

# Half a Diagnosis: Gap in Confirming Infection among Hepatitis C Antibody-positive Patients

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## ABSTRACT

**BACKGROUND:** Recent guidelines recommend testing all individuals born during 1945-1965 for hepatitis C virus (HCV) antibody. For antibody-positive patients, subsequent RNA testing is necessary to determine current infection status. This study aimed to assess whether clinicians order HCV RNA tests as recommended for antibody-positive patients and to identify barriers to such testing.

**METHODS:** We sampled individuals newly reported to the New York City Department of Health and Mental Hygiene's HCV surveillance system and collected information from clinicians. For patients without RNA test results, we asked the reason an RNA test was not ordered and requested that the clinician order the test.

**RESULTS:** Of 245 antibody-positive patients, 67% were tested for HCV RNA (for 21% of these, the test was ordered only after our request); 33% had no RNA testing despite our request. Patients without RNA testing were seen in medical facilities (47%), detox facilities (30%), and jail/prison (15%). Reasons RNA testing was not done were that the patient did not return for follow-up (35%), the facility does not do RNA testing (22%), and the patient was tested in jail (15%).

**CONCLUSIONS:** In our study, one third of patients did not get complete testing for accurate diagnosis of HCV, which is essential for medical management. Additional education for clinicians about the importance of RNA testing may help. However, with improved antiviral treatments now available for HCV, it is time for reflex HCV RNA testing for positive antibody tests to become routine, just as reflex Western blot testing is standard for human immunodeficiency virus.

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**KEYWORDS:** Hepatitis C; Surveillance; Testing

Hepatitis C virus (HCV) is a major cause of cirrhosis, liver failure, and liver cancer, and is a serious public health issue;<sup>1,2</sup> about 3.2 million people in the US have chronic HCV infection.<sup>3</sup> In New York City (NYC), an estimated 129,000 people are currently infected with HCV.<sup>4</sup> Managing and treating chronic HCV can be challenging because it occurs disproportionately in injection drug users, homeless, and incarcerated individuals, groups that often lack continuous access to health care.<sup>1</sup> Antibody screening tests for HCV are

recommended for patients with risk factors, including any history of injection drug use or receipt of a blood transfusion before 1992, and all individuals born from 1945-1965.<sup>5-7</sup> Fifteen percent to 25% of patients who test HCV antibody positive have no detectable HCV RNA in their blood, usually indicating that they have either resolved their infection or had a false-positive antibody test.<sup>3,8</sup> Therefore, national guidelines recommend that all patients with a positive HCV antibody test undergo HCV RNA testing to determine their infection status;<sup>5</sup> this is critical for 2 main reasons. First, patients with HCV infection can be managed to decrease their chances of progression to serious liver disease. For example, patients should be counseled to avoid alcohol use, a key contributor to disease progression, and can be screened to detect liver cancer early, improving liver cancer outcomes.<sup>5</sup> Second, patients with HCV can, in many cases, be cured with a regimen including ribavirin, interferon, and a protease inhibitor; with this regimen the cure rate is higher than

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previously seen using only ribavirin and interferon, and the duration of treatment in some cases can be shortened.<sup>9,10</sup>

HCV antibody tests have been available since the early 1990s. The first test for HCV RNA was approved by the US Food and Drug Administration in 2001, and HCV RNA testing was commonly used only after Medicare and Medicaid began reimbursing for it in 2003.<sup>11</sup> Several studies of patients seen in health systems across the US have found that not all patients receive recommended HCV RNA testing after a positive antibody.<sup>12,13</sup> Some clinicians may be unaware of the current widespread availability of HCV RNA tests and recommendations for determining viral status for patients who screen positive for HCV antibodies.<sup>14</sup> Also, because HCV RNA tests are expensive, confirmatory testing may not be ordered for patients who are HCV antibody positive but lack insurance coverage.<sup>15</sup>

As part of routine HCV surveillance, NYC requires laboratories and providers to report positive HCV antibody (enzyme immunoassay with high signal-to-cutoff ratio or recombinant immunoblot assay) and RNA tests for all NYC residents to the NYC Department of Health and Mental Hygiene (DOHMH). In 2010, the DOHMH received 92,440 laboratory positive HCV reports, which, after de-duplication, resulted in 10,065 patients being newly reported.<sup>16</sup> Because of the high volume of reports and limited staffing resources, the DOHMH does not typically investigate all reports. Data about HCV patients, therefore, are limited to information available on the initial report, for example, patient age, sex, and address. In July 2009, the DOHMH began an ongoing project to investigate a sample of newly reported patients. Among other objectives, this public health surveillance project aimed to assess whether clinicians order HCV RNA tests as recommended for antibody-positive patients, and to identify barriers to HCV RNA testing.

## METHODS

Starting July 1, 2009, we sampled patients for case investigations every 2 months. To generate the sample, we first created a dataset of patients who were reported to the DOHMH for the first time with a positive HCV test (antibody, RNA, or both) with a collection date in the 2- to 3-month period before the sampling date. We then selected a simple random sample of 20 patients for investigation using the survey select procedure in SAS (SAS Institute Inc., Cary, NC). We phoned the clinician who ordered the HCV test to explain that we were faxing a standard

questionnaire; we followed-up by telephone to remind the clinician to fax back the completed questionnaire. If clinicians did not respond by fax, we interviewed them by telephone or conducted chart reviews. We also interviewed patients with a standard questionnaire that included asking the names of all of the clinicians they were seeing. If either the clinician who ordered the HCV test or the patient mentioned that the patient was seen by a different clinician, we contacted that clinician as well, and faxed the questionnaire. Questionnaires included demographic, clinical, and health care questions. We also asked clinicians to provide the most recent hepatitis laboratory results. If the HCV RNA test had not been ordered, the questionnaire asked clinicians to identify reasons for not ordering the test. We also sent a follow-up letter requesting that the clinician order the RNA test and included guidelines explaining the recommendation.<sup>17</sup> The letter also requested that the RNA test results be faxed to us.

For patients who had not had an RNA test after the above investigation, we conducted additional follow-up. Nine months after the initial investigation, we contacted all clinicians known to have seen the patient and ascertained whether an HCV RNA test had been ordered for the patient.

Because this project was part of routine public health surveillance, approval from the health department's institutional review board was not needed.

## RESULTS

From July 1, 2009 to July 31, 2011, we sampled a total of 260 patients newly reported to the DOHMH with a positive HCV test for investigation. Diagnosis dates ranged from April 1, 2009 to May 27, 2011. Sampled patients had similar age, sex, and borough of residence distribution as all newly reported patients from which the sample was drawn (data not shown).<sup>16</sup> Of these 260 patients, we excluded 15 from analysis: 8 did not have a positive HCV test and had been reported in error, 4 were not NYC residents, and 3 were belatedly discovered to be duplicate reports of patients reported to the DOHMH in prior years. We obtained information from clinicians for 100% of the remaining 245 patients included in this analysis: by fax for 196 (80.0%) patients, by chart review for 36 (14.7%), by telephone for 7 (2.9%), and by mail for 6 (2.4%). After the initial investigation, there were 90 patients for whom no RNA testing had been ordered; these were eligible for additional follow-up investigation 9 months later. Of the 90 with completed 9-month follow-up, we found additional RNA test results for 9 (10.0%).

## CLINICAL SIGNIFICANCE

- One third of hepatitis C virus (HCV) antibody-positive patients did not get the recommended RNA testing to determine HCV infection status.
- Reasons RNA testing was not done were that the patient did not return for follow-up, the facility does not do RNA testing, and the patient was tested in jail.
- One approach to this problem is for reflex HCV RNA testing for positive antibody tests to become routine, similar to the human immunodeficiency virus testing protocol.

RNA status is summarized in **Table 1**. Of 245 patients, 119 (48.6%) had a positive RNA test; of these, 22 had the HCV RNA test only after DOHMH staff requested that the clinician order the test. Forty-five (18.4%) patients were categorized as not having HCV infection: 44 had a negative RNA test, and one patient had a subsequent negative antibody test with no RNA test done (the clinician interpreted the initial positive antibody result as a false positive). Twelve of these patients tested HCV RNA negative only after DOHMH staff contacted the clinician and requested the RNA test be ordered.

After investigation, including requesting that the clinician order the HCV RNA test and additional follow-up 9 months later, 81 of 245 patients (33.1%) still did not have an HCV RNA test done. **Table 2** summarizes characteristics of these 81 patients; 38 patients (46.9%) had their initial positive HCV antibody test in medical facilities, 24 (29.6%) in drug or alcohol rehabilitation facilities, and 12 (14.8%) in jails. Clinicians gave the following reasons for not ordering the RNA test: 28 patients (34.6%) did not return for follow-up, 18 (22.2%) were seen in facilities that did not do HCV RNA testing or referred the patient elsewhere for RNA testing, 12 (14.8%) were tested in jail, 5 (6.2%) had died, and 2 (2.5%) did not have insurance coverage.

## DISCUSSION

This surveillance project used data collected from clinicians and laboratory reports to assess whether HCV antibody-positive patients received the recommended follow-up RNA testing. One third of HCV antibody-positive patients did not have HCV RNA testing to determine if they had HCV infection. Among those who did have RNA testing, one fifth had testing only after DOHMH staff requested that the clinician perform it.

National guidelines recommend that all HCV antibody-positive patients undergo HCV RNA testing.<sup>5</sup> Patients who fail to be tested for HCV RNA will not know if they are infected and thus may not receive optimum counseling and medical management. With better treatment regimens increasingly available,<sup>9,10</sup> proper diagnostics are important for providers to make appropriate treatment recommendations and for patients to make informed decisions. Antiviral

**Table 2** Selected Characteristics of Patients for whom Hepatitis C RNA Was Not Done (n = 81), New York City, April 2009-May 2011

	n	%
Type of facility where patient had hepatitis C antibody test		
Medical care setting	38	46.9
Drug treatment/detox center	24	29.6
Jail	12	14.8
Other*	3	3.7
Unknown	4	4.9
Reasons hepatitis C RNA not ordered		
Patient did not return for follow-up	28	34.6
Facility does not do RNA testing and/or refers patients to outside facilities for RNA testing	18	22.2
Facility type was jail	12	14.8
Patient died	5	6.2
Patient does not have insurance coverage	2	2.5
Unknown	16	19.8

\*Other facilities: psychiatric facility (n = 2), nursing home (n = 1).

treatment can prevent complications of chronic HCV infection, such as cirrhosis and liver cancer. Additionally, if clinicians tell their patients they have HCV infection based on a positive antibody test alone, patients may think that they are infected with HCV when, in fact, they may have resolved a prior infection or had a false-positive antibody test; such patients therefore may not take steps to avoid acquiring HCV infection. A 2009 survey of injection drug users in Seattle showed that injection drug users preferred to share injection drug equipment with others of the same HCV infection status (known as serosorting).<sup>18</sup> Because antibodies to HCV do not confer immunity to reinfection,<sup>19</sup> if a patient believes he is currently infected based on a positive antibody test alone and is actually not infected, serosorting based on perceived HCV infection status will put the patient at risk for a new HCV infection.

Our study had several important strengths. We selected patients for investigation by taking a simple random sample of those newly reported to NYC DOHMH with a positive HCV test. Randomly sampling increases our confidence that results from this study are representative of NYC's newly reported HCV population. Similar sampling methods have been used for HCV and other public health surveillance projects in the past.<sup>20-23</sup> We sampled a relatively small number to ensure that sufficient staff time was available for investigations to be thorough. Our staff was able to follow-up with all clinicians known to have seen the patient, including those mentioned by reporting clinicians and by patients themselves.

We can use these investigation findings to estimate the number of individuals in NYC who tested HCV antibody positive but whose infection status is not known.<sup>16</sup> If we assume that 33% did not have RNA testing, then we estimate that 3332 of the 10,065 patients newly reported with a positive HCV test in NYC in 2010 were not tested for

**Table 1** Hepatitis C RNA status (n = 245), New York City, April 2009-May 2011

RNA status	n	%
RNA positive	119	48.6
RNA positive after DOHMH staff contact	22	18.5
RNA negative*	45	18.4
RNA negative after DOHMH staff contact	12	26.7
RNA not done	81	33.1

DOHMH = Department of Health and Mental Hygiene.

\*Includes one patient who was initially antibody positive and subsequently antibody negative (no RNA was test done); the clinician interpreted the initial result as a false-positive antibody.

HCV RNA. Alternatively, if we used the percentage of patients who never had RNA testing plus those patients who got RNA testing only after our request (47%), then we estimate that 4721 patients would not have received RNA testing.

In 2009, an assessment of HCV antibody-positive patients in the Veterans Administration Southern California Network found that 75% of HCV antibody-positive patients received RNA testing,<sup>12</sup> which is somewhat higher than in our sampled population. Another study assessed electronic health records from 4 different health systems across the US and found that only 62% of patients who tested HCV antibody positive had a follow-up HCV RNA test.<sup>13</sup> While neither of these studies is comparable to ours in terms of the patient populations included, they do suggest that this is a widespread problem in the US, and a nationwide approach is needed.

Many patients did not receive the recommended RNA testing because they were seen in a facility that does not do RNA testing, or a facility that refers patients elsewhere for RNA testing (22%), or because they were seen in jail (15%). HCV RNA tests are usually not available at drug treatment facilities, often because of lack of funding.<sup>1</sup> For patients seen in jail, inmate stays can be short and inmates may have been released by the time antibody results are available, so follow-up RNA testing cannot be ordered.

There were several limitations to our study. First, it is possible that patients got HCV RNA testing that we did not ascertain through our investigation, especially if their results were negative, which are not reportable to the DOHMH. This probably happened rarely, however, because as part of our investigation protocol, we asked both patients and clinicians to name all clinicians known to have seen the patient and contacted those clinicians as well, increasing the likelihood that we obtained all HCV test results. Second, we might not have interviewed the clinician who knew the most about the patient. Identifying the clinician who best knew the patient was more challenging in settings such as jails where lengths of stay are short, and jail staff may not have information about a patient's primary care provider. Lastly, we did not ask providers about the extent of their efforts to get patients to return for follow-up. It is possible that some clinicians lacked systems to recall patients who missed follow-up appointments.

Our findings highlight one of the many challenges to HCV diagnosis, management, and treatment. Educating clinical staff as well as social workers and counselors in drug rehabilitation facilities and jails on the importance of HCV RNA testing will help ensure that more patients get RNA testing. In response to our findings, in December 2010, the NYC DOHMH developed a bulletin for primary care providers about diagnosis and management of HCV.<sup>17</sup> In particular, the bulletin highlights the need for HCV RNA testing for antibody-positive patients. Another potential method for educating clinicians is adding alerts to electronic health records to remind clinicians to order HCV RNA for antibody-positive patients.<sup>24</sup> Also, laboratories could add

messages on antibody-positive laboratory results that explain the need for follow-up RNA testing.

In addition to educational measures, appropriate resources need to be allocated to make HCV RNA testing available and affordable in facilities that screen for HCV, especially because the newest Centers for Disease Control and Prevention recommendations for testing all individuals born during 1945-1965 for HCV antibody will likely increase the number of patients being screened.<sup>6</sup> While patient follow-up is challenging with any screening test, it may be particularly difficult with the HCV population.

We believe it is time for reflex HCV RNA testing for all positive antibody tests to become routine, just as reflex Western blot testing became routine for human immunodeficiency virus.<sup>25</sup> Alternatively, for facilities that use the rapid HCV antibody test, after a positive antibody result, a specimen for RNA testing can be drawn at the same visit.<sup>26</sup> Either method would ascertain infection status without requiring a follow-up visit for blood draw. Knowing which patients have HCV infection after a single visit would greatly streamline the process of ensuring that patients who screen HCV antibody positive get the additional testing necessary; patients with positive RNA can then be counseled about measures for protecting their liver and improving their health, and evaluated for antiviral treatment.

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