Special Presentation: Advancing diagnosis of current HCV infection: new tools, new opportunities

Overview of Hepatitis C Guidelines, Tests, and Upcoming Innovations and Policy Changes

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Division of Viral Hepatitis

Centers for Disease Control and Prevention

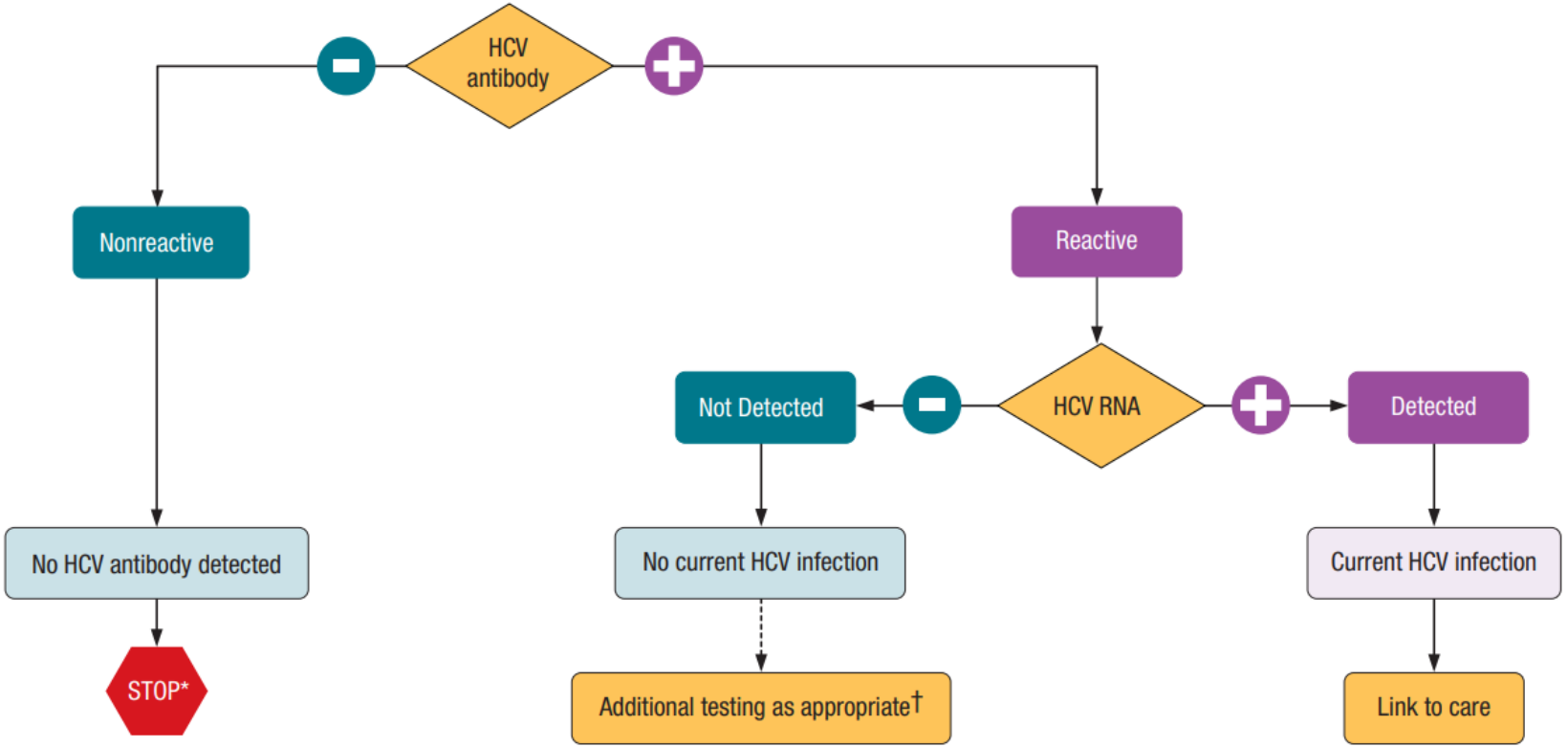
CHAC Meeting

April 2024

CDC's 2020 HCV Screening Guidelines recommend universal adult screening, during each pregnancy, and interval testing for people with ongoing risk.

Schillie S et al. CDC Recommendations for Hepatitis C Screening Among Adults - United States, 2020. MMWR Recomm Rep. 2020 Apr 10;69(2):1-17. doi: 10.15585/mmwr.rr6902a1.

CDC Recommended Testing Sequence for Identifying Current HCV Infection



CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18)

Currently Available FDA-Approved HCV Antibody Tests

Several Large Platform HCV Antibody Tests

Manufacturer	Platform	Assay
Abbott	ARCHITECT	ARCHITECT anti-HCV
Abbott	Alinity I	Alinity I Anti-HCV
Diasorin	LIAISON® XL	Murex HCV Ab
Quidel Ortho-Clinical Diagnostics	*Vitros* ECi	*Vitros* Immunodiagnostics Anti-HCV
Roche	Cobas e 601	Elecsys Anti-HCV II
Siemens	Advia Centaur	HCV (aHCV)

One Point-of-Care HCV Antibody Test

APHL. Optimizing Hepatitis C Virus Testing: Key Considerations for Reflexing HCV Antibody Reactive Specimens to Confirmatory HCV RNA Testing. February 2024. https://www.aphl.org/aboutAPHL/publications/Documents/ID-HCV-Reflex-Guide.pdf

Currently Available FDA-Approved HCV RNA Tests

Several Large Platform HCV RNA Tests

Manufacturer (PMA #)	Device[a]
Abbott Molecular (P00017)	Abbott RealTime HCV
Hologic (P020011)	Aptima HCV Qual Dx Assay
Hologic (P160023)	Aptima HCV Quant Dx Assay
Roche Molecular (P150015)	cobas-HCV (for 6800/8800)
Roche Molecular (P060030)[e]	COBAS Ampliprep/ COBAS Taqman HCV Test

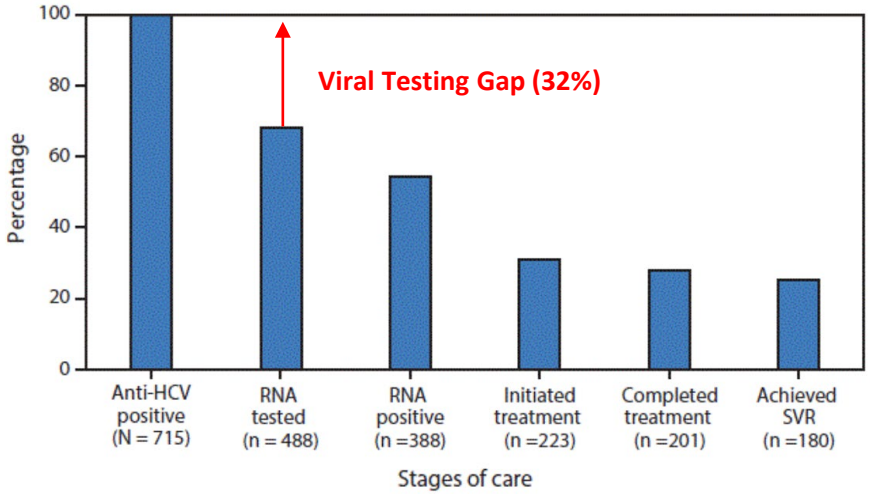
Currently no Point-of-Care HCV RNA Tests

APHL. Interpretation of Hepatitis C Virus Test Results: Guidance for Laboratories. January 2019. https://www.aphl.org/aboutAPHL/publications/Documents/ID-2019Jan-HCV-Test-Result-Interpretation-Guide.pdf

Challenges with the Current Diagnostic Algorithm

- Incomplete testing
- Loss to follow up
- Longer time to diagnosis
- Misses early HCV infection
- No POC viremia test
- Same visit test and treat not possible

Hepatitis C Care Cascade — Cherokee Nation Health Services
October 2012–July 2015

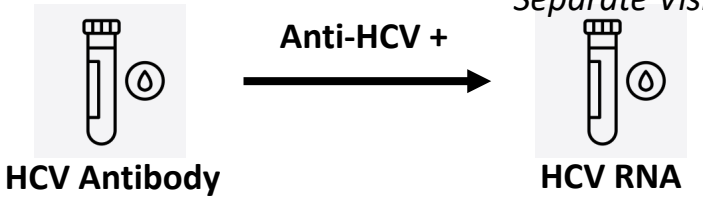


(Before Implementation of Reflex Testing)

Mera J et al. Identification and Clinical Management of Persons with Chronic Hepatitis C Virus Infection - Cherokee Nation, 2012-2015. MMWR Morb Mortal Wkly Rep. 2016 May 13;65(18):461-6.

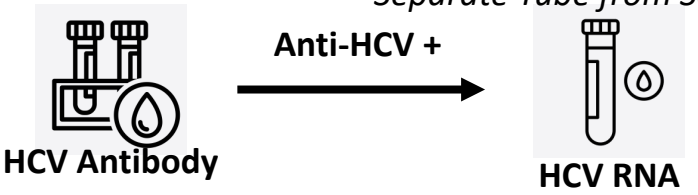
Current HCV RNA Testing Pathways

1) Two Encounters: 1 Tube Each

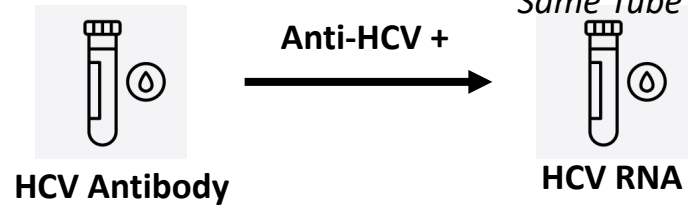


CDC no longer recommends Strategy 1

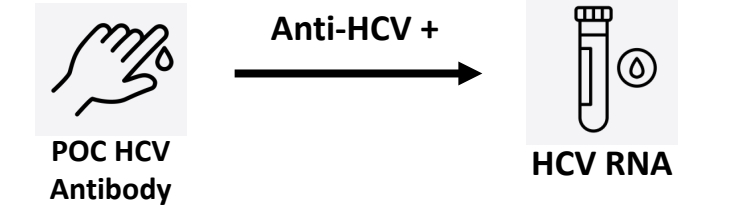
2) Single Encounter: 2 Tubes



3) Single Encounter: 1 Tube

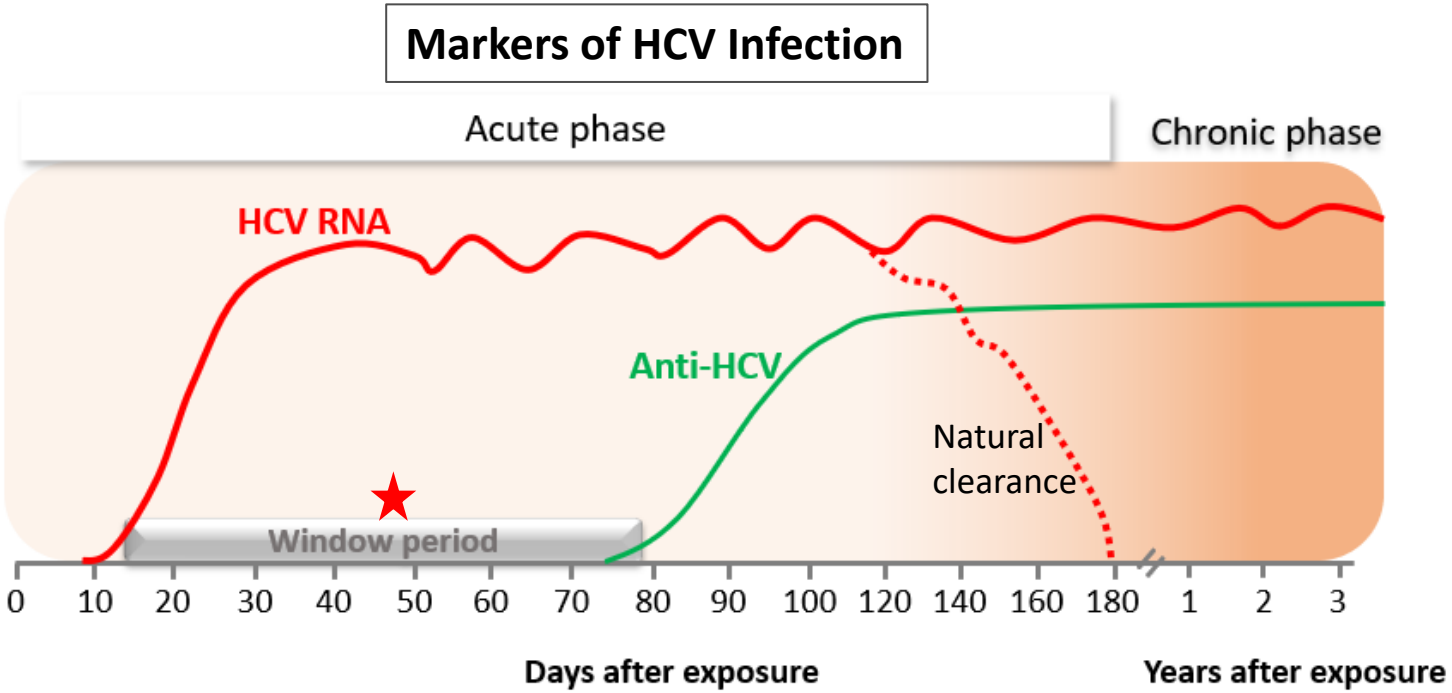


4) Single Encounter: FS and 1 Tube



Cartwright EJ et al. Updated Operational Guidance for Implementing CDC's Recommendations on Testing for Hepatitis C Virus Infection. MMWR Morb Mortal Wkly Rep. 2023 Jul 14;72(28):766-768.

The traditional HCV antibody to RNA approach misses early infection, limiting opportunities to interrupt transmission.



https://www.cdc.gov/hepatitis/statistics/SurveillanceGuidance/HepatitisC.htm

New Diagnostic Approaches that Promote Viral First Testing

POC HCV RNA Tests

Large Platform HCV Ag/Ab Tests

New Diagnostic Approaches that Promote Viral First Testing

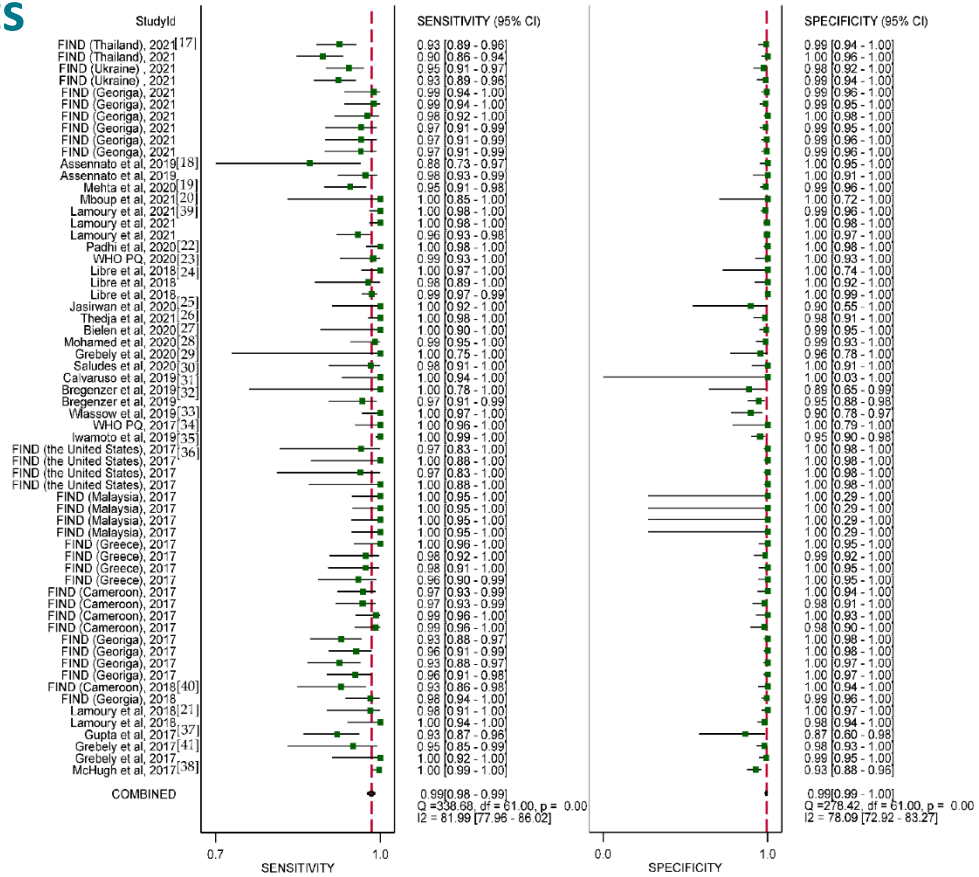
POC HCV RNA Tests

Large Platform HCV Ag/Ab Tests

Globally Available POC HCV RNA Tests

POC HCV RNA tests available outside the U.S. have high sensitivity (95% CI: 98–99%) and specificity (95% CI: 99–100%).

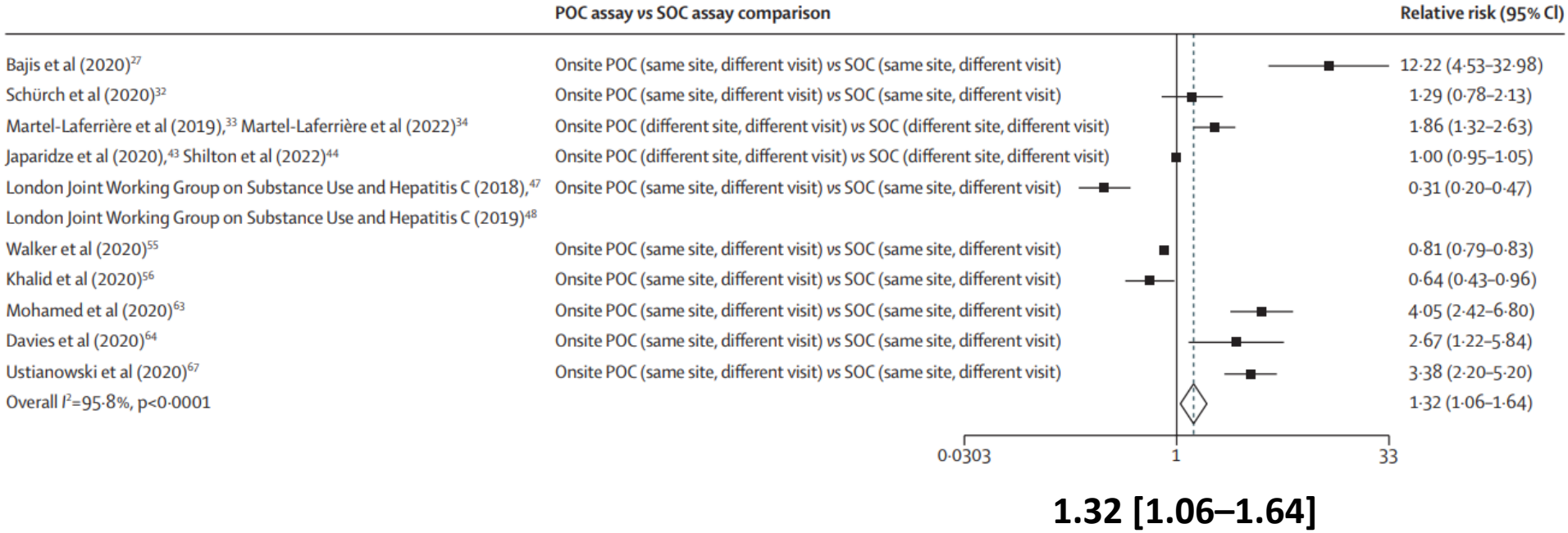
Manufacturer	Assay
Cepheid	Xpert HCV Viral Load Xpert HCV VL Fingerstick
Genedrive	HCV ID Kit
Molbio Dignostics	Truenat HCV RNA
Diagnostics for the New World	SAMBA II HCV Qualitative Whole Blood Test



Tang W et al. Diagnostic Accuracy of Point-of-Care HCV Viral Load Assays for HCV Diagnosis: A Systematic Review and Meta-Analysis. Diagnostics (Basel). 2022 May 18;12(5):1255.

POC HCV RNA testing is associated with a higher rate of treatment uptake across several studies.

Meta-analysis of within-study comparisons of HCV RNA POC versus SOC for the relative risk of treatment uptake



1.32 [1.06–1.64]

Trickey A et al. Impact of hepatitis C virus point-of-care RNA viral load testing compared with laboratory-based testing on uptake of RNA testing and treatment, and turnaround times: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2023 Mar;8(3):253-270.

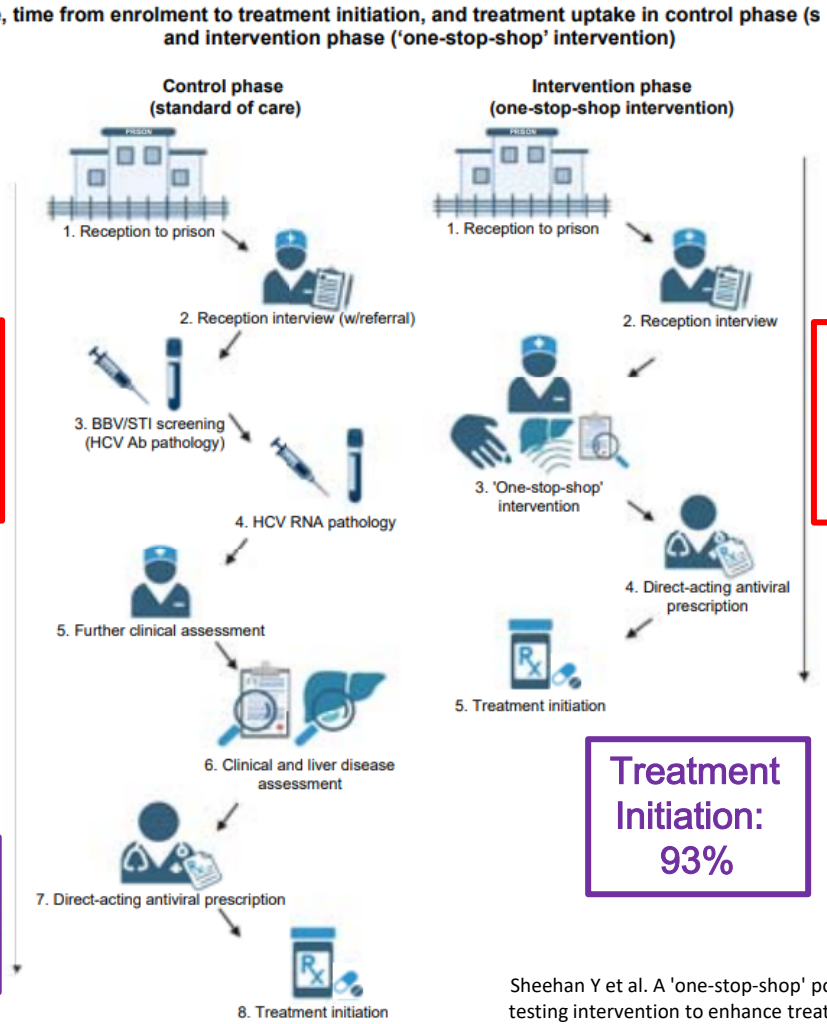
Example: POC HCV RNA testing shortens time to treatment and increases treatment uptake.

PIVOT Study

- Setting: Australian prisons
- Comparators: Sequential phlebotomy vs single visit POC testing
- Outcomes:
  - Time from enrollment to treatment initiation
  - Treatment uptake

Enrollment to Treatment: 99 Days

Treatment Initiation: 22%



Enrollment to Treatment: 6 Days

Treatment Initiation: 93%

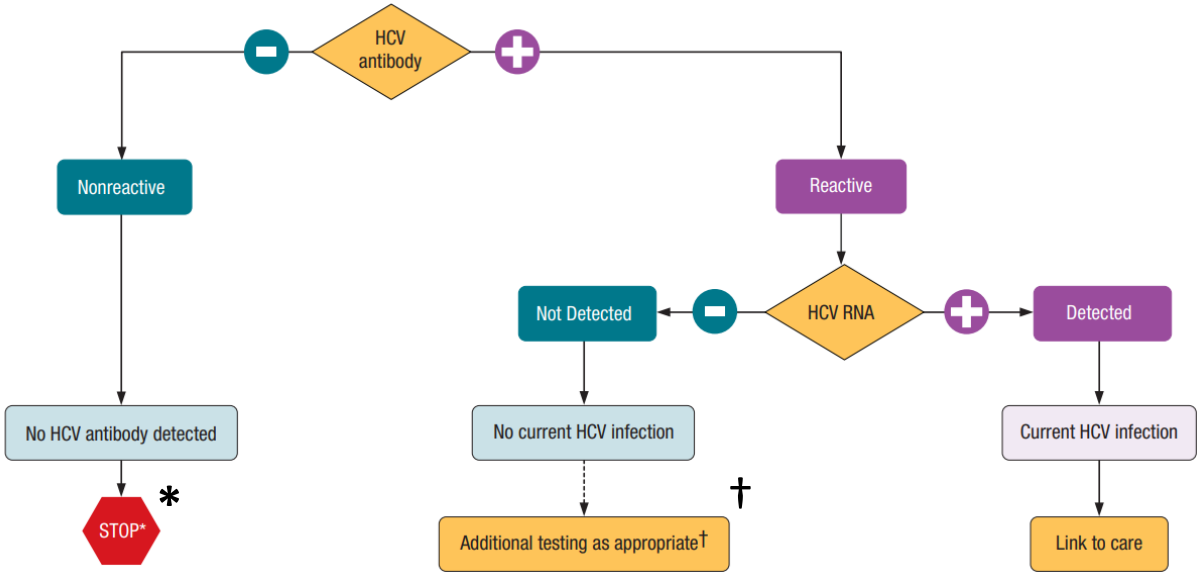
Sheehan Y et al. A 'one-stop-shop' point-of-care hepatitis C RNA testing intervention to enhance treatment uptake in a reception prison: The PIVOT study. J Hepatol. 2023 Sep;79(3):635-644.

Analytic and clinical trial studies of a CLIA-waived POC HCV RNA test are underway.

CDC is working with the Independent Test Assessment Program (ITAP)

- Mid-2023: ITAP identified 1 manufacturer to move through the ITAP process
- Late 2023: Started independent laboratory testing, analytic studies, and clinical trial prep
- Early 2024: Launched clinical trials
- Summer 2024: Anticipated completion of analytic and clinical trial studies for FDA review

CDC 2013 guidance for laboratorians and clinicians already recommends HCV RNA testing for people with recent HCV exposure.



*For persons who might have been **exposed to HCV within the past 6 months**, testing for HCV RNA or follow-up testing for HCV antibody is recommended.

† …Repeat HCV RNA testing if the person tested is suspected to have had **HCV exposure within the past 6 months** or has clinical evidence of HCV disease.

Summary

HCV RNA testing is currently recommended for the diagnosis of HCV infection among persons who might have been exposed to HCV within the past 6 months (regardless of anti-HCV result).

CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18)

Envisioning a Same Day Test and Treat Approach for Hepatitis C

POC HCV RNA testing opens the possibility of same-day test and treat.

One-Stop Shop

<u>Remaining Barriers</u>

- Lack of POC HBsAg diagnostics to rule out HCV/HBV co-infection
  - Several POC HBsAg tests exist outside of the U.S.
  - FDA has signaled HBV downclassification to Class II eminent

- Simplified guidelines still require lots of labs and visits
  - The AASLD/IDSA Guidelines Group is working on same-day hepatitis C treatment guidance

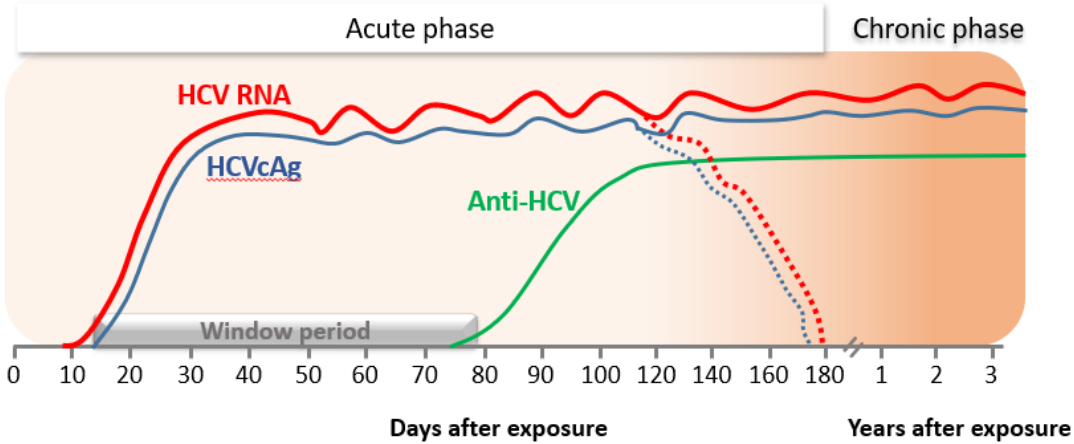
New Diagnostic Approaches that Promote Viral First Testing

POC HCV RNA Tests

Large Platform HCV Ag/Ab Tests

Hepatitis C core antigen (HCV Ag) is a large platform test for viremia.

- Detectable within 1–2 weeks after HCV infection
- Less sensitive than HCV RNA (LLoD 500–3,000 IU/mL)
- Can run on the same sample/aliquot used for HCV antibody testing
- Priced lower than HCV RNA globally

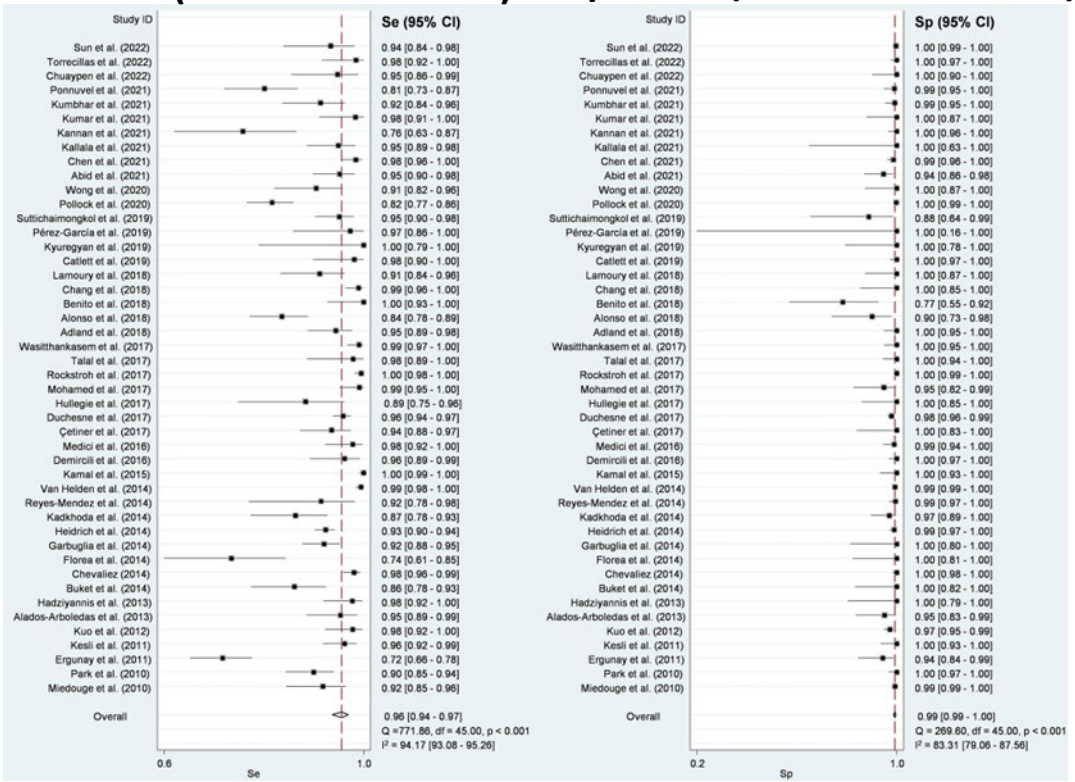


HCV Ag testing alone is not sufficient for testing in the general population.

- The lower sensitivity of HCV Ag creates challenges of its use in low prevalence settings (i.e., the general population)
  - E.g., Risk of a false negative in someone receiving their one-time universal screening

- HCV Ag can be combined with HCV antibody to improve performance

Sn= 0.96 (95% CI= 0.94-0.97) **Sp= 0.99 (95% CI = 0.99-1.00)**



Platform: Abbott ARCHITECT HCV Ag assay

Sepúlveda-Crespo D.. Diagnostic performance of hepatitis C core antigen assay to identify active infections: A systematic review and meta-analysis. Rev Med Virol. 2023 May;33(3):e2436.

Globally Available HCV Ag/Ab Tests

Large Platform HCV Ag/Ab

Manufacturer	Assay
Roche	Elecsys® HCV Duo
Abbott	Murex Ag/Ab
Bio-Rad	Monolisa™ HCV Ag/Ab Ultra

Currently no Point-of-Care HCV Ag/Ab Tests

Unlocking the Potential of HCV Ag/Ab Testing

HCV Ag/Ab testing can reduce incomplete testing, shorten the time to diagnosis, and capture early HCV infection.

It may be possible to develop a POC HCV Ag/Ab test

<u>Remaining Barriers</u>

- Lack of an FDA-approved HCV Ag/Ab test
  - CDC is working with FDA to evaluate large platform HCV Ag/Ab tests

- Lack of guidelines to HCV Ag/Ab use in the United States
  - CDC is conducting cost-effective analyses and revising its HCV testing guidance for clinicians and laboratorians

The additional diagnostics needed to eliminate hepatitis C are coming soon

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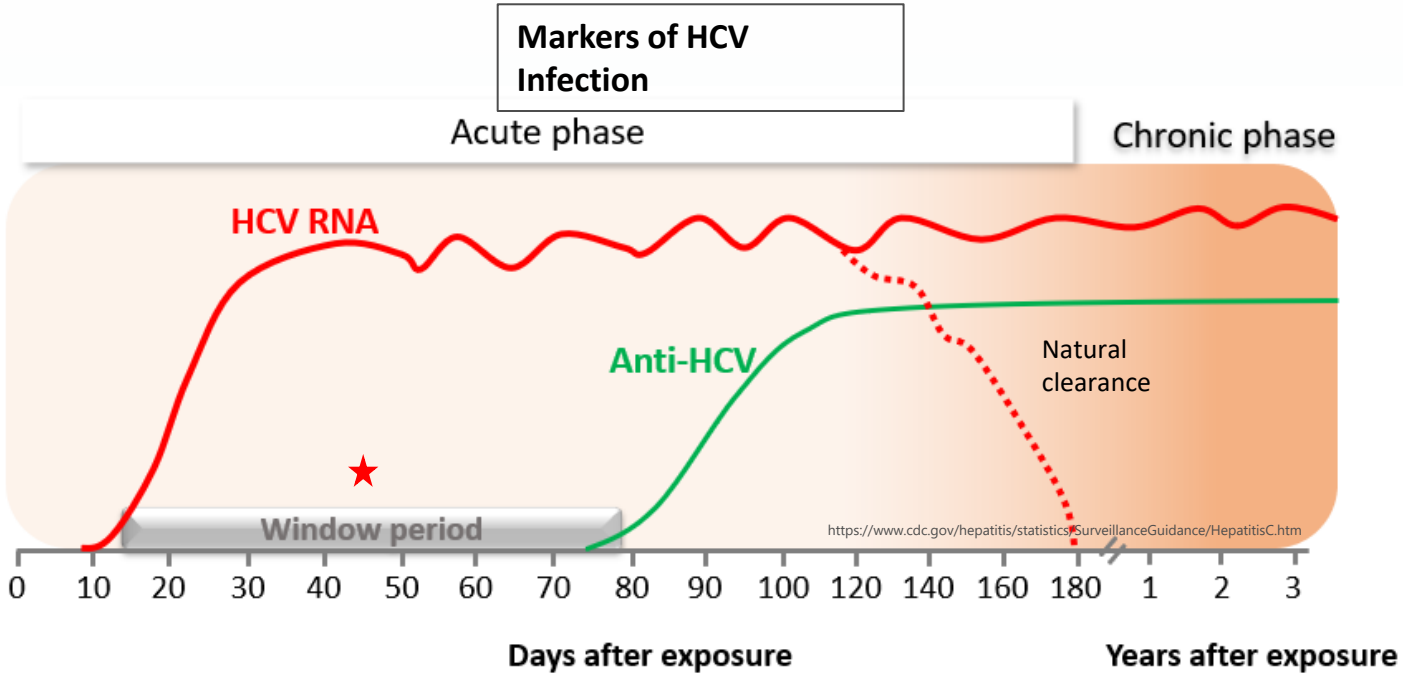
For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Cost-effectiveness Analysis of Hepatitis C Testing Strategies for Diagnosis of US Adults

Eric Hall, PhD, MPH
Oregon Health & Science University
OHSU-PSU School of Public Health

The traditional HCV-Ab to RNA approach misses early infection, limiting opportunities to interrupt transmission.



Centers for Disease Control and Prevention (CDC). Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013 May 10;62(18):362-5. PMID: 23657112; PMCID: PMC4605020.

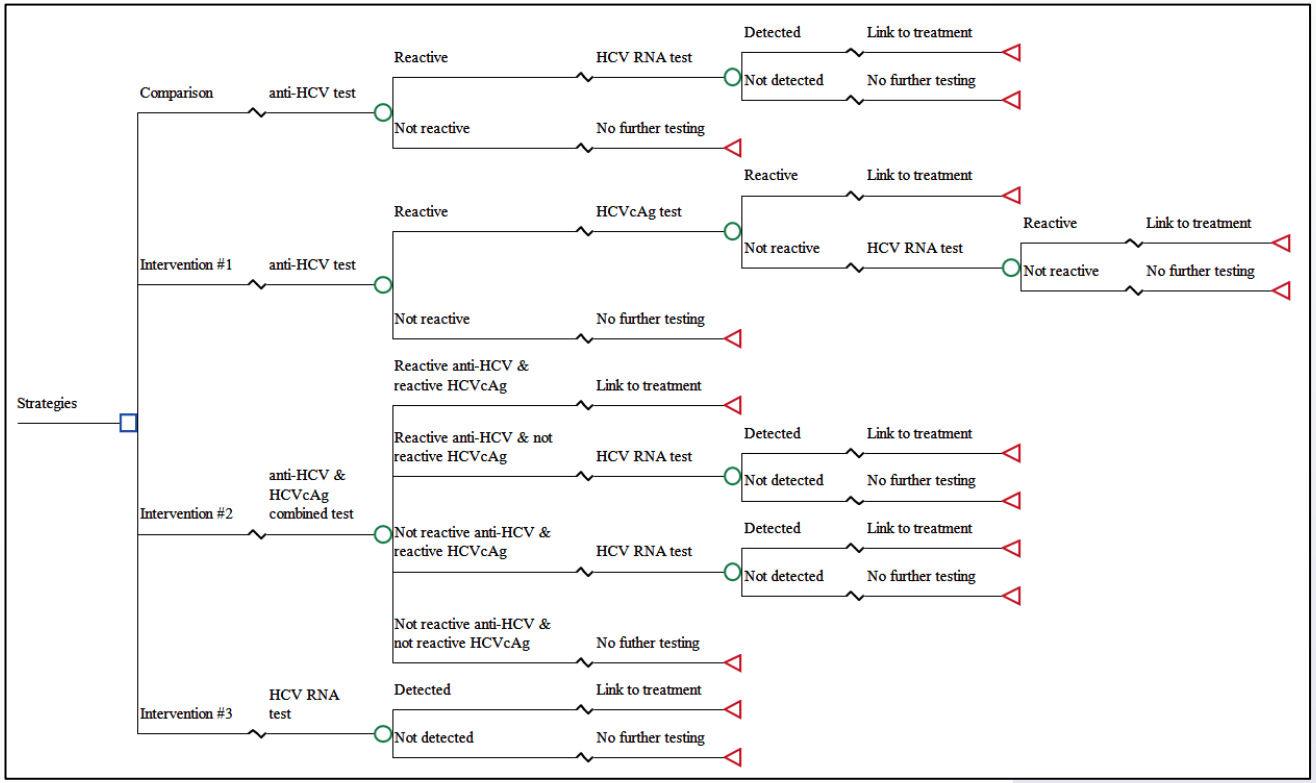
Objective and Strategies Considered

- **Objective:** Assess the cost-effectiveness or various HCV testing strategies compared to current two-step testing algorithm.

- **Strategies**:
  - Comparison
    1. Anti-HCV followed, when reactive, by
    2. HCV RNA
  - Intervention 1
    1. Anti-HCV followed, when reactive, by
    2. HCVcAg followed, when non-reactive, by
    3. HCV RNA
  - Intervention 2
    1. Anti-HCV and HCVcAg concurrent testing test followed, when Ab/Ag results discordant, by
    2. HCV RNA
  - Intervention 3
    - HCV RNA

Model Details

- *Model:* Decision-tree with a Markov model of HCV progression
- *Cohort*: US adults
- *Outcomes* (lifetime of cohort):
  - Cost (2023 USD)
  - QALYs
  - HCV-related health outcomes



HCV Test and Treatment Inputs	Base Case	Range	Reference
Anti-HCV			
Sensitivity (%, ≥ 2 months)	98.1	(92.6-99.7)	1
Specificity (%, ≥ 2 months)	99.8	(99.2-99.9)	1
Cost (2023 USD)	14.27	(10.70-17.88)	2
HCV cAg			
Sensitivity (%)	96.0	(94.0-97.0)	3
Specificity (%)	99.4	(99.0-100.0)	3
Cost (2023 USD)	14.27	(5.00-25.00)	Assumption
HCV RNA			
Sensitivity (%)	100.0	(94.0-100.0)	3,4,5
Specificity (%)	100.0	(98.3-100.0)	3,4,5
Cost (2023) USD	42.84	(31.14-53.55)	2
P of linkage to treatment	80.0	(60.0-100.0)	6
P of treatment to SVR	97.0	(95.0-100.0)	7
Cost of treatment	25,200	(7,500-75,000)	8

Input Notes

- All trials are tested at a single point in time.
- HCV RNA and HCV cAg was detectable within the first month.
- Anti-HCV was first detectable at the end of the second month.
- Anti-HCV & HCV RNA costs are from CMS (Clinical Diagnostic Laboratory Fee)
- Assumed cost of HCV cAg test is the same as an anti-HCV test (base case).
- 80% linkage to treatment
  - WHO treatment targets

Analysis

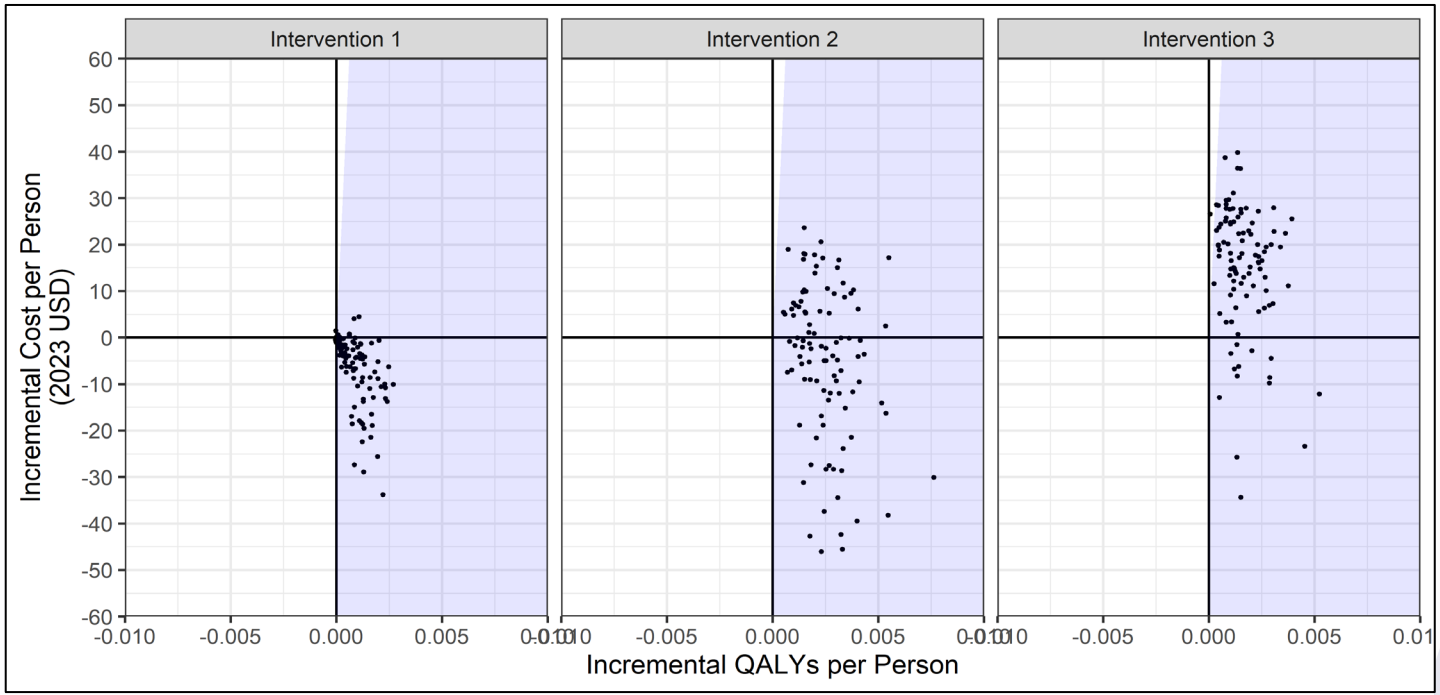
- Compared each intervention to the comparison strategy
  - Fewer QALYs: comparison strategy preferred
  - More QALYs, lower cost: intervention strategy preferred
  - More QALYs, higher cost: incremental-cost effectiveness ratio (ICER)

- Base Case Analysis
  - Point estimate (i.e. “best value”) for all inputs
- Sensitivity Analyses
  - Probabilistic sensitivity analysis: sample from ranges for all inputs concurrently
  - One-way sensitivity analysis on cost of HCV cAg test
    - $10.00 to $50.00, in increments of $5.00

Results: Base Case Analysis of HCV Testing Strategies, Relative to Comparison Strategy

Outcome	Intervention 1: Anti-HCV (+) → HCVcAg (–) → HCV RNA	Intervention 2: Anti-HCV & HCVcAg (+/–) → HCV RNA	Intervention 3: HCV RNA
Economic outcomes (per person)			
Cost (2023 USD)	-0.26	8.60	21.48
Life-years	0.0000	0.0010	0.0010
QALYs	0.0000	0.0017	0.0017
ICER (USD per QALY)	n/a	8,467	20,513
Health outcomes			
Diagnosed infections	0.00%	2.05%	2.14%
Treated infections	0.00%	2.05%	2.14%
HCV-related deaths	0.00%	-3.86%	-4.09%

Results: Probabilistic Sensitivity Analysis



Note: The comparison strategy for all intervention strategies is an anti-HCV test with automatic HCV RNA test when anti-HCV is reactive. The following intervention strategies were considered: anti-HCV, with automatic HCV cAg for all when anti-HCV is reactive, followed by an HCV RNA test for subsequent HCV cAg results that are not reactive (Intervention 1); anti-HCV and HCV cAg combination test, with automatic HCV RNA test for discordant results (Intervention 2); HCV RNA test alone (Intervention 3). All trials were tested once at a single point in time. The shaded area represents regions in which results that would indicate the intervention strategy is preferred over the comparison strategy, at a willingness-to-pay threshold of $100,000 per QALY gained.

Results: One-way Sensitivity Analysis

Cost of HCVcAg test	Intervention 1: Anti-HCV (+) → HCVcAg (–) → HCV RNA	Intervention 2: Anti-HCV & HCVcAg (+/–) → HCV RNA	Intervention 3: HCV RNA alone
10.00 USD	Lower cost, same QALYs	ICER=$5,723	ICER=$20,513
15.00 USD	Lower cost, same QALYs	ICER=$10,839	ICER=$20,513
20.00 USD	Lower cost, same QALYs	ICER=$15,956	ICER=$20,513
25.00 USD	Lower cost, same QALYs	ICER=$21,073	ICER=$20,513
30. 00 USD	Higher cost ($0.12/person), same QALYs	ICER=$26,189	ICER=$20,513
35.00 USD	Higher cost ($0.27/person), same QALYs	ICER=$31,306	ICER=$20,513
40.00 USD	Higher cost ($0.42/person), same QALYs	ICER=$36,423	ICER=$20,513
45.00 USD	Higher cost ($0.57/person), same QALYs	ICER=$41,540	ICER=$20,513
50.00 USD	Higher cost ($0.72/person), same QALYs	ICER=$46,656	ICER=$20,513

Abbreviations: USD, US dollars; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.
Note: The comparison strategy for all intervention strategies is an anti-HCV test with automatic HCV RNA test when anti-HCV is reactive. All trials were tested once at a single point in time. For each analysis, Intervention 1 results in the same number of QALYs

Considerations

- *Intervention 1* can be a cost-saving approach.
- The strategies that incorporated viral detection in the first step (*Interventions 2 & 3*) resulted in increased detection of infection and improved health outcomes.

- Limitations
  - Static risk of infection did not model impact of early diagnosis on reduction of ongoing transmission
    - Likely underestimate of the benefits of interventions 2 & 3
  - Modeled an average of the entire US adult population
    - Potential for additional benefits among persons with higher HCV prevalence or risk of infection
  - Assumed test performance (sensitivity and specificity) is the same for all persons
  - Modeled test cost and performance, but did not incorporate potential impact on linkage to care.
    - Point-of-care testing can play a unique role in advancing same-day testing and treatment.

Partners and Acknowledgements

CAMP Support:

- Monica Trigg, Emory University
- Abby Tighe, Emory University

CDC Collaborators:

- Carolyn Wester, DVH
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- Emily J. Cartwright, DVH
- Kevin Heslin, DVH
- Saleem Kamili, DVH
- Hasan Smymu, DVH
- Taiwo Abimbola, NCHHSTP

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Updating HCV Testing Guidance for Laboratorians and Clinicians

Emily J. Cartwright, MD

Medical Officer

Clinical Interventions Team

CDC/HRSA Advisory Committee meeting

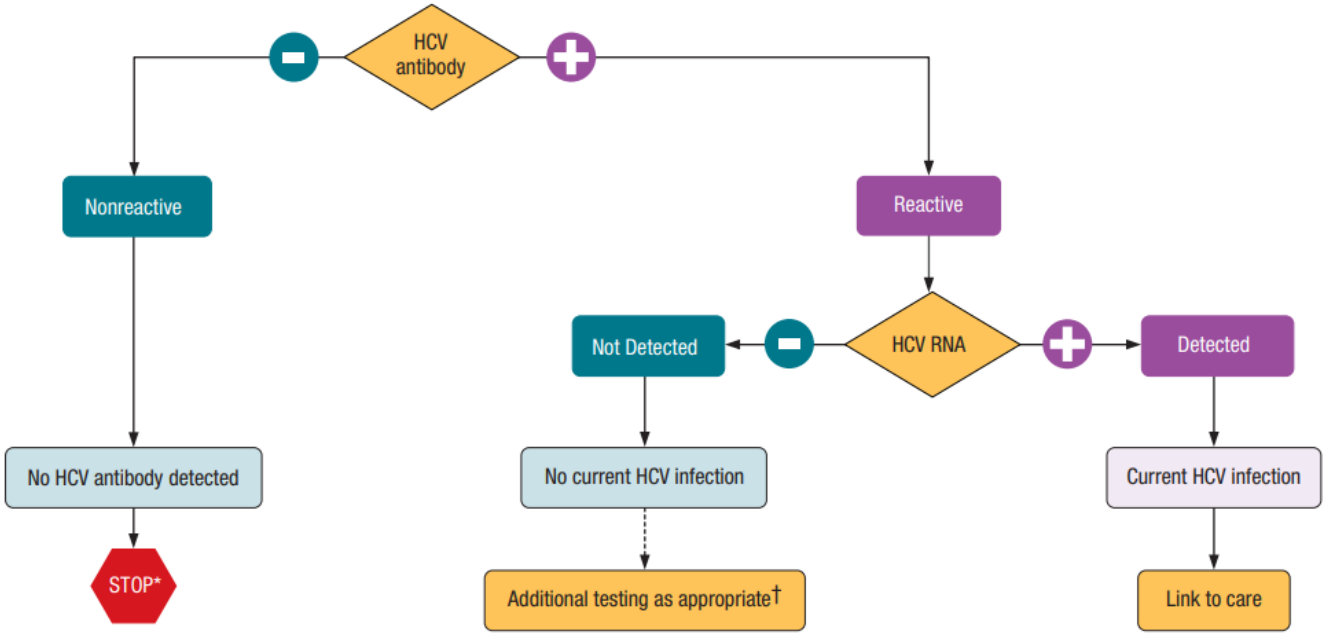
April 10, 2024

Testing for HCV Infection: An Update of Guidance for Clinicians and Laboratorians

MMWR / May 10, 2013 / Vol. 62 / No. 18

Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention



Updated Operational Guidance for Implementing CDC's Recommendations on Testing for Hepatitis C Virus Infection

Weekly / July 14, 2023 / 72(28);766–768

- **Hepatitis C testing should be completed in a single visit**

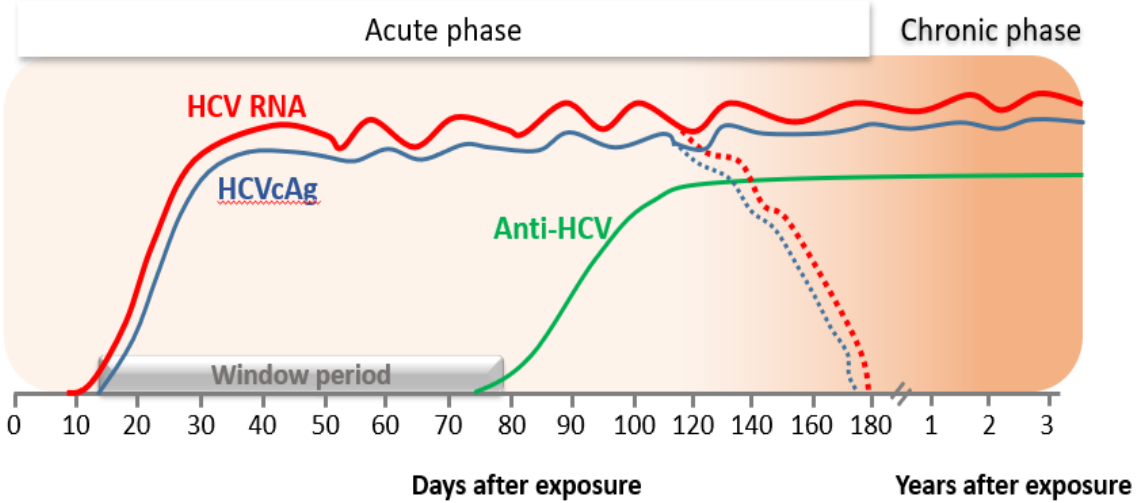
- **<u>Automatic</u> HCV RNA testing should be performed on all HCV antibody reactive samples**

- **Testing strategies that require multiple visits to collect HCV testing samples should be discontinued**

HCV Testing – Window Period

- **Following infection:**
  - **HCV RNA: 1-2 weeks[1]**
  - **HCV cAg: 2-3 weeks[2]**
  - **Anti-HCV: 7-8 weeks[1]**

(HCV cAg = HCV Core Antigen)
(Anti-HCV = HCV antibody)



- **Virologic tests shorten the window period to HCV diagnosis**

1) Dufour DR et al, *Clin Chem,* 2000; 2) Sepúlveda-Crespo D et al, *Rev Med Virol,* 2023.

Objective

- **Update the 2013 Hepatitis C Testing Guidelines**
- **Use assays that detect viral markers (HCV RNA or HCV cAg) in the first step of the testing sequence (“viral-first”)**
  - Shorten the window period
  - Increase early diagnosis of HCV infection

PICO Questions

- **Population:** General adult population
- **Intervention(s):** Viral-first hepatitis C testing strategies
  - #1: Concurrent anti-HCV/ HCV cAg followed, when discordant, by HCV RNA
  - #2: HCV RNA
- **Comparison:** Current HCV antibody-first strategy
  - Anti-HCV followed, when reactive, by HCV RNA
- **Outcomes:**
  - Diagnosed current HCV infections
  - Treated HCV infections
  - Hepatitis C morbidity and mortality

Research Questions

Compared to the comparison strategy,

- **Does Intervention 1**
  - 1. Increase the diagnosis of current HCV infection
  - 2. Increase HCV treatment
  - 3. Decrease morbidity and mortality attributable to HCV infection?
- **Does Intervention 2**
  - 1. Increase the diagnosis of current HCV infection
  - 2. Increase HCV treatment
  - 3. Decrease morbidity and mortality attributable to HCV infection?

How many additional cases diagnosed?	How many additional cases treated?	Do benefits outweigh harms?	What is the effect on morbidity and mortality attributable to HCV infection?*
K.Q.1.a What is the prevalence of past or present HCV in the U.S.?	K.Q.2.a. What proportion of persons who are diagnosed with current HCV infection are treated in the U.S.?	K.Q.3.a. What are the benefits of hepatitis C screening?	K.Q.4.a. What is the effect of DAA treatment on HCV viral load?
K.Q.1.b What is the prevalence of current HCV infection in the U.S.?		K.Q.3.b. What are the harms of hepatitis C screening?	K.Q.4.b. What is the effect of DAA treatment on hepatitis C-related morbidity (including cirrhosis and hepatocellular carcinoma)?
K.Q.1.c. What is the incidence of HCV infection in the U.S.?			K.Q.4.c. What is the effect of DAA treatment on hepatitis C-related mortality?
K.Q.1.d. What is the diagnostic accuracy of anti-HCV, HCVcAg, HCV RNA?			K.Q.4.d. What are the adverse effects of DAA treatment?

* As key questions 4.a – 4.d. have been reviewed recently, they will not be included in this review

Additional Considerations

- **Intended audience**
  - U.S. healthcare clinicians, public health officials, and organizations involved in the development, implementation, delivery, and evaluation of clinical diagnostics and laboratory testing services
- **Systematic review of the domestic and global literature from 2013 through 2023**
- **Interventions evaluated are not currently FDA approved for intended use**
  - HCV cAg test is not currently available in U.S. or FDA-approved
  - HCV RNA is currently only FDA-approved for diagnosis in context of a reactive anti-HCV

Partner Engagement Strategy

- **April 2024**
  - CDC/HRSA Advisory Committee (CHAC) presentation
- **Fall 2024**
  - Association of Public Health Laboratories (APHL) - led convening of key stakeholders
    - Similar to APHL-led convening on HCV diagnostics held in 2021
  - ID Week (IDSA) presentation, October 2024
  - The Liver Meeting (AASLD) presentation, November 2024

Timeline

Step	Duration	Target date
Complete systematic literature review	4 months	June 2024
Complete draft guidelines	3 months	September 2024
CDC Clearance of draft guideline	2–3 months	Oct–Dec 2024
Federal Register Notice of 60-day public comment period	2 months	Jan–Feb 2025
Peer review from external experts	1 month	Jan–Feb 2025
Disposition of Peer review and Public comments	1 month	March 2025
CDC clearance of finalized guideline	1 month	April 2025
MMWR Production and Publication	3–4 months	May–July 2025

Next Steps

Questions, comments, suggestions?

For more information, contact CDC
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