, etc.)
- Longer time for results
- May have interference from sample matrices: whole blood, plasma, capillary samples
- Requires skilled technical staff
- Requires equipment service and maintenance
- EIAs usually run tests in batches of 96 samples, which can delay turnaround time for results. Companies should offer different test configurations for different volumes, such as running 12 or 24 tests at a time

Core antigen (confirmatory) test platforms: Abbott ARCHITECT i2000[20 21]

Advantages

- Conducts core antigen tests: good for high-volume settings (100 tests per hour)
- Also screens HIV and other diseases; activists need to confirm whether the HIV platform is licensed for HCV in their country
- cAg is detected in the bloodstream earlier than with viral antibody tests—two weeks after infection
- Possible lower cost based on high volumes
- Allows easier oversight of quality-control activities

Limitations

- Cannot use an effective specimen transport system
- Is not validated/certified for use with dried blood spot samples
- Cannot confirm cure[22]
- Less sensitive—it might miss some infections
- Requires central labs that can handle large volumes
- Longer time for results
- HCV: US$8–23 (€7–20) per test
- Requires skilled technical staff
- Requires equipment service and maintenance

RNA (confirmatory) test platforms: Abbott Realti*me*[23]

Advantages

- Conducts RNA tests: good for high-volume settings (93 tests per batch)
- Possible lower cost based on high volumes
- Screening multiple diseases using different samples (HIV, HCV, genotyping, but activists need to confirm whether the HIV platform is licensed for HCV in their country)
- Allows easier oversight of quality control activities

Limitations

- Requires an effective specimen transport system
- Is not validated/certified for use with dried blood spot samples
- Longer time for results
- US$11–23 per test (Global Fund price, which varies depending on volume and term commitment)
- Requires skilled technical staff
- Requires equipment service and maintenance (unless a reagent rental agreement was negotiated)

RNA (confirmatory) test platforms: Cepheid GeneXpert[24]

Advantages

- Xpert Viral Load (VL) has an RNA quantification assay (using plasma samples) and fingerstick (using whole blood samples)
- RNA quantification assay has Conformité Européenne (CE) and WHO pre-qualified (PQ) quality certifications
- Xpert VL Fingerstick is CE-marked and WHO PQ
- Xpert VL Fingerstick is appropriate for people who may not have easy vein access (such as some people who inject drugs)
- Xpert VL Fingerstick cartridge allows for simplification in sample collection
- Xpert VL: very accurate, simple to operate and good for shifting tasks to auxiliary healthcare professionals to facilitate decentralized testing
- Xpert VL: same-day results in 108-110 minutes; Xpert VL FS: in 60 minutes
- The GeneXpert instrument has an extensive test menu, which means there is opportunity to integrate testing across other disease programs (e.g., TB, HIV, HPV, HBV, etc.)
- Cepheid offers preferential pricing in 145 LMICs

Limitations

- Xpert VL and fingerstick tests: Not available in many countries (not approved in the United States)
- Xpert VL: high cartridge costs if countries must pay in advance and in US dollars
- Xpert VL and Fingerstick: requires incinerator for biowaste, which may not be available in some decentralized settings
- While Xpert VL and Fingerstick tests are simplified, the GeneXpert instrument (including Edge) still requires lab infrastructure (e.g., constant electricity, air conditioning) to store reagents and function correctly
- Xpert VL: when using plasma, requires a centrifuge and transport costs for centralized testing
- Xpert VL: US$17,000 per device plus US$14.90 per test plus distributor mark-ups[25]; additional service and maintenance costs
- No volume-based pricing: price per test is fixed regardless of volumes

RNA (confirmatory) test platforms: Roche Cobas® Taqman[26 27]

Advantages

- Conducts qualitative and quantitative RNA tests: good for high-volume settings (93 tests per batch)
- Qualitative tests are cheaper than quantitative tests
- Possible lower cost based on high volumes
- HCV is part of Global Access Program, whereby reduced test pricing is offered to 85 LMICs
- Highly automated system
- Screening multiple diseases (TB, HIV, HCV, genotyping, etc.), but activists need to confirm whether the HIV platform is licensed for HCV in their country
- Allows easier oversight of quality-control activities

Limitations

- The Taqman platform is being phase out for the Cobas® 4800 and 6800 systems
- Requires an effective specimen transport system
- Is not validated/ certified for use with dried blood spot samples
- Longer time for results
- Requires large lab infrastructure to house equipment
- Requires skilled technical staff despite being fully automated
- Requires equipment service and maintenance (unless a reagent rental agreement was negotiated)
- Lack of transparency in pricing (information on preferential pricing is not publicly available)

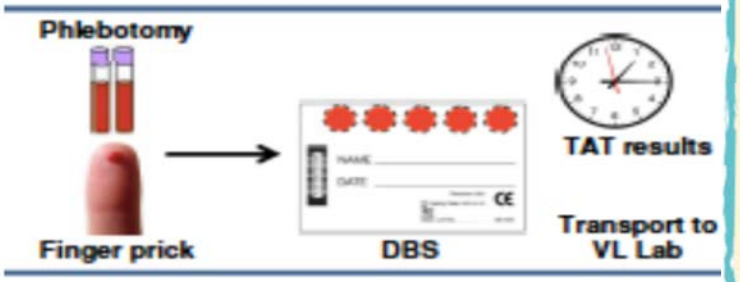
RNA (confirmatory) test platforms: Genedrive HCV[28]

Advantages

- Point of care: small, portable (weighs 1 kilogram) system
- Results are qualitative (positive or detected/negative or undetected)
- Detection in less than 90 minutes, allowing for same-day diagnosis
- For settings with low numbers of patients (few number of patients/day)
- Reagents can be stored at room temperature (no refrigeration is required)

Limitations

- High costs per patient
- Pricing US$5000 per device; US$25–35 per test
- Less sensitive than lab-based methods: lower limit of detection is above the recommended 1000 IU/mL for PoC testing (i.e., 2362 IU/mL)
- Low throughput per device: 90 min/test
- Requires 30 µL plasma, which could be challenging to obtain in PoC settings (requires phlebotomists to draw blood to obtain plasma and to use a centrifuge)
- Requires precise steps, using micropipetting instruments, for sample/reagent preparation (not fully automated)
- Requires uninterrupted power supply, which may not be reliable in some LMIC settings. WiFi connectivity is optional
- The device is not appropriate for multi-disease testing (only an HCV test is available)



Antibody screening and RNA (confirmatory) tests: dried blood spot samples[29]

Advantages

- DBS is an alternative to plasma samples: small volume samples collected by fingerstick
- DBS can be used instead of RDTs, such as in harm reduction or prison settings
- Can be used to detect HBV/HCV antibodies[30], for HBV/HCV RNA testing, for genotyping, and for treatment resistance testing
- Useful for early diagnosis of pregnant parent-to-infant HCV transmission and for detection in children
- Inexpensive
- Can be used in large-scale testing campaigns
- Facilitates decentralized collection of samples on filter paper, which can be put in the mail or delivered by courier because it is nonhazardous material
- Stable for transport at room temperature
- Requires low level of training and could be done by auxiliary health professionals, community health workers, peer educators

Limitations

- DBS requires a strong transport system to get the samples to central labs. For example, in South Africa and Tanzania, motorbike couriers are used to pick up diagnostics samples and deliver test results
- DBS has reduced analytical sensitivity for RNA compared to plasma and serum samples (due to small sample volume)
- Results are not immediately provided to the patient
- Need to develop quality standards for DBS
- DBS is currently limited to research use: companies have not yet sought stringent regulatory authority (SRA) status
- Requires additional studies and validation to scale up DBS testing in LMICs, which will take time

Advocacy Exercise

Discussion questions:

- What tests would be most appropriate for testing people in my community?
- Would an HCV self-test improve diagnosis in my community?
- How would an HIV/HCV combined test improve diagnosis in my community?

Action steps:

- How can we integrate HCV testing into existing laboratory infrastructure for multi-disease platforms?

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Updated WHO Testing Guidelines – July 2018

Key recommendations and updates

Screening:

- **All individuals** who have ever been **part of a population with high rates of HCV infection** should be screened with an antibody test. This includes people who inject drugs (PWID) and people living with HIV (PLHIV).
- RDTs recommended for resource-limited settings
- RDTs at point-of-care in community settings
- Settings where the hepatitis C **antibody prevalence is ≥2% or ≥5%** (depending on country's epidemiology), **all adults** should have access to and be offered the antibody test.
- Any person with **positive antibody test** should have a hepatitis C viral load test (also known as an HCV RNA test) to confirm.

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Updated WHO Testing Guidelines – July 2018

Confirmatory testing:

- **Qualitative** (less expensive) just as sensitive as quantitative RNA
- **Core antigen tests** are alternative confirmation tests to RNA/NAT but are less sensitive and might miss some infections.
- **Genotype testing** of the hepatitis C virus is **not needed** before treatment with a “pangenotypic” DAA regimen
- Move away from on-treatment viral load tests, especially when using pangenotypic DAAs
- Recommend **SVR12 viral load confirmation**; skip SVR4 + SVR8 tests

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Updated WHO Testing Guidelines – July 2018

Care/liver assessment

- Monitor patients with cirrhosis for HCC every 6 months with ultrasound or alpha fetoprotein (AFP) blood tests
- Additional conditions such as **comorbidity, pregnancy, or drug-drug interactions** should also be evaluated.
- Alcohol reduction intervention for those with moderate or **high levels of alcohol use**
- **PWID** should be offered information on how to prevent hepatitis B and C infection, including being **offered vaccination against hepatitis B virus** to avoid the risk of having two liver infections at the same time.
- Liver damage should be assessed using **non-invasive tests**, such as **APRI and FIB-4** (more available, less expensive)
- **Fibroscan** can be used, if available, to assess liver stiffness

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Table 3. Types of Hepatitis C Tests in the WHO Model List of Essential In-Vitro Diagnostics

	Diagnostic test	Test purpose	Assay format	Specimen type
Hepatitis C	Antibodies to HCV (anti-HCV)	Screening for HCV infection: Infants over 18 months of age, children, adolescents, adults	RDT	Venous whole blood Plasma Serum
			EIA (microplate) Manual method	Serum Plasma
			CLIA/ECL (automated instrument)	Serum Plasma
	Antibodies to HCV (anti-HCV) and HCV core antigen (HCV cAg	Screening for HCV past of present infection: infants over 18 months of age, children, adolescents, adults	EIA (microplate) Manual method	Serum Plasma
			CLIA/ECL (automated instrument)	Serum Plasma
	HCV core antigen (HCV cAg)		NAT	Serum Plasma
	HCV RNA (qualitative or quantitative)	For the diagnosis of viraemic HCV infection and monitoring of response to treatment as a test of cure	NAT	Serum Plasma

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Validating test quality

- Just like with medicines, we need to ensure the tests we use are **accurate, simple to use, and high quality**.
- We do not want to miss an active infection or give someone a false positive diagnosis.
- For HCV antibody RDTs, there are over 72 tests, with varying degrees of quality, accuracy, and pricing

The World Health Organization conducts ***pre-qualification*** (WHO PQ) assessment to examine the performance and quality of tests.

- Assesses ***specificity*** - true negative rate, or the test's ability to correctly identify people without HCV. **High specificity, which is close to 100 percent, helps to determine the quality of a test to avoid misinforming a person about being infected when they are not.**
- Assesses the ***sensitivity*** - true positive rate, or the test's ability to correctly identify people with HCV. **High sensitivity, which is closer to 100 percent, avoids missing an HCV infection.**

WHO pre-qualification process

- Not a prescriptive list
- Used as standard to help large international procurement agencies (e.g., the Global Fund on AIDS, Malaria and Tuberculosis, UNICEF, UNITAID, etc.) and countries, especially in resource-limited settings, to consider medicines and medical devices that meet high quality standards to procure for national programs
- Helps to avoid duplicative regulatory approval procedures

Steps involved

- Manufacturers submit an application for prequalification
- Dossier review to determine the safety, performance, design, and manufacturing of a product
- Site inspection to evaluate compliance with international quality management standards
- Laboratory evaluation of the product
- Post-marketing surveillance

WHO pre-qualification process

Costs

- PQ assessment fees = US$5000–12,000 per product
- Plus annual fee of US$4000 to keep products listed on the WHO PQ list

Timeline

- Ideally takes less than one year to review
- Months may be added to process to clarify and gather info from manufacturers

Other regulatory standards

- Food and Drug Administration (FDA)
- Conformité Européenne (marked as CE or CE-IVD)
- However, there are few PQ and CE–marked HCV products
- Countries procuring diagnostics through the Global Fund are limited to these

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Table 4. WHO Prequalified and CE-Marked HCV Tests: Challenges Remain [40 41 42 43]

Test	Sample	Result time	Multi-plexing	Price (ex works or free carrier) [46 47]	Regulatory Status	Under WHO PQ Review	Suitable for LMICs; Needs Advocacy
Enzyme Immunoassay							
INNOTEST HCV Ab IV	Serum, plasma	179 min	Yes (HIV & other markers)	ND	**WHO PQ**		Suitable for central labs
INNO-LIA HCV Score	Serum, plasma	1 day	No	ND	**WHO PQ** **CE-marked**		Strip-based method but requires cold chain and other small equipment

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Table 4. WHO Prequalified and CE-Marked HCV Tests: Challenges Remain [40 41 42 43]

Test	Sample	Result time	Multi-plexing	Price (ex works or free carrier)	Regulatory Status	Under WHO PQ Review	Suitable for LMICs; Needs Advocacy
Enzyme Immunoassay							
Bioelisa HCV 4.0	Serum, plasma	150 min	Yes (HIV, HBV, HEV, among others)	ND	**WHO PQ, CE-marked**		Suitable for central labs
Murex Anti-HCV 4.0	Serum, plasma	120 min	Yes (HIV, HBV, HEV, among others)	ND	**WHO PQ, CE-marked**		Suitable for central labs
Enzygnost Anti-HCV 4.0	Serum, plasma	120 min	Yes (HBV, HAV)	ND	Did not receive WHO PQ approval		Suitable for central labs

Rapid Diagnostic Tests							
OraQuick HCV RDT	Oral, fingerstick, venous blood	20 min	No	US$8 (MSF price); US$12 per test	**WHO PQ** **CE-marked** **FDA approved**		Price remains too expensive for LMICs
SD Bioline	10 µL whole blood, serum, plasma	5-20 min	HIV	US$1-2.40 per test	**WHO PQ**		
Intec Rapid anti-HCV	10 µL, whole blood, serum, plasma	15-20 min	No	<US$1-2.40 per test	**WHO PQ**, **CE-marked**		
Standard Q HCV Ab Test	Whole blood, serum, plasma	5 min	No	ND		WHO PQ under review	
Premier Medical Corporation First Response® HCV Card Test	Whole blood, serum, plasma	ND	No	US$0.60-1 per test	**CE-marked**	**WHO PQ** under review (Expert Review Panel for Diagnostics)	
ABON HCV Rapid Test Device	Whole blood, serum, plasma	ND	No	ND		**WHO PQ** under review	

Viral Load (RNA/NAT)							
Cepheid Xpert VL Assay (use with Cepheid GeneXpert)	Plasma samples, can be PoC	Same-day results in 108-110 min	HIV, TB	US$17,000 per instrument; US$14.90 per test (for all virological tests in LMICs)	**WHO PQ**, **CE-marked**, not approved in United States		Can be used for all genotypes; need WHO recommend-ations for use in all genotypes
Cepheid Xpert VL Fingerstick	100 µL, capillary blood, Fingerstick Tertiary PoC: harm reduction settings, may be easier to give for some PWID with poor vein access	Within 60 min	HIV	ND			Modified version of the VL assay; **CE-marked**, not approved in United States
Genedrive HCV RNA	30 µL plasma, serum	90 min	No	US$5000 per device; US$25-35 per test		**CE-marked**, **WHO PQ** under review	

Test	Sample	Result time	Multi-plexing	Price (ex works or free carrier)	Regulatory Status	Under WHO PQ Review	Suitable for LMICs; Needs Advocacy
(Viral Load (RNA/NAT) cont'd)							
RealTime HCV Viral Load	0.5 mL plasma, 0.2 mL serum, DBS	ND	HIV	US$11–23 per test; Global Fund price varies according to test volume/term commitment		**CE-marked** for HIV DBS and HCV RNA plasma and serum only, **WHO PQ** under review	
Abbott Alinity m HCV assay RNA	Plasma, serum	ND	No	US$50 per test		**CE-marked**, **WHO PQ** under review	
Hologic Aptima HCV Quant	Serum, plasma Lab-based	ND	HIV	US$10–15 per test; US$12 all-inclusive price for HCV VL			**CE-marked**, FDA-approved
Biocentric Generic HCV PCR assay	Serum, plasma	ND	HIV	US$23 per test US$13.50–17 (€12–15) per test (updated price expected by end-2019)			**CE-marked**

Test	Sample	Result time	Multi-plexing	Price (ex works or free carrier)	Regulatory Status	Under WHO PQ Review	Suitable for LMICs; Needs Advocacy
(Viral Load (RNA/NAT) cont'd)							
Roche Cobas 6800/8800 systems (HCV RNA)	Lab-based, high-volume clinical settings	First 96 results <3.5 hours, every 90 min for 96 more results (Cobas 6800 System); first 96 results <3.5 hours, every 30 min for 96 more results (Cobas 8800 System)	HIV	US$35–45 per test; US$340,000-US$475,000 per instrument (depending on instrument and volume)			**CE-marked**, FDA-approved

Core Antigen							
Abbott ARCHITECT HCV Ag	Serum, plasma	ND	Yes (HIV, HBV, HAV, among others)	US$8-23 (€7–20) per test; US$100,000 per instrument	**CE-marked, WHO PQ**		Suitable for central labs
Monolisa HCV Ag-Ab ULTRA V2	Serum, plasma	ND	Yes (HIV, HBV, HAV, among others)	ND	**CE-marked**	**WHO PQ** under review	Suitable for central labs

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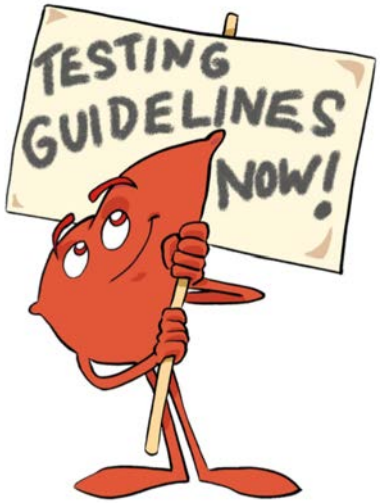
Advocacy Exercise

Discussion questions:

- What is included in our national testing guidelines?
- How does this differ from WHO Testing Guidelines?
- What tests are availablein our healthcare system?
- How does this differ from the WHO Essential Diagnostics List?

Action steps:

- How can we effectively change and improve testing guidelines in my country?
- Have there been any campaigns to widen access to HCV diagnostics for key affected communities in my country or region?
- What are some ways that we can demand simpler, non-invasive, more affordable tests in my country?



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Determining Whom to Test

- **Everyone has the right to know their health status and to be diagnosed with accurate, high-quality diagnostics.**
- A number of factors determine who is tested and treated and how national plans incorporate WHO screening and testing strategies, including:
  - Epidemiology
  - funding and resources, and
  - health priorities in the country

- WHO Guidelines focus on **three testing strategies** to assist countries with identifying new active infections

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Testing Strategy	Settings / Populations	Recommendations
Targeted testing in the most affected populations (key populations). These communities are considered most affected due to the significant stigma, discrimination, criminalization, marginalization, vulnerability, high HIV and HCV incidence and prevalence, and tremendous barriers they face in access in healthcare services.	People who inject drugs, men who have sex with men, incarcerated people, sex workers, indigenous people, people coinfected with HIV/HCV	1 Antibody tests should be offered, and adults and adolescents, either from communities with high HCV seroprevalence, who have had a history of exposure to infectious diseases, and/or who engage in higher-risk behaviors, should be linked to prevention, harm reduction, treatment, and care services. 2 Adults, adolescents, and children who are suspected to have chronic viral hepatitis, such as through symptoms, laboratory markers, or other signs, should be offered testing. 3 People who show ongoing risks of acquiring HCV or who have been reinfected should be considered for periodically retested for HCV with viral load tests. 4 In FIND studies, one-step screening and antibody rapid diagnostic tests are shown to reduce patients who may be lost to follow-up visits. 5 In FIND studies, when patients take rapid diagnostic tests, the results are given on the same visit. If a patient tests antibody positive, then two samples are taken: one for RNA and one for liver staging. Patients who return can be given their RNA and liver staging results on the same visit, then assessed for treatment.

Testing Strategy	Settings / Populations	Recommendations
General population testing	Settings with greater or equal to 2% or 5% HCV antibody prevalence (depending on the overall epidemiological context)	1 All adults in this setting should have access to and be offered HCV antibody testing with linkage to prevention, harm reduction, treatment, and care services. 2 Countries can make use of existing community or lab-based testing, such as at HIV/sexual health or TB clinics, drug treatment facilities, or antenatal clinics. 3 In FIND studies, one-step screening and antibody rapid diagnostic tests are shown to reduce patients who may be lost to follow-up visits. 4 In FIND studies, when patients take rapid diagnostic tests, the results are given on the same visit. If a patient tests antibody positive, then two samples are taken: one for RNA and one for liver staging. Patients who return can be given their RNA and liver staging results on the same visit, then assessed for treatment.

Testing Strategy	Settings / Populations	Recommendations
Birth cohort testing	Specific identified birth cohorts at higher risk of infection and death relative to the general population, such as older adult exposure to unscreened blood products or unsterile vaccination injections	1 Antibody tests should be offered to all adults in this birth cohort. 2 In FIND studies, one-step screening and antibody rapid diagnostic tests are shown to reduce patients who may be lost to follow-up visits. 3 In FIND studies, when patients take rapid diagnostic tests, the results are given on the same visit. If a patient tests antibody positive, then two samples are taken: one for RNA and one for liver staging. Patients who return can be given their RNA and liver staging results on the same visit, then assessed for treatment.

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Diagnosing HCV in key affected populations

People who are disproportionately affected by HCV should be prioritized in national testing strategies:

- People who receive hemodialysis
- People who have had a blood transfusion or received blood products that may not have been screened by national blood banks
- Health professionals exposed to blood products
- People living with HIV
- Men who have sex with men
- Transgender or gender non-conforming people
- People who inject or use drugs (and their sexual partners)
- Women of reproductive age (due to lack of preventative vaccine and prophylaxis to prevent parent-to-child transmission of HCV)
- Incarcerated persons
- Sex workers

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Diagnosing HCV in key affected populations

- Screening and testing wherever people are receiving services links them to other essential prevention, sexual health, and harm reduction services.
- Different populations will require different strategies and outreach to conduct HCV screening.
- A combination of targeted screening among key affected populations and universal screening in settings with high prevalence, such as prisons, harm reduction sites, overdose prevention centers, and migrant or detention centers, could reduce transmission and work toward elimination.

Peer-led, informal, safe, community-friendly discussions about HCV and referral to services could be more appropriate, especially in current stigmatized, criminalized contexts.

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Diagnosing HCV in key affected populations

- Harm reduction services in the response to HIV can be scaled up for HCV, yet these services need to be expanded and adapted according to changing drug use patterns in your country.
- People who use stimulants, including MSM, recreational users, participants in the ‘chemsex’ scene, and sex workers, may be accessing care through sexual health clinics.
- People conducting screening and counseling need to consider the range of higher-risk behaviors and that people who use drugs and their sexual partners should be offered comprehensive health services, including testing.

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Diagnosing HCV in key affected populations

- Community leaders, such as mentors or “house mothers or fathers” for LGBTQ+ youth, should be part of outreach and screening strategies.
- Prison health budgets are limited for the full range of HCV care. In this setting, ‘opt-out’ HCV screening can be offered to everyone. This gives incarcerated individuals the choice not to take the antibody test. ‘Opt-out’ HCV screening can link people to confirmatory testing, treatment, and care following their release from prison.

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World Hepatitis Alliance

Find The Missing Millions.

#findthemissingmillions

To raise awareness the World Hepatitis Alliance, a global patient advocacy organization, launched the global 'Missing Millions' campaign. HCV advocates across the civil society spectrum can take part in the campaign on World Hepatitis Day (every 28th of July) or any hepatitis C-related events in your country.

Campaign objectives:

1. To raise awareness of the importance of increasing diagnosis and linkage to care
2. To encourage people to get tested
3. To underscore the need for national testing policies
4. To educate and inform wider audiences about viral hepatitis, with a specific focus on prevention, treatment and testing

Sample messaging:

"300 million people living with viral hepatitis don't know it. Unless detected and treated, it can lead to disease, cirrhosis or liver cancer. Get tested."

Advocacy Exercise

Discussion questions:

- Do you know where people can get tested for HCV in your community?
- What questions should people ask their doctors to know their HCV status?
- Does the doctor take time to explain the different tests?
- Are there free testing sites? If not, how much do the tests cost?

Action steps:

- What can we do to make HCV testing easier to access?
- What can we do to increase access to expensive tests?
- What are some good examples of where people can be tested outside a laboratory or central hospital?

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Minimizing steps to diagnosis

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 (screening) test should be tested for RNA automatically (known as reflexive testing);
2. A liver staging test: FibroScan, APRI Score (a formula that calculates the aspartate aminotransferase [AST] to platelet ratio index), FIB-4, or other test should be done to determine the level of cirrhosis; and
3. The appropriate DAA regime should be provided.

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Minimizing steps to diagnosis

- In many settings, especially those without access to pangenotypic DAAs, the numerous steps to diagnosis, treatment initiation, and test-of-cure at week 12 or 24, after treatment, are complicated for the patient

  = result in losing patients to follow-up visits
- Often, many patients from marginalized populations who receive an HCV antibody test do not return for confirmatory testing
- When antibody and confirmatory testing is only available at central labs, this presents costly barriers that require patients to take a lot of time and to sometimes travel great distances.

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Minimizing steps to diagnosis

- Decentralized testing, such as wherever people are receiving their services, and can retain people in care
- When simpler diagnostics become more available, the HIV, sexual health, and harm reduction infrastructure can be leveraged for HCV testing.
- This creates opportunities to shift and expand diagnostics tasks, such as conducting blood tests, from physicians and nurses to other health professionals, including community health workers and peer educators, with the appropriate training.

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Minimizing steps to diagnosis

Adding Steps: Adding Costs

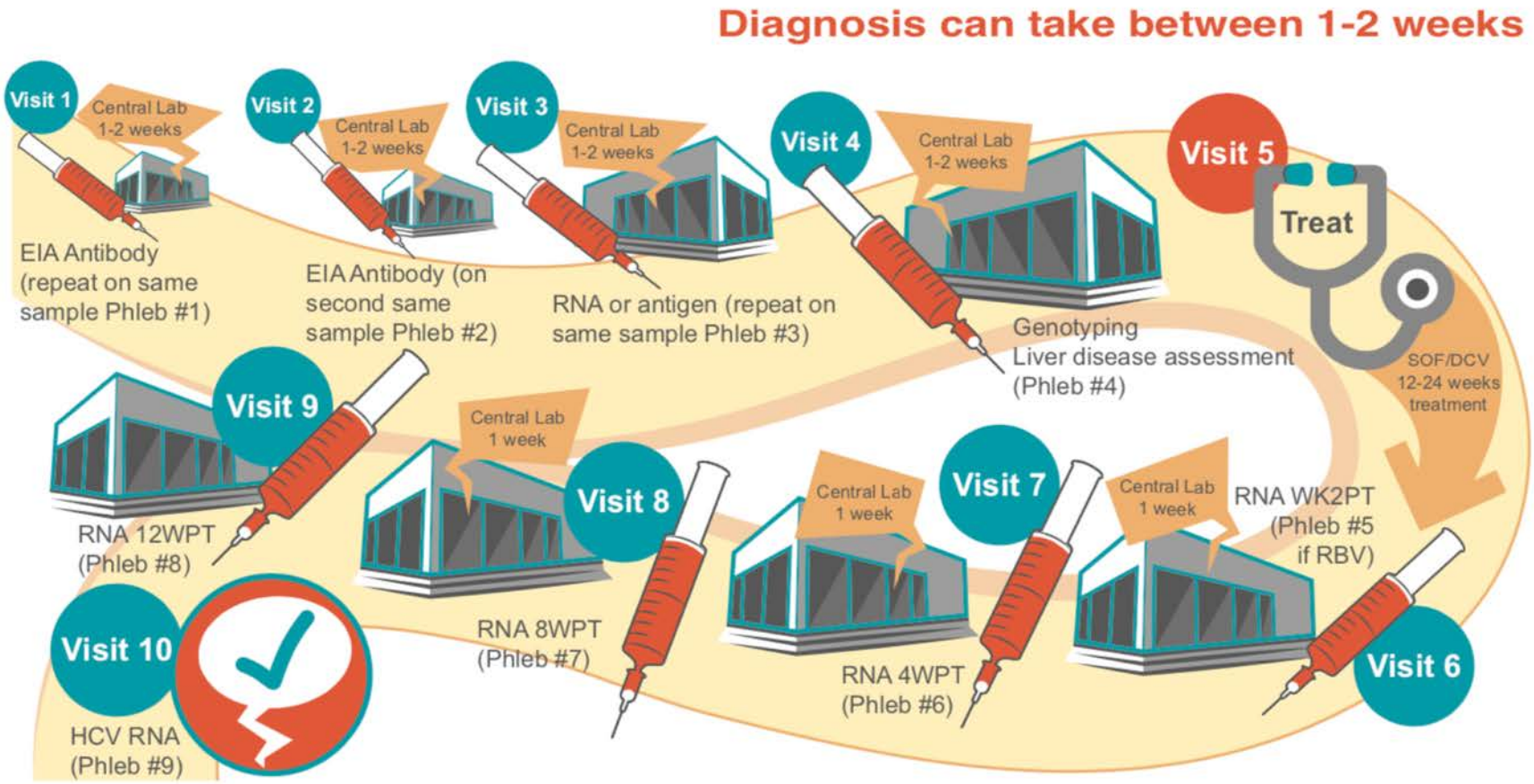

Figure 3. Example of previous, complicated diagnostics pathway.[52]

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Minimizing steps to diagnosis

- The steps to diagnosis could be reduced by taking a sufficient quantity of a patient's sample so that when a patient has a positive antibody test, the sample, if correctly stored, is automatically ordered for confirmatory (RNA or cAg HCV) testing (also known as **reflex testing**).
- The same sample could be used for liver disease staging, too.
- Patients below or above a FIB-4 score of 3.25 would start treatment. Someone with a FIB-4 score higher than 3.25 should be assessed for cirrhosis and other liver complications.
- Confirmation can be done by qualitative ("positive"/"negative") RNA tests, which may have reduced sensitivity but a shorter time to result.
- The extent of liver damage determines the length of DAA treatment. In resource-limited settings, the generic pangenotypic combination of sofosbuvir and daclatasvir is a cost-saving, effective regimen.
- With a pangenotypic regimen, genotype testing would not be necessary.
- RNA tests to confirm that a patient achieved sustained virological response should be conducted at week 12 (or week 24 for patients with cirrhosis).

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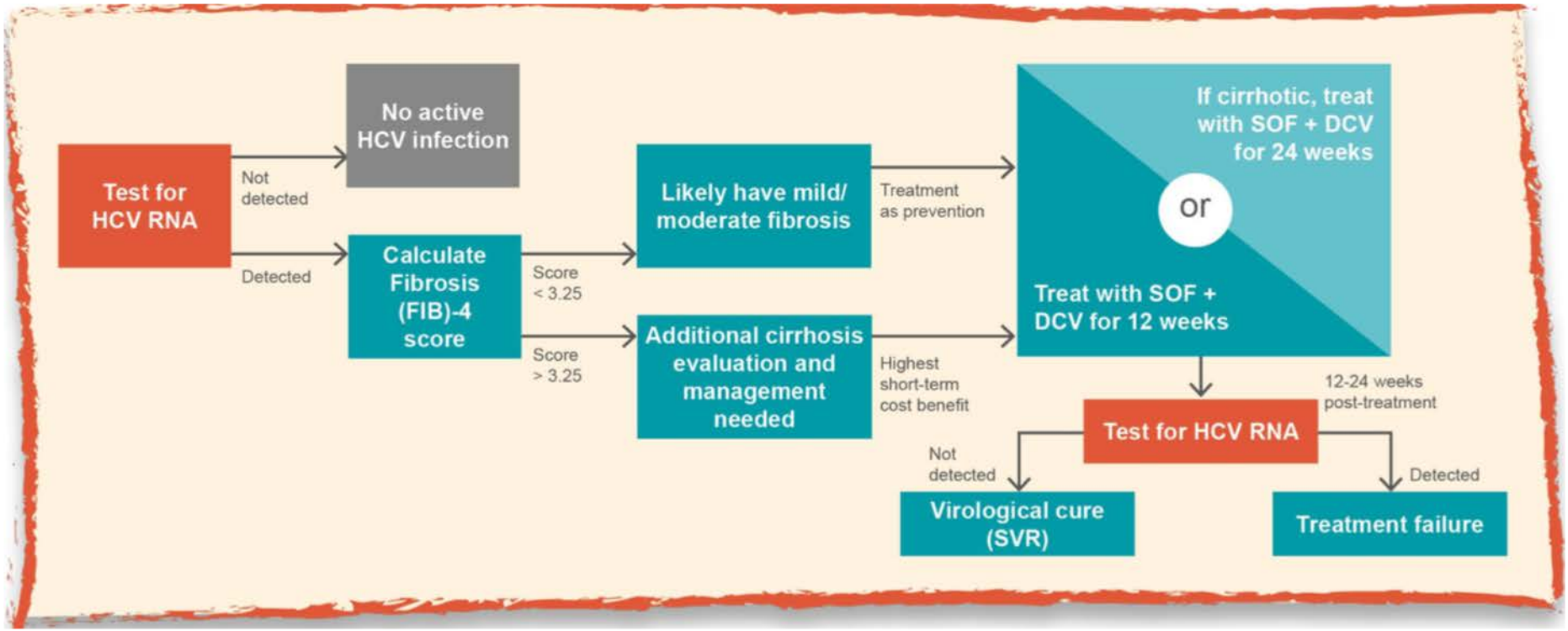
Minimizing steps to diagnosis



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Minimizing steps to diagnosis

- In communities or settings with high HCV prevalence, such as among people who inject drugs or in prisons, it might be advisable to skip antibody screening and start with confirmatory testing, in order to prevent loss to follow up and to increase treatment starts.

In LMICs, an example to reduce number of patient visits:

- **Visit 1:** HCV antibody and PoC RNA tests can be conducted along with liver disease assessment, such as APRI, FIB-4 or FibroScan.
- **Visit 2:** Patient receives test results, check-in and counseling with physician/healthcare professional, and prescription for generic pangenotypic DAA.
- **Visit 3:** SVR12 test depending on whether patient completed treatment.
- **Follow-up visits:** For people who may be at risk of reinfection or who have advanced liver disease, re-testing and monitoring for liver cancer would need to be performed.

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Minimizing steps to diagnosis

- **Decentralization** brings testing closer to people, wherever they may be receiving services, and provides opportunities to link and retain patients in care.
- In urban areas, **one-stop shops** are poly-clinics that offer all HCV test-and- treat services or multiple healthcare services in one clinic.
  - HCV care is being integrated into HIV, sexual health, and family planning clinics, and integration can be considered for expanding HCV care to rural and remote areas.
- In countries with existing harm reduction programs, HCV is being integrated at harm reduction centers and in mobile clinics that serve people who inject drugs.

- Other settings to decentralize services and offer community-based testing/care:
  - Primary healthcare
  - Community health clinics
  - Needle syringe exchange programs
  - Substance use disorder treatment centers
  - Overdose prevention sites
  - Prisons
  - Homeless shelters
  - Youth centers
  - Pharmacies

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Minimizing steps to diagnosis

Telemedicine and the Extension for Community Health Outcomes (ECHO) model

- Involves training physicians, physician assistants, nurses, pharmacists, and educators in HCV, using web-based software.
- Clinical knowledge is brought to patient
- Physicians who are treating patients with HCV are responsible for managing patients' health outcomes through 'teleECHO' clinics to provide case-based guided practice.
- Data, health outcomes, and the cost-effectiveness of programs are collected centrally, such as a main city with access to specialists and resources.

The ECHO model is one way to build capacity of general practitioners and auxiliary health professionals, complement the decentralization of diagnostics, and help improve HCV treatment uptake.

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Minimizing steps to diagnosis

Task-shifting

- Decentralization of testing and treatment requires massive training and capacity building of a wide range of healthcare workers.
- Continued medical education and community health education need to be included in national HCV programs.
- Testing and treatment guidelines need to be simplified so that service delivery can be shifted to other health professionals (**task-shifting**) and made more efficient.
- People living with HIV/HCV or most affected by these diseases should be consulted and included in the design, leadership, and decision-making in the HCV response.
- Policy and regulatory changes should be fast-tracked:
  - Shifting RDT testing to community health workers through training and simplified reporting systems
  - Lifting restrictions on prescriber status for DAAs, and
  - Establishing standardized medical certifications required for administering HCV care by other healthcare workers.

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Minimizing steps to diagnosis

Task-shifting also involves:

- Clinical mentoring and supportive supervision to healthcare workers
- Opportunities to evaluate competency and performance

> People with lived experience, such as peer educators, play a critical role in scaling up diagnostics and increasing the number of people cured.

- Shifting testing tasks to more community health workers and peer educators, with the appropriate training and fair remuneration, can be an efficient and cost-saving way to help with patient follow-up and retention in care

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Advocacy Exercise

Discussion questions:

- What steps can be minimized to simplify the diagnostic pathway in your country?
- What are the guidelines toward viral load adherence?
- What are the guidelines toward genotype testing?

Action steps:

- What ways can community members contribute to reducing the number of patients lost to follow-up?

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Diagnostics Access and Barriers: Social Determinants of Health

- Health inequities stem from societal conditions, known as the social determinants of health.
- Inclusive, equitable, and healthy communities and the health of a person determined by:
  - ✓ Economic status
  - ✓ Education
  - ✓ Housing conditions
  - ✓ Employment and decent work
  - ✓ Environment and access to clean natural resources
  - ✓ Fair legal system, and
  - ✓ Whether people are treated with respect and dignity

- Criminalization makes it nearly impossible for gay, MSM, and gender-nonconforming people, people who use drugs, and sex workers to access preventative and treatment services for HIV, HCV, and sexually transmitted infections.

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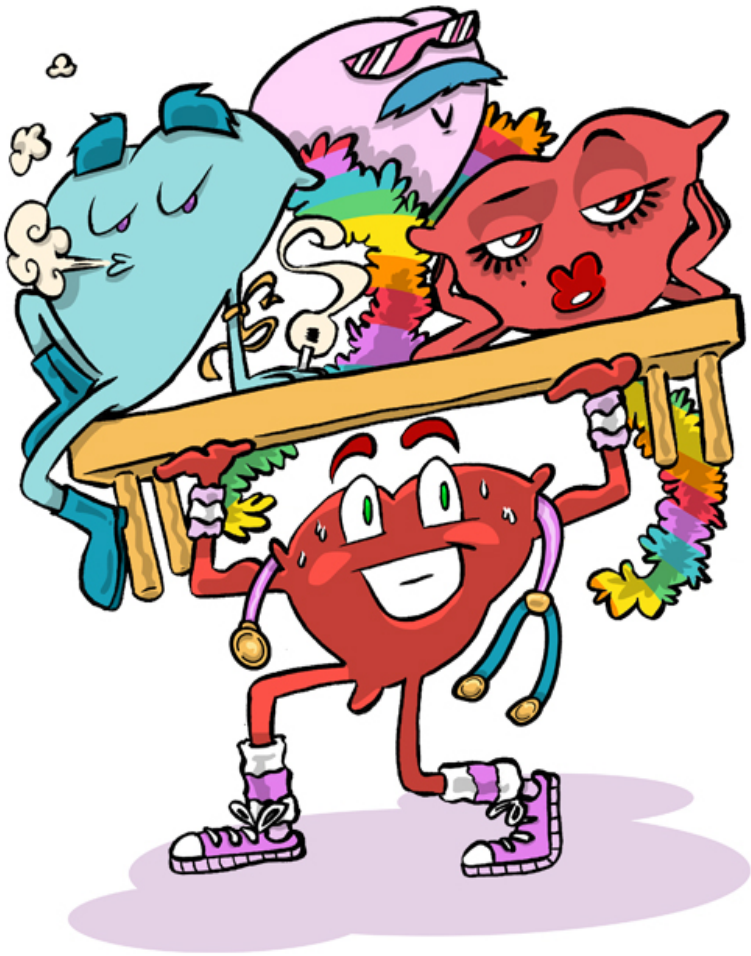
Diagnostics Access and Barriers: Health System Challenges

Stronger health systems require:

- a deeper understanding about viral hepatitis among the general public as well as medical providers;
- additional trainings and cultural competency by medical providers about affected communities;
- easily accessible testing;
- streamlined procurement;
- more affordable tests for public and private laboratories;
- insurance coverage for diagnostics to remove patient out-of-pocket costs; and
- social support for patients to meet their follow-up visits.
    - This includes prevention and harm reduction counseling, employment, housing, legal, transportation assistance, child care, and other social services.



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Diagnostics Access and Barriers: Health System Challenges

- Strong political commitment is needed to put HCV on national and global health agendas.
- Stronger surveillance, monitoring, and reporting systems should also be part of efforts to strengthen health systems for the HCV response.
- The quality of data on HCV prevalence, access to prevention tools, the availability and pricing of diagnostics and DAAs, and what is included in national HCV plans dramatically differs across countries.
- Online dashboards that document national health indicators offer opportunities for affected communities to discuss and provide feedback about the results and hold health systems and public officials accountable. Dashboards have become useful, transparent tools for civil society to monitor HIV and HCV responses.

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Community monitoring of the HCV care cascade, including testing and treatment uptake, is an essential part of tracking progress toward national elimination targets

Who counts in our national hepatitis plans?

Activists and community members need meaningful ways to talk with policy-makers about how to improve national hepatitis targets. Remember to ask your Ministry of Health when monitoring results along the hepatitis C care cascade:

What does our epidemic look like in our country? How do you take into the account our issues and the concerns of key populations? What reliable data and sources are being used?

What opportunities exist for strengthening the political education of patients, people at risk, and community members to meaningfully participate in the national hepatitis/ elimination process?

How are people accessing accurate health information on the hepatitis C virus? How is national progress on hepatitis C disseminated to key populations? What mechanisms are in place for community members to provide feedback on the results?

Who can access and who is covered for using affordable needle syringe programs, opioid substitution therapy, and overdose prevention services?

Who can access affordable hepatitis C testing? How much do people need to pay out-of-pocket?

In active hepatitis C antibody screening campaigns, what is the percentage of people who have received confirmatory testing? What is the percentage of people who have been diagnosed?

Where is hepatitis C testing available? What measures have been taken to shift testing from hospitals to alternative, point-of-care settings?

Community monitoring of the HCV care cascade, including testing and treatment uptake, is an essential part of tracking progress toward national elimination targets

How are people diagnosed with hepatitis C counseled and linked to affordable treatment? Are high quality, generic, direct-acting antivirals available? How much do people need to pay out-of-pocket?

How many people have been treated with direct-acting antivirals? How many people have been effectively cured by achieving a sustained virological response?

How many people are engaged in hepatitis prevention programs after they completed treatment?

How many people are monitored post-treatment for liver damage and liver cancer?

How many reinfections have been diagnosed and treated?

How are we funding the viral hepatitis response? What is the national budget for viral hepatitis? What is included in the viral hepatitis budget?

What policy reforms, trainings, awareness-building, and other measures have taken place to create an enabling environment for stigmatized and marginalized communities to seek essential healthcare and other services?

- Another online crowdsourcing platform, mapCrowd, is designed to gather and publicize the most up-to-date country-level information on HCV.

mapCrowd
Online global data on hepatitis C

- Providing free access to national, regional, and international data, **mapCrowd** allows users to draw visual comparisons between countries, using interactive graphs, tables, and maps.
  - In-country contributors who collect the data must build relationships and interact with health authorities
  - Process of asking the specific, pointed questions on diagnostics and treatment availability and pricing are an advocacy tactic in itself, in that they provoke a public response.

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Advocacy Exercise

Discussion questions:

- What are the top three barriers to achieveing diagnosis in your community?
- Do members of your community access diagnostics without discrimination?
- How do medical providers treat members of your community when administering HCV tests?

Action steps:

- What steps are needed to lift treatment restrictions in your country?
- How can we guarantee social supports and assistance for people seeking HCV testing?
- What are some apporaches that can reduce the number of patients who drop out between screening and confirmatory testing visits?

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Diagnostics Access and Barriers: Monopolies and Licensing Barriers

- There are only a few diagnostics companies with NAT platforms that can confirm HCV diagnosis.
- Abbott, Roche, and Cepheid are the primary companies with PoC viral load or lab-based core antigen devices.
- Having only one or two companies in a country creates a monopoly condition that allows them to set high prices on the sale of their platforms as well as the testing kits/consumables required.
- They may also add high fees for equipment maintenance, repairs, and the specific reagents and cartridges required.
- Their own cartridges may fit only with their platforms, locking countries into paying their prices.

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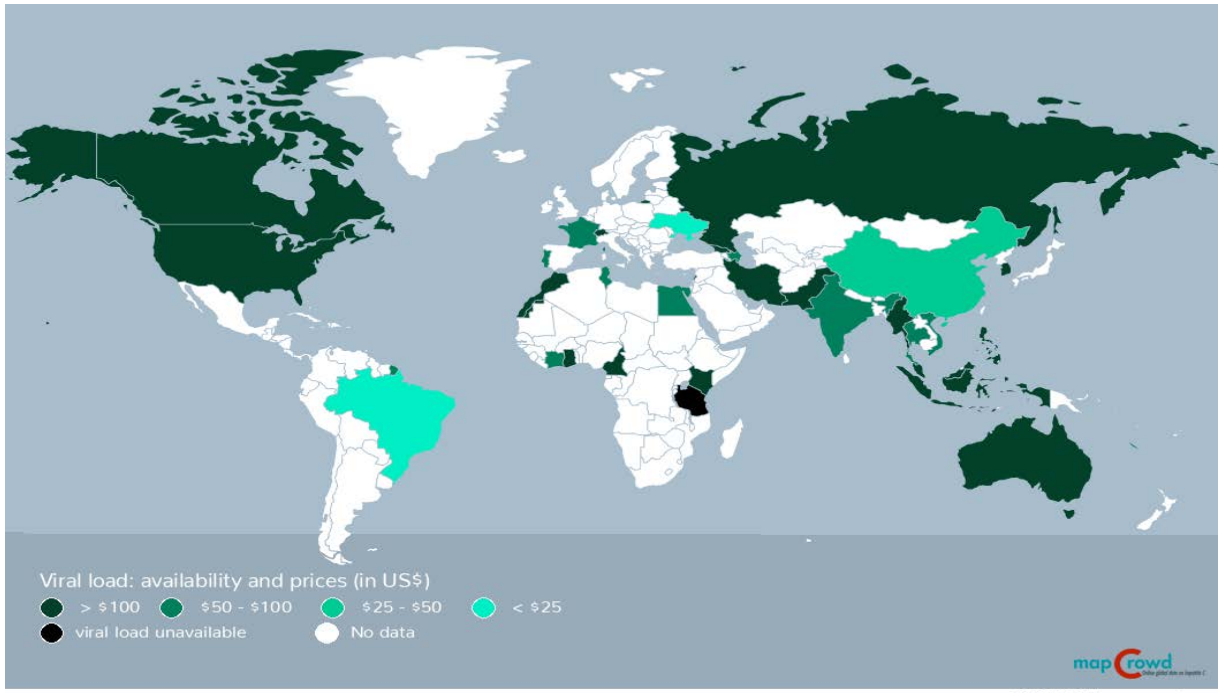
Diagnostics Access and Barriers: Monopolies and Licensing Barriers

- Some platforms may be available to diagnose only specific diseases, such as HIV or TB, depending on how they are procured and funded by donors.
- Abbott, Cepheid, and Roche have multiplex platforms, but exclusive licenses might permit countries to run only HIV, HCV, or TB tests.
- As a result, limited viral load availability and pricing that is unaffordable in LMICs:



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Diagnostics Access and Barriers: Monopolies and Licensing Barriers

- Instead, countries could renegotiate their agreements to open up the platforms for HBV or HCV viral load testing.
- Countries could consider open licensing agreements. The BLINK company has developed an open-license, polyvalent diagnostics platform (in early prototype stage).
  - It has been developing a PoC HCV RNA assay that can return results in less than 20 minutes
  - Any developer can develop its own assay for any molecular diagnostics and then use (or 'rent') the BLINK technology to perform the chemical reactions needed to diagnose the disease.
  - Aligns with integrated service delivery approach and could bring down diagnostics costs if multiple tests could be bundled together during procurement.

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Diagnostics Access and Barriers: Monopolies and Licensing Barriers

- Patent landscape for diagnostics requires further study
  - Product and process patents for Abbott, Roche, Qiagen, Siemens, bioMerieux, and Life Technologies expired
- Development of both diagnostics and medicines relies on public and philanthropic funding to invest in the earlier, riskier stages. Yet once proven as viable candidates, they may be acquired by larger companies and the benefits privatized under patents or exclusive licensing.
- This is the case for FibroScan and FibroTest/ActiTest (both under patent), which were developed by French public research institutions and universities. The companies set extortionate pricing, making these technologies unaffordable for many LMICs.
- As these devices are not widely available in LMICs, countries can use FIB-4 and APRI liver function tests to assess liver damage, but they require labs and can add additional steps and time before a patient is diagnosed and started on treatment.

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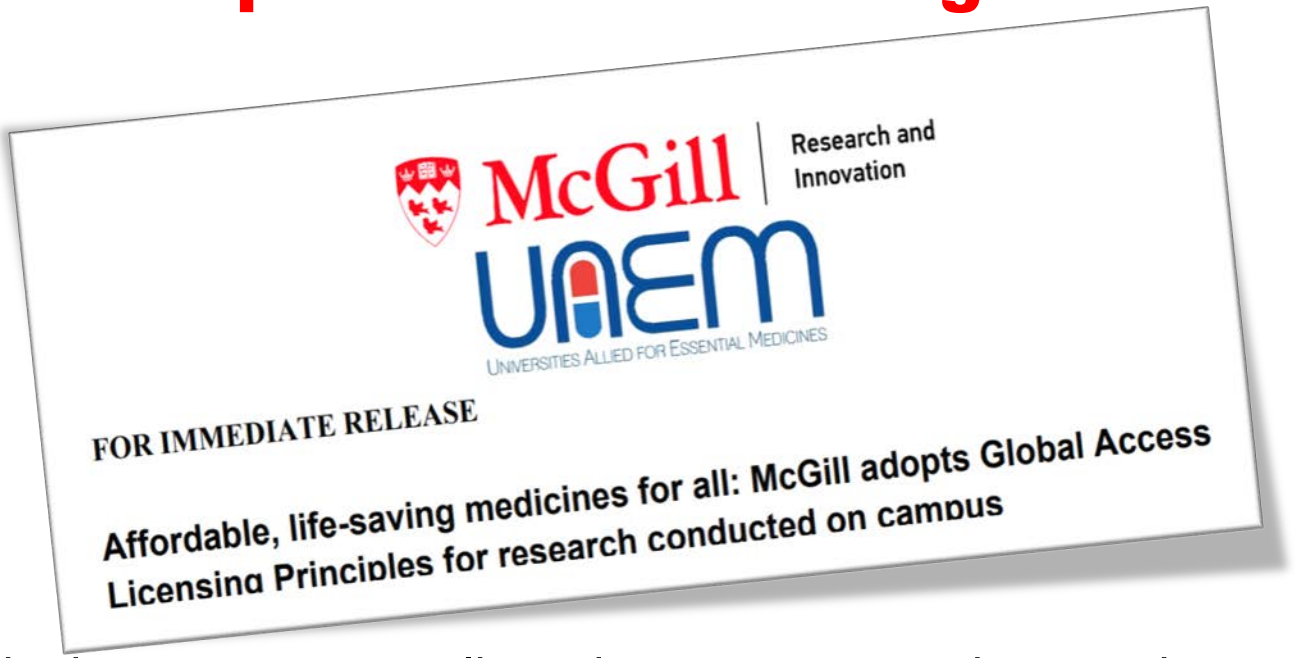
Diagnostics Access and Barriers: Monopolies and Licensing Barriers


McGill | Research and Innovation

UAEM
Universities Allied for Essential Medicines

FOR IMMEDIATE RELEASE

Affordable, life-saving medicines for all: McGill adopts Global Access Licensing Principles for research conducted on campus

- Public institutions can prepare licensing agreements that require royalty payments for use of technologies that they financed. Revenue can help sustain these institutions.
- Student advocacy through Universities Allied for Essential Medicines adopted a Global Access Licensing Framework at universities in Canada.
  - The Framework works towards transparency and equitable licensing on medicines in order to increase access in LMICs, and similar approaches can be applied to open up licensing on diagnostic technologies.

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Advocacy Exercise

Discussion questions:

- What are the licencing agreements for the diagnostics available in your country?
- What alternative agreements or flexibilities are available that will expand access to diagnostic technologies?

Action steps:

- What steps are needed to prevent monopolies on diagnostic technologies in your country?
- What partners and campaigns can inform our efforts for open licence platforms?

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Diagnostics Access and Barriers: Pricing Barriers

- A diagnostics platform can cost tens of thousands of US dollars, which can be priced out of reach for LMICs.
- Machines procured through international donors still require costly cartridges, reagents, and maintenance, and only the disease areas that fit within the scope of the donor-funded project may be covered.
- Distributor markups, value-added taxes, and customs fees present additional barriers.
- Local distributors may apply additional markups, resulting in increases to the final price of the tests.

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Diagnostics Access and Barriers: Pricing Barriers

Companies set HIC prices on diagnostics that many LMICs cannot afford

Example: Viral load tests can range US$15-200 per test (including confirmatory + post-treatment monitoring)

Country	HCV prevalence among people who inject drugs	RNA public health system price (USD$)	Fibroscan public health system price (USD$)	Per Capita Gross National Income/month (USD$)
Portugal	3%	56	28.30	20,530
USA	12%	78.77 (329 private)	46.14	55,980
Brazil	19%	8.50	6.30	9,850
Myanmar	7%	160	50	1,160
Malaysia	19%	120.84	144	10,570
Kenya	4%	130.84	34	1,340
Tanzania	1%	Unavailable	Unavailable	920

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mapCrowd.org data

Diagnostics Access and Barriers: Pricing Barriers

Transparency on diagnostics prices and volume-based discounts that companies offer to different countries is needed to inform government negotiations and procurement decisions.

Test	Prices
Rapid diagnostic test	= US$1
Test to confirm active infection Nucleic acid testing (NAT)	= US$15 to US$200
Test to assess level of fibrosis APRI or FIB-4	= US$0.83 to US$3.70
Fibroscan	= US$0 to US$200
FibroTest	= US$50
Test to evaluate efficacy of cure Nucleic acid testing (NAT)	= US$15 to US$200
Genotyping	= US$10 to US$350
Total average for tests needed to confirm HCV diagnosis and cure	= **US$44 to US$951**

Figure 5. Price range of HCV diagnostics in standard use.[80]

Based on data from in-country advocates

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Diagnostics Access and Barriers: Pricing Barriers

- To help health budgets cover diagnostics costs, countries could waive value-added taxes and customs fees for essential diagnostics aimed at combatting infectious diseases
- Countries could also set caps on distributor markups, thereby putting a price control and reducing end prices on the tests.
- Countries can bundle tests and procure diagnostics commodities in bulk. This can help with price negotiations and with healthcare cost savings.

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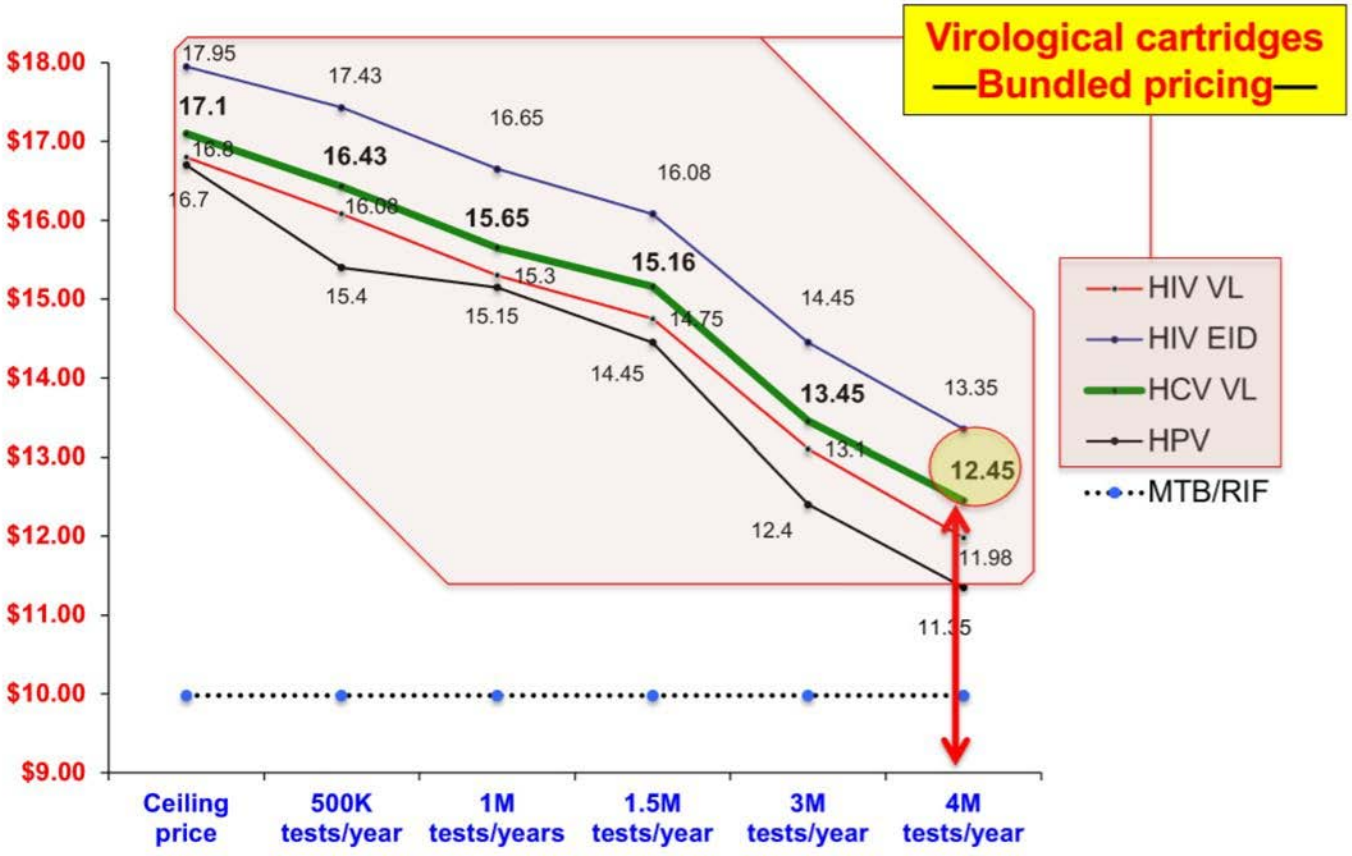
Financial barriers to diagnosis

High volume > lower unit prices



Source: Fajardo E. 2018 June.

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Advocacy Exercise

Discussion questions:

- What are the out-of-pocket costs in your country for diagnostics?
- What tests are covered by national insurance schemes?

Action steps:

- How can we use diagnostics pricing information from similar countries to add pressure on our government during procurement negotiations?
- What are some approaches that can reduce drop off of patients between screening and confirmatory testing visits?

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Activist Lessons

People living with HCV and community voices need to be centered in HCV elimination efforts

- Diagnostics and treatment literacy for people disproportionately affected by HCV is essential to ensure communities are represented and meaningfully participate in national elimination planning and policy processes.
- Community engagement should involve opportunities to strategize ways to overcome diagnostics barriers, regular consultations, and provide feedback on mechanisms to improve the implementation of national HCV plans.

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Activist Lessons

Determine the national epidemiology and tailor the HCV response to communities who are disproportionately affected

- Communities need to be included at the start and in all phases of developing national HCV strategy and response. They can identify opportunities for integrating HCV into existing services and the kinds of trainings and skill-building required for including community health workers and peer educators in the HCV response.
- Peer-led and peer-designed programs are more effective in linking and retaining often overlooked and underserved communities to treatment and care.
- Decentralized testing services and peer-led programs would need to use simpler diagnostic tools, such as viral load with fingerstick or dried blood spot samples.

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Activist Lessons

Decriminalize the communities most affected and destigmatize HIV/HCV

- Need massive policy reforms that decriminalize key affected communities: people who use and inject drugs, MSM, transgender and gender nonconforming people, sex workers, immigrants, and migrants.
- Drug policy reforms must decriminalize personal use, possession, and low-level drug-related offenses.
- Harm reduction services should be expanded for people who use and inject drugs to access sterile injecting and smoking equipment, treatment for substance use disorders, and other services such as mental health and social services.
- Access to NSPs and OST while taking DAAs can prevent reinfection and onward transmission of HCV.

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Activist Lessons

Learn from HIV activism and response

- There are opportunities to leverage the HIV and harm reduction infrastructure and resources as part of the HCV fight.
- Many diagnostics platforms, lab resources, medical trainings, and community education/outreach can be utilized for the HCV response.
- Massive awareness raising, screening ("Know Your Status") campaigns, and prevention messaging can integrate HIV and HCV.
- Additional community health workers and peer educators would need to be increased and trained, but this approach can be cost-saving and effective in retaining patients in care.
- We can learn from HIV activism in deploying numerous access-to-medicines strategies, such as **challenging patents** and issuing **compulsory licenses** to win access to generic DAAs.

Activist Lessons

Just do something!

- Even if a country is off track of the WHO HCV targets by 2030, it could use the 2020 targets as milestones in its national response.
- Multiple strategies can be undertaken by Ministries of Health in countries, such as conducting awareness-raising campaigns and providing medical/community trainings, while government agencies work on regulatory and approval processes that open up greater access to diagnostics and DAAs.
- Health programs must focus on retaining people in care while they wait to start treatment.
- Lack of access to DAAs in the public sector or waiting for a windfall in funding is not an excuse to delay planning and implementation of an HCV response.

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Activist Lessons

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Activist Lessons

"Take back our diagnostics"

- Diagnostics developed with public (tax revenue) and philanthropic funding should be kept as public goods so that they are affordable and accessible for every patient and every country.
- FibroScan and FibroTest/ActiTest were developed by French public research institutions and universities but are patented and exclusively licensed.
- The patent and licensing barriers set extortionate pricing, making these simpler, PoC liver disease assessment technologies unaffordable for many LMICs.
- FIB-4 and APRI (recommended by the WHO) can still be conducted in resource-limited settings, but they require laboratory blood tests and can add additional steps and time to the diagnostics pathway.
- Open diagnostics platforms for viral load, such as for HIV, HBV, and HCV, can generate competition and lower prices for tests.
- Countries can bundle tests and procure diagnostics commodities in bulk.

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Activist Lessons

Budget and funding advocacy provokes and kickstarts dialogue with policy makers

- Budget advocacy involves determining advocacy targets at the Ministries of Finance and Health in countries and directing specific, technical questions about spending, e.g., for HIV/HCV and harm reduction, during budget cycles.
- Several arguments can be effective:
  - Early treatment can save healthcare costs in the long term
  - Increasing and fairly remunerating peer educators can employ knowledgeable, experienced skilled healthcare workers while retaining patients from key affected communities in care
- Advocacy toward donors needs to be ramped up to secure funding for HCV monoinfection
- Civil society delegates on boards of multilateral agencies and community representatives (e.g., Country Coordinating Mechanisms of the Global Fund) can raise concerns and offer strategies to expand access to diagnostics and treatment.

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Key Messages and Demands

- Decriminalize drugs and end the war on drug users!
- Universal antibody screening should be used in high-prevalence settings.
- In high-prevalence populations, it could be possible to skip antibody tests and start with confirmatory testing, then start treatment once HCV diagnosis is confirmed.
- Skip genotyping if pangenotypic DAAs are used.
- Remove HCV viral load monitoring until week 12 to confirm SVR. DAAs achieve SVR in over 95 percent of patients and viral load monitoring can be skipped.
- Treat everyone! Reinfections will occur and must be considered in national responses. People should be offered unlimited treatment regardless of whether they have been reinfected.

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Key Messages and Demands

- ‘One-stop shops’ can offer a range of services: HIV/HBV/HCV screening, testing, and treatment; harm reduction services; and referrals to mental health and other social services.
- Integrate HBV vaccination and sexual health services for MSM and PWID.
- Peer-led and peer-designed programs are an important part of achieving national HCV elimination. They would require continued training and education, task-shifting key aspects of HCV care, and buddy programs that aim to refer peers to services.
- Housing and employment are healthcare.
- Gender-sensitive harm reduction services need to include intimate partner violence, childcare, counseling, and legal aid programs for womxn and gender nonconforming people who use drugs.
- National HCV budgets need to estimate costs to test and treat the populations disproportionately affected by HCV, such as people who inject drugs, incarcerated people, and MSM.
- National HCV dashboards can be transparent and participatory tools for communities to be involved in the monitoring of the HCV care cascade and the implementation of national elimination plans.

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Activist Tools

- Crowd-sourced data/surveillance

www.mapCrowd.org

- Calculator on cost-effectiveness of treatment

https://www.hepccalculator.org/

- Dashboard comparing HCV elimination policies

http://www.letsendhepc.com/

- PREP-C Assessment Tool for HCV adherence (Mt Sinai, New York)
- HepCure Patient Mobile App (maybe available only in HICs)
- NOhep Advocacy Toolkit

https://www.nohep.org/wp-content/uploads/2018/05/Race-to-2030-Advocacy-Toolkit-online-FINAL-1.pdf