

Performance of Premarket Rapid Hepatitis C Virus Antibody Assays in 4 National Human Immunodeficiency Virus Behavioral Surveillance System Sites

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Background. The Centers for Disease Control and Prevention (CDC) estimates that 4.1 million Americans have been infected with hepatitis C virus (HCV) and 75%–80% of them are living with chronic HCV infection, many unaware of their infection. Persons who inject drugs (PWID) account for 57.5% of all persons with HCV antibody (anti-HCV) in the United States. Currently no point-of-care tests for HCV infection are approved for use in the United States.

Methods. Surveys and testing for human immunodeficiency virus (HIV) and anti-HCV were conducted among persons who reported injection drug use in the past 12 months as part of the National HIV Behavioral Surveillance System in 2009. The sensitivity and specificity of point-of-care tests (finger-stick and 2 oral fluid rapid assays) from 3 manufacturers (Chembio, MedMira, and OraSure) were evaluated in field settings in 4 US cities.

Results. Sensitivity (78.9%–97.4%) and specificity (80.0%–100.0%) were variable across assays and sites. The highest assay-specific sensitivities achieved for the Chembio, MedMira, and OraSure tests were 94.0%, 78.9% and 97.4%, respectively; the highest specificities were 97.7%, 83.3%, and 100%, respectively. In multivariate analysis, false-negative anti-HCV results were associated with HIV positivity for the Chembio oral assay (adjusted odds ratio, 8.4–9.1; $P < .01$) in 1 site (New York City).

Conclusions. Sensitive rapid anti-HCV assays are appropriate and feasible for high-prevalence, high-risk populations such as PWID, who can be reached through social service settings such as syringe exchange programs and methadone maintenance treatment programs.

The Centers for Disease Control and Prevention (CDC) estimates that 4.1 million Americans have been infected with the hepatitis C virus (HCV), 75%–80% of whom are living with chronic HCV infection [1]. The CDC recommends routine HCV antibody (anti-HCV) testing for persons at risk of infection [2], yet recent studies

have estimated that 45%–85% of HCV-infected persons are unaware of their status [3–5]. Knowledge of HCV status is a prerequisite for persons to make health-promoting behavior changes and treatment decisions.

Persons with a history of injection drug use (IDU) account for 57.5% of all anti-HCV positive persons in the United States [1], and the CDC estimates that IDU accounted for 48% of acute hepatitis C cases in the United States in 2007 [6]. Studies reported elsewhere have found anti-HCV prevalence of 30%–70% among persons who inject drugs (PWID), depending on the frequency and duration of IDU [7]. Although they are at high risk for bloodborne infections such as HCV and human immunodeficiency virus (HIV), PWID have

Received 6 April 2011; accepted 28 June 2011.

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Clinical Infectious Diseases 2011;53(8):780–786

Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2011.

1058-4838/2011/538-0005\$14.00

DOI: 10.1093/cid/cir499

limited access to health care [8]. They are tested infrequently for anti-HCV with conventional laboratory assays, and when tested for HIV with conventional assays they are less likely to return for results [9]. In contrast to conventional assays, rapid assays allow specimens (eg, finger-stick blood or oral fluid) to be collected and tested at the point of care and do not require a follow-up visit to receive test results. Given that rapid HIV testing improves receipt of HIV test results [10–13], access to care, and health outcomes [10, 14], rapid anti-HCV assays could benefit PWID in the same ways.

The CDC recently completed a laboratory-based evaluation of 3 rapid anti-HCV assays [15]. However, the most likely use of these rapid assays is in point-of-care settings such as HIV testing centers and agencies that provide services to PWID. We report the performance characteristics of these rapid tests in 4 study sites participating in the National HIV Behavioral Surveillance System (NHBS) [16]. After data collection ended for this study, the US Food and Drug Administration (FDA) approved the OraSure assay for venous and finger-stick blood samples. This assay was on the US market for laboratory testing as of June 2011.

MATERIALS AND METHODS

National HIV Behavioral Surveillance System Monitoring

The NHBS monitors the prevalence of and trends in HIV-related risk behaviors, including sex and drug use, HIV testing, and use of HIV prevention services among persons at high risk for HIV transmission [16]. NHBS is a community-based survey that conducts interviews and HIV testing among men who have sex with men, heterosexuals at increased risk for HIV infection, and PWID in a triennial cycle. NHBS uses respondent-driven sampling [17] to recruit PWID. Participants recruit their peers, who are screened for eligibility (≥ 18 years of age, living in the participating metropolitan statistical area, able to provide informed consent, able to complete the survey in English or Spanish, and having injected drugs during the past 12 months) in the local NHBS field office or van. During the 2009 data collection period, 4 cities (of 21 participating NHBS cities) conducted supplemental rapid and conventional anti-HCV testing. Blood from consenting participants was anonymously tested for anti-HCV through standard laboratory-based procedures (results provided to participants). Specimens from these consenting participants also were tested with the rapid anti-HCV kits (results not provided to participants because the tests were not approved for diagnostic use by the FDA at that time).

Rapid Anti-Hepatitis C Virus Assays

In 2009, 3 developmental rapid anti-HCV assay manufacturers responded to a Federal Register notice announcing an opportunity to collaborate in the evaluation of candidate rapid

anti-HCV assays. The assays selected for evaluation were the Chembio DPP HCV test (Chembio Diagnostic Systems), Multiplo Rapid HIV/HCV Antibody Test (MedMira Laboratories) and OraQuick Rapid HCV Antibody Test (OraSure Technologies). All rapid assays are single-use, disposable-chamber, in vitro, qualitative, immunochromatographic assays to detect anti-HCV, which provide visual results in <40 minutes. More detailed descriptions of each assay can be found elsewhere [15].

Assay Performance

The rapid assay manufacturers provided documentation and instruction manuals for performing the assays and interpreting the results. In addition, on-site training was provided by the manufacturers. The assays were performed according to manufacturers' instructions using finger-stick blood and/or oral specimens. An assay was interpreted as invalid if the control line was missing or broken, as negative if a control line was present (regardless of intensity) with no corresponding test line, and positive if both control and test lines were present. Each specimen was tested on site and interpreted by 2 operators.

Reference Assays

All specimens in the evaluation panel were tested for anti-HCV by FDA-approved immunoassays in local laboratories according to local study protocols. The Ortho HCV Version 3.0 enzyme-linked immunosorbent assay (Ortho-Clinical Diagnostics) was used in Denver, Colorado, the Abbott AxSYM anti-HCV microparticle immunoassay (Abbott Laboratories) in New York, New York, and Seattle, Washington, and the Bayer Advia Centaur HCV chemiluminescent immunoassay (Bayer Healthcare) in Dallas, Texas.

A third-generation recombinant immunoblot assay (RIBA) (Chiron RIBA HCV 3.0 SIA; Novartis Vaccines and Diagnostics) was used to confirm antibody positivity for reactive specimens with a signal-to-cutoff ratio below the CDC-recommended threshold for each assay [18], except in Dallas; the commercial laboratory in Dallas did not follow the protocol established by the study site and did not use a confirmatory assay.

Specimen Panel

We report data on rapid anti-HCV testing of blood and/or oral specimens collected from participants in New York City, Denver, Seattle, and Dallas. The New York City site staff conducted the Chembio ($n = 207$) or OraSure ($n = 285$) rapid assay using oral fluid specimens from participants. They integrated the rapid anti-HCV assays into their testing protocol one at a time to have the least impact on HIV testing. OraSure was integrated first and Chembio second, resulting in a lower sample size for Chembio. The Denver site staff conducted the Chembio rapid assay with 389 participants who provided blood specimens, and of those, 282 provided oral specimens. Similar to New York City site staff, those in Denver integrated the assays

one at a time for minimal impact on HIV testing, integrating the Chembio blood assay first, followed by the Chembio oral fluid assay. Four specimens were excluded from analysis owing to indeterminate RIBA results. The Seattle site staff conducted the OraSure rapid assay, and participants provided blood and oral specimens ($n = 269$). Five specimens were excluded; 3 specimens had invalid anti-HCV screening results, 1 oral fluid specimen result was missing, and 1 specimen was RIBA indeterminate. The Dallas site staff conducted the MedMira rapid assay using 448 blood specimens; 16 specimens were excluded from the analysis due to invalid rapid assay results.

Data Analysis

The performance of each rapid anti-HCV assay was evaluated at the site level in comparison with results from the 2 conventional reference methods most commonly used in public laboratories [19]. First, we compared the results of the rapid assays with those of FDA-approved anti-HCV screening assays, used as directed by the immunoassay manufacturers (screening assay [SA] reference method). Second, we compared the results of the rapid assays with those of the CDC-recommended HCV testing algorithm, which considers a sample anti-HCV positive if the anti-HCV screening assay signal-to-cutoff ratio exceeds the threshold or supplemental confirmation (RIBA) on screening reactive samples with a signal-to-cutoff ratio below the CDC-recommended threshold is positive (CDC reference method) [18].

Sensitivity and Specificity

Sensitivity and specificity were assessed by comparing results of each rapid assay to each reference method. Sensitivity was defined as the number of reference assay–positive specimens identified as positive by the rapid assay divided by the total number of reference assay–positive specimens. Specificity was defined as the number of reference assay–negative specimens identified as negative by the rapid assay divided by the total number of reference assay–negative specimens. Confidence intervals (CIs) for sensitivity and specificity were calculated using the Wilson score method [20]. Multivariate logistic regression was used to determine whether false-positive or false-negative results were predicted by selected demographic variables (sex, birth year, race/ethnicity, and HIV status). Separate models were created for each site across false-positive and false-negative results, for a total of 8 models. Data analysis was performed using PASW software (version 18.0).

RESULTS

Of the 1861 participants who consented to receive rapid and conventional anti-HCV testing, 1596 (85.8%) had test results included in this analysis (490 in New York City, 389 in Denver, 269 in Seattle, and 448 in Dallas). The mean age of participants across the 4 sites was 45 years (range, 18–75 years), and 69% were male (Table 1).

Table 1. Selected Demographic Proportions of Sample Population by City

Characteristic	Proportion of population, %			
	New York (n = 490)	Denver (n = 389)	Seattle (n = 265)	Dallas (n = 448)
Sex				
Male	77	68	64	70
Female	23	32	36	30
Year of birth				
1975–1990	30	26	25	12
1965–1974	37	24	28	13
1955–1964	27	29	33	40
1945–1954	6	19	15	33
1939–1944	0	2	0	2
Race/ethnicity				
Hispanic	57	26	5	7
American Indian/Alaska Native	0	3	6	0
Asian	0	0	0	0
Black, not Hispanic	7	13	11	74
Native Hawaiian/Pacific Islander	0	1	0	0
White, not Hispanic	34	52	69	16
Other	0	5	9	3
HIV test result				
Negative	88	95	95	98
Positive	12	4	6	2

Some categories do not total 100% due to rounding error.

Table 2. Performance Characteristics of Hepatitis C Virus Antibody Rapid Assays

Manufacturer (specimen type) no. of specimens	Sensitivity (95% CI), %	Specificity (95% CI), %	True-positive, %	False-negative, %	True-negative, %	False-positive, %
Chembio (oral)						
New York City						
SA (n = 197)	88.8 (82.8–92.9)	80.0 (66.2–89.1)	69	8	18	5
CDC (n = 197)	91.2 (85.6–94.8)	81.6 (68.6–90.0)	69	7	20	5
Denver						
SA (n = 282)	91.3 (86.5–94.5)	97.7 (92.0–99.4)	63	6	30	1
CDC (n = 279)	92.2 (87.5–95.2)	97.7 (92.0–99.4)	63	5	30	1
Chembio (blood)						
Denver						
SA (n = 389)	93.0 (89.5–95.4)	97.1 (91.8–99.0)	68	5	26	1
CDC (n = 385)	94.0 (90.6–96.2)	97.1 (91.8–99.0)	69	4	26	1
MedMira (blood)						
Dallas						
SA (n = 432)	78.9 (74.6–82.7)	83.3 (71.0–91.5)	70	19	9	2
OraSure (oral)						
New York City						
SA (n = 285)	94.4 (90.4–96.8)	95.8 (88.5–98.6)	71	4	24	1
CDC (n = 285)	94.7 (90.8–97.0)	92.1 (83.8–96.3)	69	4	25	2
Seattle						
SA (n = 265)	90.8 (85.4–93.7)	98.6 (92.4–99.8)	67	7	26	0
CDC (n = 264)	92.2 (87.5–95.2)	97.2 (90.9–99.3)	67	6	27	1
OraSure (blood)						
Seattle						
SA (n = 266)	95.9 (91.6–97.6)	100 (94.9–100.0)	71	3	26	0
CDC (n = 265)	97.4 (94.1–98.9)	98.6 (92.9–99.8)	71	2	27	0

Some categories do not total 100% because of rounding.

Abbreviations: CDC, Centers for Disease Control and Prevention reference method; CI, confidence interval; SA, screening assay reference method.

There was considerable variability in assay performance across sites and reference approaches (Table 2). Sensitivity and specificity for the assays were as follows: Chembio oral fluid assay, 88.8%–92.2% for sensitivity and 80.0%–97.7% for specificity; Chembio blood assay, 93.0%–94.0% and 97.1%; MedMira blood assay, 78.9% and 83.3%; OraSure oral assay, 90.8%–94.7% and 92.1%–98.6%; and OraSure blood assay, 95.9%–97.4% and 98.6%–100.0%. For all sites and assays, sensitivities increased with use of the CDC reference method compared with the SA reference method.

For both reference methods, false-negative rapid anti-HCV results were associated with HIV positivity for the Chembio oral assay in New York City (adjusted odds ratio [aOR] for SA method, 8.36 [95% CI, 2.23–31.45; $P < .01$]; aOR for CDC method, 9.10 [95% CI, 2.11–39.34; $P < .01$]). Neither false-positive nor false-negative rapid anti-HCV results were associated with HIV positivity for any of the other sites or assays. Of the 99 total HIV-positive specimens, 88% were anti-HCV positive. For the SA reference method, false-positive results were negatively associated with birth years between 1945 and 1954 for the MedMira assay in Dallas (aOR, 0.04; 95% CI, .00–.41; $P < .01$). Neither false-positive nor false-negative OraSure assay

results were associated with any specific patient characteristic. Demographic data regarding sex and race or ethnicity were not predictive of false-positive or false-negative results for any of the rapid assays.

DISCUSSION

This field evaluation of 5 premarket rapid assays found considerable variability in performance characteristics across sites and assays. Sensitivity ranged from 78.9% to 97.4%, and specificity from 80.0% to 100.0%. HIV infection was a significant predictor of false-negative rapid anti-HCV test results for the Chembio assay in New York but not for the other assays or sites.

These results are similar to the findings of a recent CDC laboratory evaluation of these assays [15], although, as might be expected, performance in field use was slightly poorer than in laboratory use (Figure 1). Chembio and OraSure assay sensitivities were slightly different, but Figure 1 highlights the fact that their CIs overlap in all settings using both reference methods, whereas the MedMira assay is considerably lower. Chembio and OraSure assay specificities also follow the same pattern across settings with overlapping CIs in all settings except

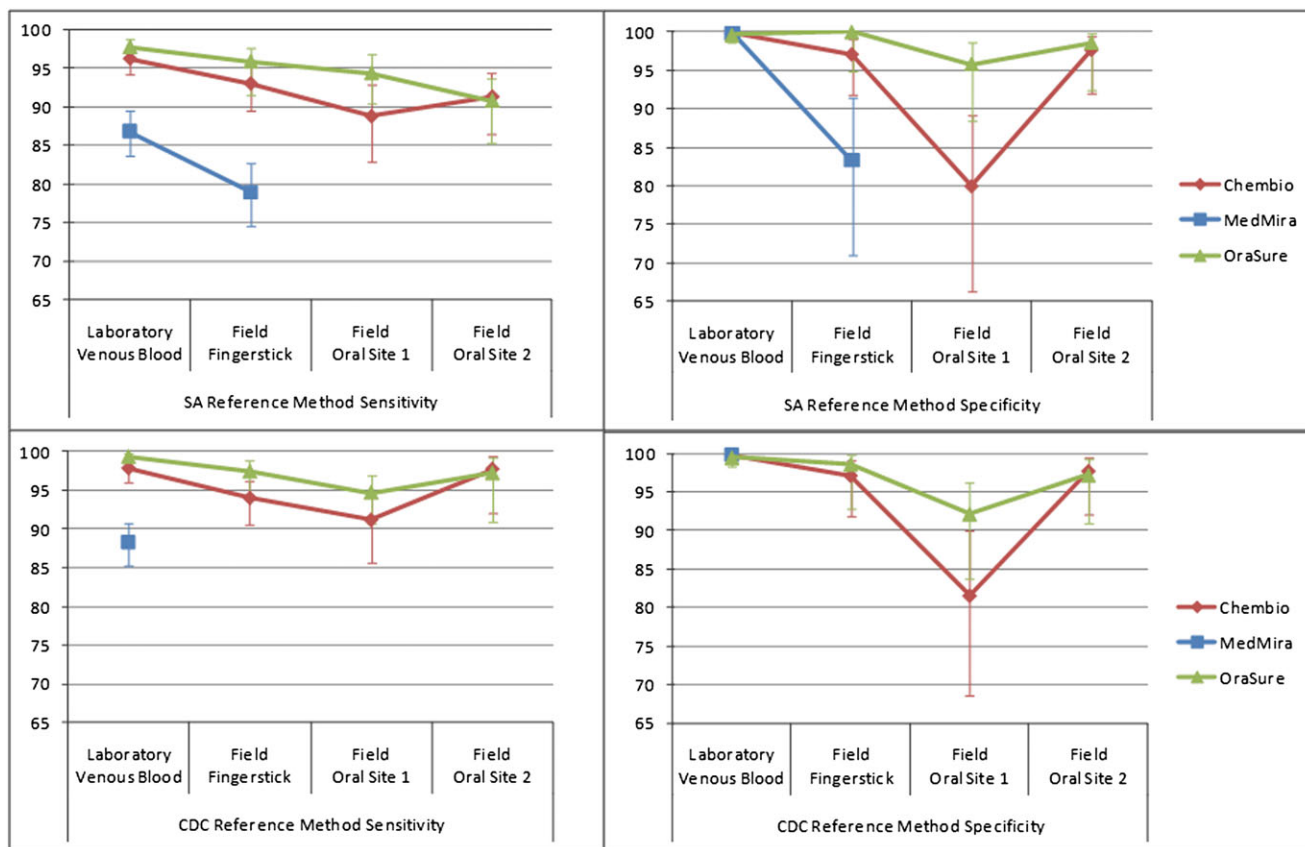


Figure 1. Laboratory and field test performance characteristics of rapid anti-HCV assays for anti-hepatitis C virus antibody by assay and reference method. Field fingerstick specimens were obtained from Denver, Dallas, and Seattle field sites. Field Oral Site 1 specimens were obtained from New York City field site. Field Oral Site 2 specimens were obtained from Denver and Seattle field sites. Values represent percentages. CDC, Centers for Disease Control and Prevention; SA, screening assay.

for field oral site 1 (New York City). It also seems that performance characteristics were generally lower in field oral site 1 than in almost all other settings across reference methods, but it is uncertain why. The sensitivities of the blood assays seem to trend somewhat higher than those of the oral assays, but the CIs overlap. These differences in rapid assay sensitivity between laboratory and field settings are similar to those found for rapid HIV assays [21, 22]. They may be due to the use of recently collected whole blood in the field versus stored serum in the laboratory, differences in technical expertise among those performing the assays, and possible contamination in field settings compared with sterile laboratory settings. As expected, use of the CDC reference method resulted in somewhat higher sensitivity for all assays than use of the SA reference method. However, given the small sample sizes of antibody-positive specimens in the panel (range, 148–384 specimens), the CIs for the SA and CDC reference methods are wide and overlap.

The unweighted HIV prevalence of 6.3% among all rapid assay evaluation participants was similar to that found among PWID in other studies [23]. The rate of coinfection with HIV and HCV was very high in this sample (73.3%–93.0% among

persons with HIV infection across sites). The false-negative anti-HCV results associated with HIV positivity for both the Chembio oral and OraSure oral assays in New York City may be related to the high prevalence of HIV infection (12.0%) at that site. For the Chembio assay, but not the OraSure assay, the HIV-positive specimens were more likely than the HIV-negative specimens to have a false-negative anti-HCV result.

The proportion of false-negative anti-HCV results (11.3%) among HIV-positive persons across all 3 assays compares favorably with that in a European study using a rapid anti-HCV (22.4%) [11], but in other studies using conventional anti-HCV screening assays, false-negative results among HIV-positive individuals have ranged from 3.8% to 5.5%, lower than the 11.3% in the current study [10–12].

Sensitive rapid anti-HCV assays are appropriate for high-prevalence, high-risk populations, such as PWID who can be reached through specific social service settings (eg, syringe exchange programs and methadone maintenance treatment programs). First, PWID would receive their results the same day as opposed to waiting 2–4 weeks to receive conventional results, increasing the likelihood that prevention counseling messages

and referrals for follow-up can be provided at the point of care. Second, difficulty obtaining blood from persons whose veins were heavily damaged from years of IDU was a barrier to testing in Seattle and Dallas, but less so in Denver and New York City, where experienced phlebotomists were on staff. Rapid anti-HCV assays that use oral fluid or capillary blood have the benefit of not requiring a phlebotomist and can be provided at the point of care. HCV treatment models also have been shown to be successful in methadone maintenance treatment programs, expanding care options for PWID [24, 25].

There are a number of potential settings for using rapid anti-HCV assays. Given the 20%–25% HCV coinfection rate among persons infected with HIV [26], HIV testing settings may find a significant yield of previously unidentified anti-HCV-positive persons. For laboratories that provide a low volume of HCV testing, rapid assays offer a cost-effective alternative to conventional anti-HCV screening assays. They could provide quick results in settings where poor infection control practices may have exposed persons to HCV. Rapid anti-HCV assays also are used by military personnel in the field [27] to prevent transmission of bloodborne infections in emergency blood transfusions.

Although qualitative data on the integration of rapid anti-HCV testing into HIV testing settings were not systematically collected, 2 sites (Seattle and New York City) submitted final reports and 2 sites (Denver and Dallas) presented findings on their integration at a national conference [28]. All sites reported that the rapid anti-HCV testing did not have a negative impact on HIV testing or study recruitment, although time had to be added to the procedures for their inclusion, and standardized educational materials and guidance for HCV posttest counseling were needed.

There are some limitations to this study. With the exception of comparing the blood and oral assay findings in Seattle and Denver, the results cannot be compared across sites or manufacturers because there were differences in reference screening assays, operators, participants, and laboratories. Because of the lack of a confirmatory assay in Dallas, the CDC reference method could not be applied, limiting our ability to assess the sensitivity of the MedMira rapid assay; its sensitivity may have been higher if the CDC reference method had been used. Although it was not the intention of this study to evaluate the performance of rapid anti-HCV assays in the diagnosis of chronic infection, use of an additional reference method such as polymerase chain reaction assay to assess for HCV RNA would also be expected to increase sensitivity somewhat by reducing the number of false-negative results.

There are several opportunities for further study and evaluation of rapid anti-HCV assays. First is an evaluation method that would enable a direct comparison of performance characteristics between rapid assays that controlled for training, operator, testing protocol, and immunoassay and confirmatory tests.

Second, testing for HCV RNA could identify individuals with anti-HCV but without detectable virus—a phenomenon that most often represents past HCV infection that has subsequently cleared—as well as persons with detectable virus but without detectable anti-HCV; thus, these data would improve our ability to assess the sensitivity of rapid anti-HCV tests as well as the specificity of positive rapid anti-HCV assay results for identifying active viral infection. Third, the apparent relationship between false-negative rapid anti-HCV assay results and HIV infection in this study and the CDC laboratory evaluation suggests that rapid anti-HCV assays need to be evaluated using an HIV-positive specimen panel. Fourth, given that rapid anti-HCV assays will probably be adopted in HIV testing settings, demonstration projects should be conducted to evaluate the impact of integrating these assays into current protocols. Finally, standardized posttest educational materials and guidance for posttest counseling for persons with positive rapid anti-HCV assay results need to be developed and evaluated. In conclusion, sensitive rapid anti-HCV assays are useful for the detection of HCV antibodies among persons at risk for HCV, and candidate rapid assays demonstrated acceptable sensitivity and specificity, comparable to assays currently in use.

Notes

Acknowledgments. The authors would like to thank all the NHBS participants who agreed to participate in this study. This project also would not have been possible without the staff of the 4 participating sites in Denver, New York City, Seattle, and Dallas, as well as the 3 manufacturers: Chembio, MedMira, and OraSure. Data support was also provided by Nevin Krishna at CDC.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Financial support. This work was supported by the Divisions of Viral Hepatitis and HIV/AIDS Prevention at the CDC. All assays were provided in kind by the manufacturers. The use of trade names and commercial sources is for identification only and does not imply endorsement by the CDC.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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