Laboratory-based Hepatitis C Virus Clearance Cascade

Program Guidance for Local and State Health Departments

July 20, 2021

Purpose

As the United States implements hepatitis C virus (HCV) elimination plans, jurisdictions will need tools to measure the impact of public health interventions and identify opportunities for improvement. An HCV clearance cascade can be developed using longitudinal HCV surveillance laboratory data and be used at a population level to quantify and identify opportunities to improve HCV clearance. Once developed, the HCV clearance cascade can be regularly updated to monitor changes over time and track progress toward established goals. Further analysis of the HCV clearance cascade can help identify disparities in progression through the cascade by population or geography.

The purpose of this document is to assist jurisdictions that have systematic reporting and processing of all positive anti-HCV, plus positive ("detected") and negative ("not detected") HCV RNA and–in the future–HCV core antigen test results to develop a standardized, replicable, laboratory-based HCV clearance cascade. This information in turn can be used by viral hepatitis programs to identify barriers and develop strategies and interventions to improve outcomes.

Minimum Requirements

To develop an HCV clearance cascade, health departments first need to have a longitudinal, HCV surveillance database capable of housing, extracting, and deduplicating all HCV laboratory test results reported to the jurisdiction, including type of test, test result, and date of specimen collection. HCV cases in the database should include laboratory results independent of whether they meet the Council of State and Territorial Epidemiologists (CSTE) acute or chronic surveillance case definitions, as some cases that are included in the cascade might not meet the CSTE case definition. Laboratory results can be reported to the surveillance system from commercial laboratories, public health laboratories, health care systems, or providers. The HCV laboratory result date can be used as a proxy if specimen collection date is not available. Positive anti-HCV, positive/"detected" HCV RNA, negative/"not detected" HCV RNA, and HCV core antigen, when available, test results must be reportable to the health department. Ideally, an automated process for cleaning and classifying HCV RNA results (e.g., "detected", "not detected") is highly beneficial.

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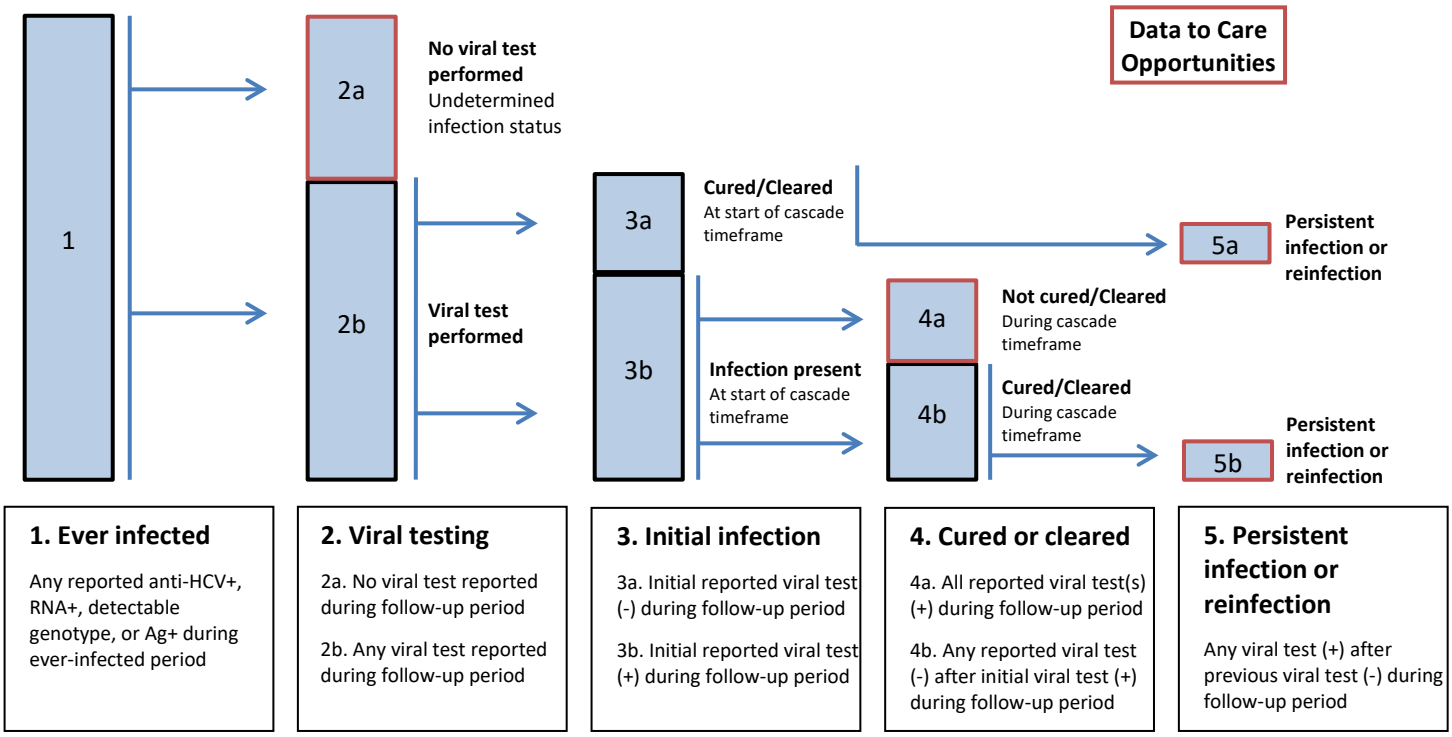
Figure 1. Laboratory-based Hepatitis C Virus Clearance Cascade for "202X" Evaluation Year—[Jurisdiction], [Starting point]–[End of follow-up period]



Abbreviations: anti-HCV+, antibody positive; Ag+, antigen positive; RNA+, ribonucleic acid positive

Note: Viral testing includes any HCV RNA, HCV genotype, or HCV core antigen test. (+) is defined as detectable HCV RNA or antigen; (-) is defined as undetectable HCV RNA or antigen.

Viral Testing Definitions

HCV RNA test. Any test that detects HCV RNA, including quantitative and qualitative nucleic acid detection tests. Quantitative and qualitive RNA results of "not detected" are test results in which HCV RNA was not detected. Quantifiable results with an exact number reported indicate levels of HCV RNA detected. Quantitative results may report "below the lower limit of detection" (e.g.., < 12 IU/mL, < 15 IU/mL, etc.) yet simultaneously indicate that HCV RNA was detected but not quantifiable because the levels are above the limit of detection but below the lower limit of quantification; these individuals should be considered as HCV RNA "detected" despite not having quantifiable HCV RNA levels. For additional details on the variability in reporting by assay, refer to this interpretation guide from the Association of Public Health Laboratories.

HCV genotype test. Genotyping results for which a specific genotype is reported should be considered as HCV RNA "detected." Genotype tests that report "detected but unable to genotype" indicate that HCV RNA was detected, but genotype was not able to be resolved. For the purposes of this HCV clearance cascade, these individuals should be considered as HCV RNA "detected."

HCV core antigen test. There are currently no FDA-approved HCV core antigen tests; however, core antigen tests may become available in the future.

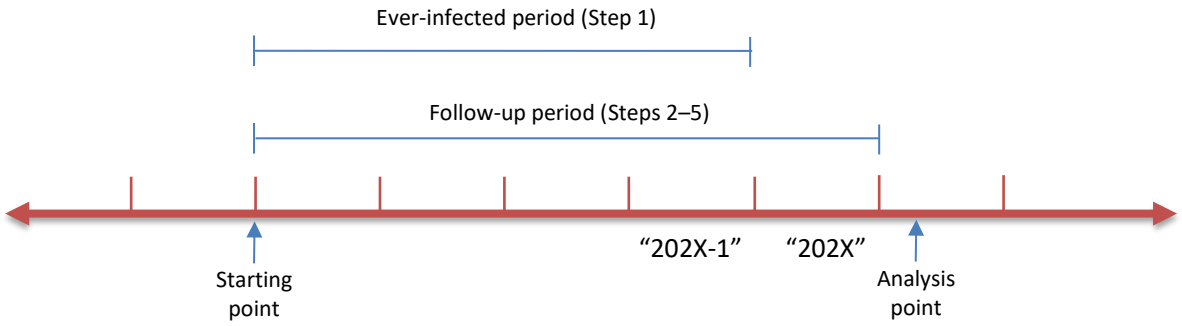
HCV viral test. HCV viral tests include HCV RNA tests, genotyping tests, and core antigen tests.

Cascade Timeframe

Cascade starting point. The time point when HCV RNA negative/"not detected" reporting was fully implemented in the jurisdiction.

Evaluation time frame. The time period from the starting point to the analysis point

Figure 2. Hepatitis C Virus Clearance Cascade Time Frame for Evaluation Year "202X"



As an example, if negative/"not detected" reporting was fully implemented January 1, 2018 and the cascade evaluation year was 2020, then the "ever-infected" period would occur from January 1, 2018 through December 31, 2019, and the "follow-up period" would occur from January 1, 2018 through December 31, 2020. To allow for lab reports to be fully entered into the system, the analysis should be conducted in April 2021, 3 full months after the end of the follow-up period.

Cascade Steps

Step 1—Ever infected. All individuals with any positive/"detected" HCV test (anti-HCV, RNA, detectable genotype, or core antigen) performed from the starting point through the end of the ever-infected period (December 31, "202X-1"). The test performance date is the specimen collection date (or laboratory result date if specimen collection date is not available). All individuals who are known to be living outside the jurisdiction or deceased as of the end of the follow-up period (December 31, "202X") should be excluded entirely from the cascade.

Step 2—Viral testing performed. This category includes all individuals who were ever infected (Step 1):

- *2a - No HCV viral test reported*—All individuals who have no HCV viral test performed by the end of the follow-up period (December 31, "202X").
- *2b - HCV viral test performed*—All individuals who have any HCV viral test performed by the end of the follow-up period (December 31, "202X"), regardless of the result.

Step 3—Initial infection status. This category includes all individuals with viral testing performed (Step 2b):

- *3a – Initial HCV infection cured or cleared*—All individuals whose initial HCV viral test result performed during the follow-up period (through December 31, "202X") was "not detected."
- *3b - Initial HCV infection present*—All individuals whose initial HCV viral test result performed during the follow-up period (through December 31, "202X") was "detected."

Note: Initial HCV infection cured or cleared might include false positive antibody results.

Step 4—Cured or cleared. This category includes all individuals with an initial HCV viral test result "detected" (Step 3b):

- *4a – HCV infection not cured or cleared during the cascade timeframe*—All individuals where no subsequent HCV viral test results were performed or where all subsequent HCV viral test results during the follow-up period (through December 31, "202X") were "detected."
- *4b – HCV infection cured or cleared during the cascade timeframe*—All individuals where a subsequent HCV viral test result "not detected" was performed during the follow-up period (through December 31, "202X").

Note: The cascade is unable to distinguish between cured (referring to successful treatment response) and cleared (referring to natural, spontaneous clearance).

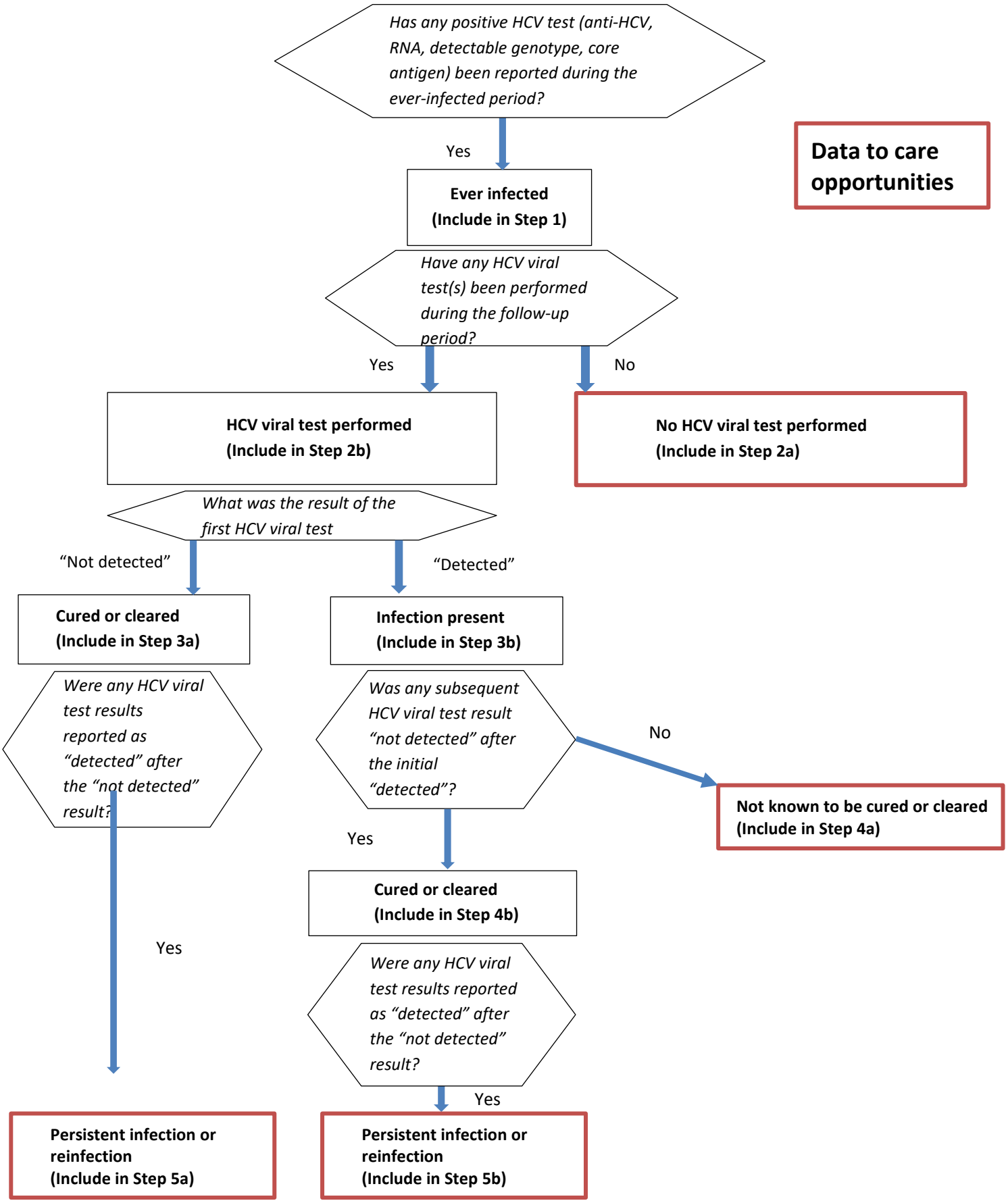
Note: A patient with a single, detectable HCV RNA result would populate all of the first four Steps—Step 1, Step 2b, Step 3b, and Step 4a

Step 5—Persistent infection or reinfection.

- 5a – Persistent infection or reinfection—All individuals where a negative/ "not detected" result (Step 3a) is followed by an HCV viral test result positive/"detected."
- 5b – Persistent infection or reinfection—All individuals where a negative/ "not detected" result (Step 4b) is followed by an HCV viral test result positive/"detected."

Note: The cascade is unable to distinguish among the reasons for persistent infection (e.g., incomplete treatment, treatment failure, viral breakthrough), reinfection, or false positive reports (rare). For simplicity, there is no minimum time period after an HCV viral negative/"not detected" test result (cured or cleared) and before a subsequent HCV viral positive/"detected" test result occurs to qualify as a persistent infection or reinfection. Regardless of whether these infections represent persistent infections or reinfections, this group represents an important opportunity for linkage to care and treatment.

Figure 3. Flow Diagram to Visualize how Individuals are Assigned within the Hepatitis C Virus Clearance Cascade



Implications for Public Health Intervention

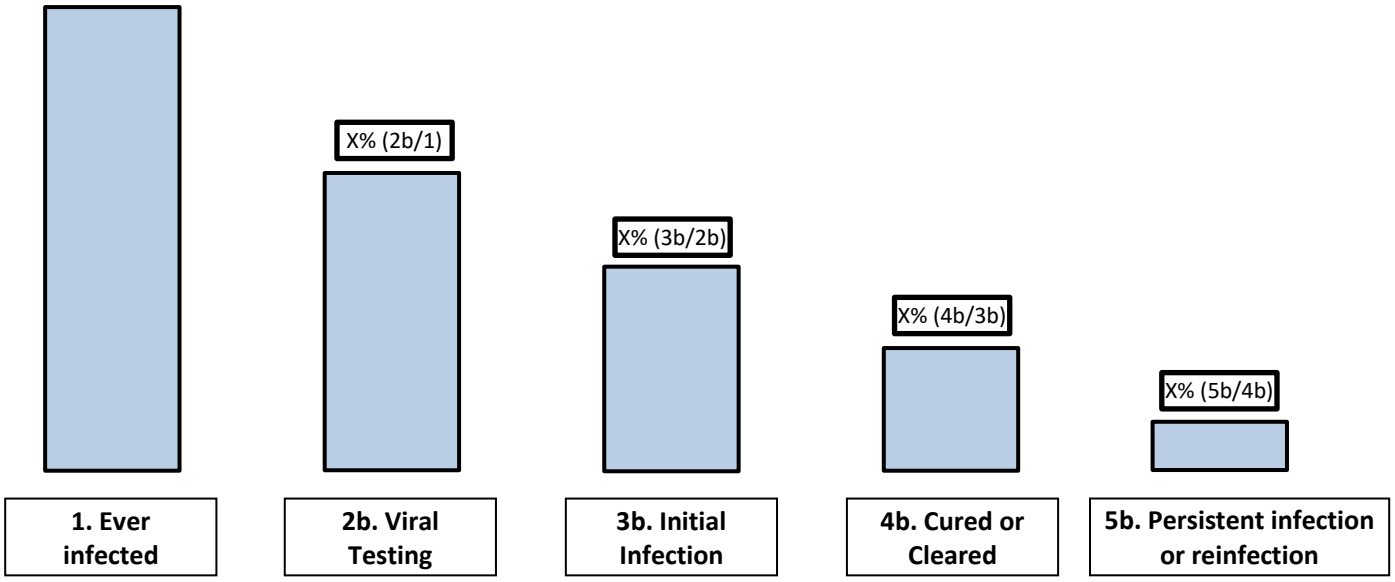
The full cascade (Figure 1) can be used to measure three important data-to-care opportunities. The first is the **proportion of individuals who were ever infected who have not had a viral test reported— (Step 2a)/(Step 1)**. Viral testing is important to distinguish past infections that are cured or cleared from current infections that require linkage to care and treatment. Jurisdictions should work to maximize the proportion of cases where viral testing is performed, as this is a critical step before starting treatment. Options to improve this proportion include expanding provider education, expanding reflex HCV RNA testing, and reviewing state policies on testing payment coverage.

The second data-to-care opportunity is the **proportion of initial HCV infections present that have not been cured or cleared—(Step 4a)/(Step 3b)**. A small proportion of this group includes people who were treated and cured or spontaneously cleared but did not have HCV viral testing reported to the health department. However, the majority of this population includes people who are not referred to treatment, do not complete treatment, or, in a small proportion, experience treatment failure. Opportunities to reduce this gap include improving linkage to care (e.g., patient navigation, same-day access to treatment initiation), expanding the number of trained HCV treatment providers, and reducing administrative or policy barriers to treatment (e.g., sobriety restrictions, fibrosis restrictions, provider restrictions, pre-authorization policies).

The third data-to-care opportunity is the **proportion of individuals who were cured or cleared during the evaluation time frame who develop persistent infection or reinfection—(Step 5b/Step 4b)**. In the full cascade (Figure 1), this also includes the proportion of individuals who were cured or cleared prior to the evaluation time frame who develop persistent infection or reinfection **(Step 5a/Step 3a)**. If a cumulative measure for all individuals with persistent infection or reinfection is needed, this could be calculated as (Step 5a + Step 5b)/ (Step 3a + Step 4b). Opportunities to reduce this proportion include access and supportive referrals to substance use treatment and harm reduction programs including education and provision of sterile drug injection equipment.

For illustration purposes, the HCV clearance cascade can be visually simplified by removing Steps 2a, 3a, 4a, and 5a. Each step of the resulting cascade continues to be a conditional proportion of the preceding step, as shown in Figure 4. Conditional proportions can be updated annually and used to monitor progress toward HCV identification and elimination.

Figure 4. Simplified Laboratory-based Hepatitis C Virus Clearance Cascade



The HCV clearance cascade can be developed for a variety of subpopulations (Table 1). Examining conditional proportions for each Step across demographic groups can help to identify disparities by age, gender identity, and race and ethnicity. Obtaining demographic data based on laboratory reporting can be challenging, but identifying disparities will help jurisdictions to successfully identify populations that can benefit from specific interventions.

Table 1. Conditional Proportions for 202X Laboratory-based HCV Clearance Cascade by Subpopulation

	Ever infected	Viral Testing	Initial Infection	Cured/ Cleared	Persistent infection/ Reinfection
	N	N, % (2b/1)	N, % (3b/2b)	N, % (4b/3b)	N, % (5b/4b)
Total	xx	xx, %	xx, %	xx, %	xx, %
Age*					
0–19					
20–39					
40–59					
60+					
Gender identity					
Male					
Female					
Transgender					
Race and ethnicity					
AIAN, NH					
Asian/Pacific Islander, NH					
Black, NH					
Hispanic					
White, NH					

Abbreviations: AIAN, American Indian or Alaska Native; NH, non-Hispanic

*Age in years during the evaluation year

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