Optimizing HCV linkage to care: Experiences implementing laboratory-based reflex testing

Hep Test webinar series
27 January 2022
In May 2021, the World Health Organization (WHO) released data showing that only 21% of those living with hepatitis C (HCV) worldwide had been diagnosed, and only 13% of those infected had received treatment by the end of 2019.

Testing is key for preventing HCV as well as for linking affected persons to care and treatment. In the effort to eliminate viral hepatitis as a public health threat by 2030, HCV programs have introduced viral load testing to reduce steps in the diagnostic pathway and to improve linkage to care. HCV antibody testing alone (anti-HCV) does not distinguish between current and past HCV infections. Viral load (RNA or antigen) testing is required to determine current HCV status. WHO guidance currently recommends single-assay testing, with a positive antibody test leading to confirmatory testing for active viremic infection. But this two-step process takes time, and some patients drop out or are lost to follow-up before treatment can be initiated.

The solution could be laboratory-based HCV reflex virologic testing, a testing algorithm in which patients have only a single clinical encounter and only one blood draw or specimen needs to be taken. HCV reflex testing has the potential to simplify the testing process and strengthen linkage to care. If the sample for anti-HCV in the lab comes back positive, then the same (existing or duplicate) sample is used for a lab-based HCV viral load test, without the patient having to come back in for a second specimen collection.
The World Health Organization (WHO) has asked the Coalition for Global Hepatitis Elimination (CGHE) to develop a body of programmatic evidence to help inform WHO guidance on lab-based HCV reflex testing. In its sixth Hep Test webinar, CGHE presented three pioneering efforts to implement the reflex testing process in the United States, Canada, and England. The case studies highlighted operational considerations faced by clinics and laboratories as they implement this new process. A panel discussion following the presentations examined logistical challenges, costs and economic benefits, equipment requirements, and the overall impact of HCV reflex testing on linkage to care and outcomes. Does lab-based reflex testing increase testing numbers, improve diagnoses, and lead to faster treatment? Panelists and presenters discussed their respective experiences and findings.

**Key takeaways:**

- Lab-based HCV RNA reflex testing is the future of HCV testing: it offers a streamlined process for the patient and is associated with earlier treatment initiation, though workflow on the lab side remains complicated. Where diagnostics are concerned, there is little utility for lab-based testing of antibodies alone.
- Clinics and care providers should be encouraged to request HCV reflex testing by making it the primary (or only) option when ordering HCV labs. Doing so could eliminate confusion on the provider’s side, though billing can still pose challenges: the cost of the test often depends on the first round of test results, which determine what additional tests are or are not required.
- With this form of reflex testing, the primary operational challenges fall to the lab. Systems should be designed around specimen storage, taking care to avoid contamination and to minimize or streamline blood volume. A single-draw lab bundle is useful for health settings but can place logistical burdens on the lab.
- Persons who inject drugs (PWID) are especially difficult to reflex test for HCV because of the difficulty of venous blood collection when multiple tubes are required. Skilled phlebotomists are needed for these blood draws.
- Dried blood spot testing (DBS) can provide an alternative method for reflex testing, but it is not yet validated in the United States. DBS is being used in some outreach settings among homeless and other at-risk populations, such as persons who inject drugs. DBS is the main method of testing for persons who inject drugs in the United Kingdom.
- Although many kit manufacturers and machinery manufacturers continue to offer only plasma testing for HCV RNA, the reality is that serum can be utilized as well. That message needs to be relayed to encourage more testing options and more versatile use of equipment.
• HCV reflex testing has shown to increase linkage to care and support earlier treatment initiation. Additional data is needed to determine the impact of the reflex process on treatment completion/SVR12 labs. Especially for lab-based reflex testing (as opposed to clinic-based), treatment completion remains quite removed from the testing process.

• Despite the many benefits of reflex testing, certain equity issues remain on the treatment completion side, with women and underrepresented groups less likely to complete treatment. Culturally specific case management is recommended to support these populations and decrease loss to follow up.

Panelists and presenters concluded that HCV RNA reflex testing is a ‘low-hanging fruit’—an intervention that should be part of a critical package of strategies to promote uptake across the care cascade. Outcomes are important to keep measuring as this intervention gains traction. The examples and case studies presented in this webinar effectively demonstrated that HCV lab-based reflex testing is programmatically feasible in a growing number of settings, especially when there is strong cooperation between lab and clinic—and between care providers and the communities they serve.
Overview of HCV in Canada:

- An estimated 250,000 people in Canada are living with HCV, and 44% of them (or 110,000) are unaware and undiagnosed.
- Until 2020, 25-35% of those who tested positive for HCV antibodies did not have a follow-up or confirmatory RNA test. This percentage rises to 73% in priority populations (remote locations, indigenous peoples, persons who inject drugs). In British Columbia, in contrast, and thanks in part to harm reduction efforts, just 17% of those who tested positive for HCV antibodies did not receive testing for HCV RNA.
- The Blueprint to Inform HCV Elimination Efforts in Canada notes that “identifying people who are undiagnosed and linking them to care/treatment before they develop HCV complications will decrease the health consequences of HCV” (Canadian Network on Hepatitis C, 2019).

HCV RNA testing workflow proposed ~2019

1. HCV antibody positive on two platforms with strong signals* & first-time positive or no prior HCV RNA testing
2. EDTA plasma available?
   - yes: Perform HCV RNA test on EDTA plasma → Report result
   - no: Perform HCV RNA test on serum sample → If positive, report result → If negative, request for follow-up EDTA plasma

*Centaur ≥11 and Architect reactive

Source: Slide 11 from Dr. Jassem's presentation
HCV reflex testing program at a glance:

- Program planning began in 2017 with a proposal for reflex RNA testing for persons (1) who are first-time antibody positives or (2) who have not been tested for HCV RNA previously. The proposal had three steps: serum PCR verification, implementation, and performance metrics.
- Serum PCR verification was done on Abbott’s RealTime HCV RNA assay. An internal validation at the BCCDC Public Health Laboratory showed good concordance between serum and plasma HCV RNA testing results. But for persons who display low levels of anti-HCV antibodies or who are serum HCV RNA negative, a follow-up blood sample for RNA testing will still be requested.
- Implementation of the new program faced multiple hurdles, including a complex workflow, the need for careful and extensive communications, the need to consider testing history and serology results for affected patients, and the involvement of three separate labs (accessioning, serology, and virology).
- Performance metrics data to date: 1,179 RNA tests were performed in 2020, and 965 were performed in 2021. There were 71.4% positive tests in 2020 and 66.4% positive tests in 2021. The median turnaround time for <99th percentile was 6.12 days in 2020 and 4.9 days in 2021.
- This improved turnaround time is key: before program implementation, the median turnaround time for plasma testing was 47 days.

In British Columbia in 2018, 17% of antibody+ persons did not get tested for HCV RNA

Source: Slide 17 from Dr. Jassem's presentation
Challenges:

- The geographic distribution of the disease is a challenge, making it hard to reach remote communities as well as other priority populations that never make it to clinic or are lost to follow up.
- The program team is still working to gather data on the impact of reflex HCV RNA testing on the cascade of care. Are fewer people being lost to follow up? More data is needed.
- The complexity of the reflex workflow poses challenges. In particular, test result look-back is still a manual process, not yet automated, and teams are stretched by COVID-19.
Reflex testing in clinics for persons experiencing homelessness
Andrew Seaman, Oregon Health & Science University

Overview of HCV in Oregon:
- The fourth highest HCV prevalence rate in the United States
- From 2013-2016, Oregon’s HCV prevalence was 1,560 per 100,000 (the national prevalence was 930 per 100,000).
- In Portland, there is a 26% HCV RNA prevalence among the 14,000 residents served by Central City Concern (CCC), a houselessness services organization.

HCV reflex testing program at a glance:
- Program aims to prevent loss to follow-up once an initial diagnosis has been made. Reflex testing has been available since 2016, but it remains difficult to help this population complete the full treatment evaluation.
- CCC collaborated with LabCorp in 2018 to link pre-treatment evaluation to HCV screening. A unique screening-to-treatment lab bundle was implemented in 2019.
- CCC offers two settings for HCV reflex testing: a health setting screening process and an outreach/opioid treatment program screening process.

Health Setting Reflexive Screening Process

- Labs ordered by intake staff, universal opt-out
- Patients proceed to internal lab
- 100-300 tests / month
- Labs result in HCV provider inbox
- Provider reviews, orders DAA, insurance Prior Auth approval
- Start treatment Visit #2

Visit #1
Labs Ordered -> Lab (Intake Staff)
Phlebotomy (Phlebotomist)
Medication Review (Provider)

Visit #2
Treatment Initiation (Provider or Pharmacist)

Source: Slide 7 from Dr. Seaman’s presentation
Health setting screening process:

- All patients who visit the clinic are screened (through universal opt-out), with labs ordered by intake staff and conducted by a phlebotomist. Venous is the preferred method, though dried blood spot testing is a second option.
- If initial test comes back positive, then the sample automatically reflexes to the lab for additional evaluation.
- 100-300 tests per month conducted. Lab results come to the HCV provider inbox. The provider reviews results, orders direct acting antivirals (DAAs) if needed, and moves forward with obtaining prior authorization approval if applicable.
- At second visit, patient receives treatment, initiated by provider or pharmacist.
- Data analysis showed no difference in treatment initiation across racial/ethnic groups, but there was less equity in treatment completion / SVR12. Female-identifying persons were less likely to complete treatment/SVR12. People with alcohol use disorders and opioid and stimulant use disorders were more likely to be screened and treated.

Outreach / Opioid Treatment Program Reflexive Screening Process

- Specimens collected by outreach workers on street, in methadone clinics, or self-testing (supported housing)
- Incentive provided at time of results relay
- Automated reflex testing
- 50-80 tests / month

Source: Slide 17 from Dr. Seaman’s presentation
**Outreach setting screening process:**

- Dried blood spot sample specimens are collected by outreach workers on the street, in methadone clinics, or are performed through self-testing in supportive housing.
- Positive test results are reflexed automatically to a central lab, with RNA results in 1-2 weeks.
  - Although HCV RNA is available on DBS testing outside US, it is not yet validated in the US. CCC partnered with Molecular Testing Labs in Vancouver to validate HCV RNA with reflex.
- The patient receives a $15 incentive from an outreach worker during the second visit, when results are given. Liver assessments (FIB-4) must still be completed prior to treatment being initiated.
- 50-80 tests a month conducted. Cost and billing structure for this process are similar to phlebotomy, but there are also programmatic costs associated with outreach workers.

**Overall impact and challenges:**

- In the clinic setting, lab bundling has been shown to decrease time to treatment. 93% of cases diagnosed in the clinic initiated treatment. 34% did not complete their SVR12 labs.
- In the outreach program, there is little clinical data to date, but CCC conducted 355 HCV reflex tests in the first five months of the program. 95% of those who tested positive for HCV antibodies successfully completed an RNA confirmation test.
- Venous blood collection is difficult to perform in a population that uses drugs. In the clinic, venous collection requires a lot of blood and multiple tubes. CCC is working with partners to streamline the process. This work requires skilled phlebotomists.
- Dried blood spot collection is also difficult in outreach settings. Training on optimal card saturation is crucial: RNA testing requires 8 punches (3-4 circles), or 2 full cards for a “treatment ready panel.” The time to results can be challenging. Patients who test positive still must complete some liver assessment prior to treatment, requiring a new blood draw.
- Self-testing is useful, especially during the pandemic, but it requires planning/support to link to payor details.
- Reflex testing is cost dependent on test results/what tests are needed and completed.
Reflex testing in England

Ruth Simmons, Public Health England
William Irving, University of Nottingham and Nottingham University Hospitals NHS Trust

HCV standards and surveillance in England:

- In addition to WHO guidance recommending reflex RNA testing, the National Institute for Health and Care Excellence (NICE) 2012 guidance and the UK Standards for Microbiology Investigations (UK SMI) 2017 guidance also recommend reflex testing for HCV RNA among those with a positive HCV antibody test.
- In the UK, HCV testing is conducted mainly in public (NHS) labs. Testing is free, with a very small contribution from private labs.
- England’s national laboratory reporting system, or SGSS, offers a routine, automated daily extract of diagnostic results from NHS and private lab data management systems and relays that information to relevant clinical teams. Sentinel surveillance of blood-borne virus testing has been in place since 2002, and collects testing regardless of result from participating laboratories.
- HCV treatment monitoring and outcome registry contains data from 2015, since the introduction of DAAs.

Current status of HCV reflex testing:

- There are variations in reflex testing commissioning and provision across England.
- Between 2015 and 2020, 2.2% of individuals tested for anti-HCV were positive (at 19 labs). The proportion of reflex testing of these individuals rose from 66.9% in 2015 to 83.9% in 2020. Previous analyses between 2008 and 2013 showed that reflex testing was 52.7% during that earlier time period.
- Among persons reflex tested, the median time to treatment following an anti-HCV positive result was 183 days. Among persons not reflex tested, it was 214 days.
- A rapid survey was conducted among UK/NHS labs in October 2021 to understand their testing practices. 26 labs were recruited from the UK Clinical Virology Network. Results found that 23 of the 26 labs do reflex RNA testing, and 5 perform reflex core antigen testing. Most do not offer RNA or core antigen as a first-line test, however. Ten labs have a platform available to do the core antigen testing if needed, and one of these is doing core antigen first line testing. Eight labs offer analyses of dried blood spot testing.
Impact and challenges:

- The proportion of reflex tests conducted has increased over time in England—a positive sign. And this reflex testing is associated with earlier treatment initiation. Efficiencies are gained by moving to reflex testing, preventing unnecessary appointments and multiple positive anti-HCV tests.
- Sample volume can sometimes be insufficient for RNA reflex testing, especially from persons who inject drugs.
- In addition, sample type can entail multiple steps and complexity, including the fact that if more than 48 hours passes, a repeat sample is needed.
- Currently there is no budget for HCV antigen testing.
- Universal reflex testing would save money, a cost comparison of a reflex and non-reflex pathway for persons diagnosed in 2019 England estimated 5.1 million pounds for the reflex pathway versus as much as 6.7 million pounds for the non-reflex pathway.
- There is a need to co-commission testing, treatment and care based on an HCV diagnosis rather than the component test result.

Cost comparison of reflex and non-reflex pathway for persons diagnosed in 2019 England and reported to SSBBV

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<th>Number of persons</th>
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Source: Slide 10 from Ruth Simmon’s presentation
WHO Guidelines and recommendations on HCV reflex testing

(Followed by discussion/Q&A)
Philippa Easterbrook, World Health Organization

WHO guidelines for the screening, care, and treatment of persons with HCV infection are being updated as public health experts systematically work through key questions. The aim is to combine existing unchanged recommendations with new/updated recommendations into a consolidated guideline by the end of 2023.

New HCV self-testing guidelines are now available. In October 2021 WHO began looking at simplified service delivery, reconciling pediatric and adult DAA regimens, and re-treatment approaches and regimens. WHO is also promoting other strategies to support linkage to care, including RNA reflex testing.

### Updating HCV Guideline Recommendations

**Proposed interventions to promote uptake and linkage**

**10.1. Recommendations**

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<th>Topic</th>
<th>Recommendations</th>
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- All facility- and community-based hepatitis testing services should adopt and implement strategies to enhance uptake of testing and linkage to care. (Strong recommendation, moderate quality of evidence)
- The following evidence-based interventions should be considered to promote uptake of hepatitis testing and linkage to care and treatment initiation: (Conditional recommendations)
  - Decentralized HCV testing and treatment
  - Provision of hepatitis testing and treatment as part of integrated services within mental health/substance use services (Conditional recommendation, very low quality of evidence)
  - Task sharing of hepatitis testing and treatment
  - Peer and lay health worker support in community-based settings (Conditional recommendation, moderate quality of evidence)
  - Clinician reminders to prompt provider-initiated, facility-based HBV and HCV testing in settings that have electronic records or analogous reminder systems (Conditional recommendation, very low quality of evidence)
  - Use of point-of-care testing
  - Reflex HCV viral load testing in those with a positive HCV antibody test result
  - Dried blood spots for serological and virological testing

*This can be achieved either through laboratory-based reflex HCV testing using a sample already held in lab, or in clinic-based reflex testing in a health facility through immediate sample collection following a positive RDT HCV antibody test.

Source: Slide 2 from Dr. Easterbrook’s presentation
Proposed interventions include:

- Decentralize testing and treatment. This means testing and treatment at the same site and even on the same day as part of integrated/bundled services.
- Task-share and task-shift to non-specialists and primary care doctors to help implement decentralization.
- Use point of care (PoC) viral load testing.
- Use reflex HCV viral load testing in those with a positive antibody test result.

Recent evidence:

- A systematic review published in Lancet demonstrated that when a patient is tested and treated at the same site (fully decentralized), there is a significant (20-30%) improvement in HCV RNA testing uptake and treatment.
- In addition, a POC viral load assay versus a lab viral load assay showed increased RNA testing uptake among homeless persons and the general population, though not among incarcerated persons.
- A systematic review of lab-based and clinic-based reflex viral load testing found a higher uptake of RNA testing for both. Linkage to care was strong for the clinic-based reflex testing but less so for the lab-based reflex testing, which had its biggest impact in testing uptake alone. There was less impact for both on treatment, which is especially removed from the lab’s control.
Discussion/Q&A highlights:

• **PoC viral load testing:** would be a great benefit but is not readily available to all programs. In Portland, for example, CCC does not have the equipment to perform real-time viral load confirmatory testing. Canada uses a GenExpert machine at some sites, but even “results in an hour” can be too long for some high-risk populations. The UK uses the High Intensity Test and Treat (HITT) program, bringing in a Cepheid machine to test an entire prison population and treat the same day.

• **Integrating historical data on test results into present-day processes:** How do programs capture those who tested for HCV in the past but never had a viral load test? In England, before the pandemic, teams pulled a list of everyone who had ever had a positive test and tried to follow up with those people to update their status and invite them back for a retest. The England team is also considering sending tests to general practitioners and mailing letters to potential patients asking if they want to come in for an HCV test. Working with the National Health Service, they are developing an aggregate dashboard to share data.

• **Contamination challenges:** These should be addressed by increasing protocols, including storing a second sample in a different location, changing lab coats, performing tests in separate areas, and addressing directional workflow, among other measures. Quality metrics are key to reducing contamination risks. In England, the introduction of real-time technology has reduced contamination, because most processes now take place in a closed tube.

• **Engaging industry:** Panelists noted that it is important to have a conversation with industry about what a given country or program needs. Many labs can adopt testing where a sample is already recommended. Pushing for more information in their packaging on the utility of serum testing is advised. CGHE can help with convening these conversations moving forward.
Conclusion

Lab-based HCV reflex testing is being shown to simplify the testing process and to strengthen linkage to care. Making this testing process standard or routine will support countries in their elimination goals, in particular where the lab infrastructure exists to manage the operational processes involved in a reflex test. Low-and-middle-income countries (LMIC) with central labs that possess the capacity to handle this testing method should be supported to implement HCV reflex testing in accordance with WHO guidelines as these continue to be finalized.

In addition, more work is needed to raise awareness about lab-based HCV reflex testing in general—and to disseminate best practices for specimen collection, storage, and other operational processes, including phlebotomy needs, dried blood spot options, and cost complexities. Reflex testing is efficient and ultimately cost-effective. Sharing strategies that work across public health will enable more countries and regions to move in this important new direction.