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MAJOR ARTICLE

Hepatitis C Screening in People With Human Immunodeficiency Virus: Lessons Learned From Syphilis Screening

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Background. The incidence of hepatitis C virus (HCV) infection is increasing in human immunodeficiency virus (HIV)-positive men who have sex with men (MSM). New guidelines recommend annual screening for HCV, similar to recommendations for syphilis screening with rapid plasma reagin (RPR).

Methods. This study compares the frequency of repeat HCV antibody (Ab) testing to repeat RPR testing in a retrospective chart review of 359 HCVAb-negative people living with HIV (PLWH) observed in an Infectious Diseases clinic. Patients were classified into risk groups based on sexual risk factors.

Results. Although 85% of PLWH had repeat syphilis screening, less than two thirds had repeat HCVAb screening. The MSM status was associated with increased HCVAb and RPR testing (adjusted odds ratio, 2.6 and 5.9, respectively). Seven persons had incident HCV infection: 3 were MSM, and 4 had symptoms or abnormal laboratory results to prompt testing.

Conclusions. Failure to find incident HCV infection in PLWH represents missed opportunities to cure HCV infection and prevent progressive liver disease. Further quality improvement studies are necessary to develop physician-focused interventions to increase HCV screening rates in PLWH.

Keywords. hepatitis C; HIV; MSM; syphilis.

In the era of effective human immunodeficiency virus (HIV) antiretroviral therapy, hepatitis C virus (HCV) has emerged as a major cause of morbidity and mortality in people living with HIV (PLWH) [1–7]. With the recent advent of more efficacious and tolerable HCV medications, many people with HIV and HCV coinfection are now receiving HCV treatment and being cured. The first step in the cascade of HCV care is aggressive identification of persons with infection. Identification of HCV is important not only for the patient's health, but from a public health perspective early diagnosis and referral into HCV treatment is one method of reducing the amount of circulating virus and preventing new infections.

In the first 2 decades of the HIV epidemic, the most common route of exposure to HCV was injection drug use (IDU), which commonly preceded HIV infection [8–10]. Hepatitis C virus screening with HCV antibody (Ab) was recommended upon HIV diagnosis, in the setting of abnormal liver enzymes, or with the report of new high-risk behaviors [11]. However, data published in 2005 from Swiss HIV Cohort Study reported an increase in incident HCV cases in HIV-positive men who have sex with men (MSM) [12]. The shift in epidemiology has subsequently been confirmed in numerous international locations and attributed to increasingly risky sexual and drug-use patterns within the MSM population [13–17]. As a result, several professional societies have recommended switching from symptom and risk-based guided HCVAb screening to annual screening of HIV-positive patients for HCV infection [18–20].

Despite these updated guidelines, HIV clinicians are not testing previously HCVAb-negative PLWH annually for incident HCV infection [21–26]. The reasons for low annual screening rates are likely multifactorial, but they may include lack of knowledge of the changing epidemic, underappreciation of risk for sexual transmission of HCV, slow dissemination of the updated guidelines into practice, and continued risk-based screening practices. The relative contributions of each of these factors are unknown. One way to further investigate whether clinicians are relying on risk-based screening methods and whether they are correctly assessing risk for sexual HCV transmission is to compare annual HCV screening to annual screening for syphilis. For over 10 years, annual syphilis testing has been recommended for all sexually active HIV patients, and physician

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compliance with annual screening for syphilis is a national HIV quality-of-care benchmark [27, 28].

This study examines the frequency of HCVAb screening and syphilis and compares this across different risk groups using multivariate analysis to identify demographic and clinical characteristics associated with repeat testing. Persons with incident HCV infection, identified during the course of the study, are described.

METHODS

Study Sample

A retrospective chart review was approved by the Tufts University Health Sciences Investigational Review Board. A query of *International Classification of Diseases, Ninth Revision* codes from clinic (042 HIV/acquired immune deficiency syndrome) identified PLWH who were seen in the Infectious Diseases clinic at Tufts Medical Center, Boston, Massachusetts between April 1, 2010 and December 31, 2013. The study was limited to patients who (1) had a negative baseline HCVAb result in the electronic medical record or a negative HCVAb was documented in the notes, (2) seen at least 2 times in clinic during the study period, and (3) had at least 365 days between visits. The goal of these criteria was to ensure our cohort was HCVAb negative, actively seen in the clinic, and would be eligible for annual HCVAb screening. A review of the electronic laboratory data (dating back to 1993) and clinic notes in electronic medical record (dating back to 1998) was performed for all people in the study cohort. The data collected included (1) demographic data and HIV risk factor from earliest recorded visit, (2) ID physician, (3) clinical data including CD4 count, HIV viral load from most recent visit, and (4) dates and results of all HCVAb tests and syphilis tests. At our institution, syphilis screening is performed using the rapid plasma regain (RPR) test. In HCV seroconverters (HCVAb negative followed by HCVAb positive), additional laboratory information was recorded including maximum values for alanine aminotransferase and aspartate aminotransferase between the negative and positive HCVAb results. Deidentified data were entered into REDCap (version 5.10.1; REDCap Software, Vanderbilt University, Nashville, TN), and 25% of the cohort was randomly selected for double entry into RedCAP.

Statistical Methods

The outcome of interest was repeat testing for HCV and syphilis with HCVAb and RPR, respectively. The outcome was evaluated both as a continuous variable (number of times tested) and a dichotomous variable (whether or not the patient was tested more than once). The cohort was categorized into 3 groups (high, moderate, and low) based on their risk for sexually transmitted diseases. The high-risk group was defined as patients with a history of positive RPR result (+RPR). The moderate risk group was defined as those who were MSM without history of +RPR. All others, including heterosexual men and women without history of positive RPR, were categorized into the low-risk group. These risk group stratifications are based on evidence that the HIV-positive MSM have a high incidence of coinfection with sexually transmitted diseases [29].

We used Pearson's χ^2 test to compare the percentage of patients who had more than 1 HCVAb with the percentage of people who had more than 1 RPR. In patients who had both more than 1 HCVAb and more than 1 RPR, we used paired Wilcoxon ranked-sum test to compare the number of tests and the time between the tests (1st and 2nd test).

We used univariate and multivariable logistic regression models to determine characteristics associated with the outcome of repeat testing for HCVAb or RPR. The first model used univariate logistic regression, and it examined independent variables including the following: sex, age, gender/sexual preference (MSM, non-MSM males, women), race (white or not white), time observed in the clinic, history of +RPR, sexual risk group, and history of IDU. For the multivariable model, we used backward elimination and included a predictor if its P value was >.20. Statistical significance was set at $P < .05$. All statistical analysis was conducted using Stata, (version 13.1; College Station, TX) [30].

RESULTS

There were 622 patients with HIV seen in the ID clinic from April 1, 2010 to December 31, 2013, and 359 patients met inclusion criteria for the study cohort. The most common reason for exclusion was a positive HCVAb result (158, 60.1% of excluded patients). Other exclusion criteria included <2 visits (10, 3.8%), <365 days between visits (37, 14.1%), and no recorded HCVAb result (58, 22.0%). In the study cohort, participants were 80% male, 57% white, and the vast majority (96.3%) had non-IDU HIV risk factors (Table 1). The median length of time observed in clinic was approximately 5 years, and 90% had achieved an undetectable HIV viral load. Fifteen percent of the cohort had a history of a +RPR. There were 6 ID providers who each treated over 30 patients during the study time period. Physicians' compliance with repeat HCVAb testing of patients under their care ranged from 50% to 94% with at least 1 repeat test per patient (median, 62.5%; interquartile range, 59.5–74.5).

Overall, in the complete cohort inclusive of all risks, patients were less likely to have repeat HCVAb testing than repeat RPR testing (62.4% vs 84.4%, $P < .001$; Table 2). Across all risk group categories, there was a longer time interval between HCVAb tests than RPR tests, and this difference was most marked in the high-risk group (2.5 years vs 0.7 years, $P < .001$). There was no difference in frequency of repeat HCVAb testing across risk group strata for HCVAb (56.4% in low risk, 66.9% in moderate risk, and 64.1% in high risk; nonsignificant).

In the univariate analysis (Table 3), there were several variables associated with repeat RPR testing including male sex, MSM, time observed in clinic, history of +RPR, history of IDU, and classification as moderate- or high-risk groups. Only male

Table 1. Descriptive Statistics for the Demographics of the Study Population (N = 359)

Demographics	N (%)	Median [IQR]
Median Age (years)		50 [45–59]
Sex		
Male[a]	288 (80.2)	
Female	71 (19.8)	
Race/Ethnicity		
White	204 (56.8)	
Black	106 (29.5)	
Hispanic	40 (11.2)	
Other	9 (2.5)	
Sexual Identification (men only)		
MSM	210 (73.0)	
Non-MSM	78 (27.0)	
Route of HIV Transmission		
MSM	206 (57.4)	
Heterosexual sex	69 (19.2)	
Undocumented	38 (10.5)	
Unknown	21 (5.8)	
IDU	11 (3.1)	
Other[b]	10 (3.0)	
Heterosexual sex or MSM	2 (0.5)	
IDU or MSM	2 (0.5)	
Clinic Information[c]		
Number of visits in clinic		20 [11–31]
Years observed in clinic		4.9 [2.7–6.8]
Laboratory Information		
CD4 count (cells/mm^3)		620 [419–806]
On antiretroviral at last visit	329 (92.4)	
HIV viral load <75 (copies/mL) at most recent visit	322 (89.7)	
History of Positive RPR	53 (14.8)	
MSM	44 (12.3)	
Male/non-MSM	6 (1.7)	
Females	3 (0.84)	

Abbreviations: HIV, human immunodeficiency virus; IDU, injection drug user; IQR, interquartile range; MSM, men having sex with men; RPR, rapid plasma reagin.

[a] One male was transgendered but, for the purposes of the analysis, was included under the male sex category.

[b] Needlestick (4), vertical transmission (2), blood transfusion (2), heterosexual sex or blood transfusion (1), needlestick or blood transfusion (1).

[c] Years observed in clinic over time period 1996–2013.

Table 2. Comparison of Multiple Testing for HCVAb and RPR in the Study Population Categorized by Sexual Transmission Risk Groups

Statistic	HCVAb	RPR	n[a]	*P* Value
Complete Cohort				
Persons with more than 1 test, n (%)[b]	224 (62.4)	303 (84.4)	359	<.001
Median number of tests [IQR][c]	3 [2–4]	7 [4–10]	209	<.001
Median time (years) between 1st and 2nd tests [IQR][b]	2.8 [1.0–5.4]	1.2 [0.6–2.1]	209	<.001
Low-risk Group (Women and Non-MSM Men)				
Persons with more than 1 test, n (%)[b]	79 (56.4)	101 (72.1)	140	<.01
Median number of tests [IQR][c]	3 [2–4]	5 [3–7]	69	<.001
Median time (years) between 1st and 2nd tests [IQR][c]	2.8 [0.9–4.5]	1.6 [0.6–3.2]	69	<.05
Moderate-Risk Group (MSM With No History of +RPR)				
Persons with more than 1 test, n (%)[c]	111 (66.9)	151 (91.0)[d]	166	<.001
Median number of tests [IQR][c]	3 [2–4]	7 [4–10][e]	106	<.001
Median time (years) between 1st and 2nd tests [IQR][c]	2.8 [1.3–3.7]	1.3 [0.8–1.9]	106	<.001
High-Risk Group (History of +RPR)				
Persons with more than 1 test, n (%)[b]	34 (64.1)	51 (96.2)[d]	53	<.001
Median number of tests [IQR][c]	3 [2–4]	10 [8–10][e]	34	<.001
Median time (years) between 1st and 2nd tests [IQR][c]	2.5 [0.6–5.9]	0.7 [0.3–1.2][f]	34	<.001

Abbreviations: Ab, antibody; HCV, hepatitis C virus; IQR, interquartile range; MSM, men having sex with men; RPR, rapid plasma reagin.

[a] The study population was 359; there were 209 persons with both multiple tests for HCVAb and multiple tests for RPR.

[b] Pearson's χ^2 test used for frequency of repeat testing.

[c] Paired Wilcoxon rank-sum test used for patients with multiple tests for HCVAb and multiple tests for RPR.

[d] Indicates a significant difference when compared with the low-risk group with $P < .001$, Pearson's χ^2.

[e] Indicates a significant difference when compared with the low-risk group with $P < .001$, Wilcoxon ranked-sum test.

[f] Indicates a significant difference when compared with the low-risk group with $P < .01$, Wilcoxon ranked-sum test.

sex and MSM were associated with repeat testing for HCVAb. In the multivariable model (Table 4), MSM remained associated with repeat testing for both the HCVAb and RPR (adjusted odds ratio [AOR] = 2.62, $P = .003$ for HCVAb; AOR = 5.92, $P < .001$ for RPR) when compared with women, and there was no increased association for repeat HCVAb or RPR testing when compared with non-MSM men (AOR = 1.88, $P = .07$ for HCVAb; AOR = 1.19, $P = .67$ RPR). A history of IDU did not have an association with repeat testing for HCVAb or RPR, although the number of persons was small. A majority of the study population of MSM were white. Bivariate analysis showed that MSM was associated with being white or not-white ($P < .001$, Pearson's χ^2). However, when both were examined in the model as independent variables, they were not collinear, as supported by a variance inflation factor of 2, much less than the conventional threshold of 10. Thus, both variables were kept in the multivariate model.

Seven people had incident HCV infection. Demographics of this population are displayed in Table 5. Four of the 7 people who seroconverted (57%) had repeat HCVAb testing prompted by symptoms or abnormal laboratory results, and 3 were found by repeat screening.

DISCUSSION

Given the tolerability and success of new interferon-free HCV treatment regimens, diagnosing incident HCV infection

Table 3. Results of a Univariate Logistic Regression: Predicting Multiple Testing for HCVAb or Multiple Testing for RPR

		Univariate Logistic Regression			
		HCVAb		RPR	
Associated Factors	n	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Sex					
Female	70	Referent		Referent	
Male	289	1.83 (1.08–3.09)	.024	2.23 (1.17–4.17)	.013
Gender/Sex Preference			.07[a]		
Female	70	Referent		Referent	
Male, non-MSM	78	1.64 (.86–3.18)	.14	0.92 (.44–1.92)	.83
Male, MSM	211	1.90 (1.10–3.29)	.021	13.86 (1.86–8.06)	<.001
Age (years)	359	1.01 (.99–1.03)	.30	1.01 (.98–1.04)	.40
Race					
Not White	155	Referent		Referent	
White	204	0.94 (.61–1.45)	.78	1.07 (.60–1.90)	.81
Time observed (years)	359	1.04 (.96–1.13)	.35	1.15 (1.02–1.31)	.023
History of Positive RPR					
No history of +RPR	306	Referent		Referent	
History of +RPR	53	1.09 (.60–2.04)	.78	5.46 (1.63–34.03)	.021
History of IDU					
No IDU	346	Referent		Referent	
IDU	13	1.37 (.44–5.14)	.61	0.28 (.09–.95)	.029
Risk Group			.17[a]		
Low	140	Referent		Referent	
Moderate	166	1.56 (.98–2.49)	.06	3.89 (2.07–7.62)	<.001
High	53	1.38 (.72–2.69)	.33	9.85 (2.86–61.99)	.002

Abbreviations: Ab, antibody; CI, confidence interval; HCV, hepatitis C virus; IDU, injection drug user; MSM, men having sex with men; OR, odds ratio; RPR, rapid plasma reagin.

[a] The *P* value indicates the overall significance level of the 3-level independent variable.

in PLWH should rise to the top of priorities for all HIV providers. In this study, we found that two thirds of the cohort had repeat HCVAb testing compared with over four fifths who had repeat RPR testing. Our results are on par with a recent multicenter retrospective cohort analysis that found overall rate of 56% PLWH receiving repeat HCVAb screening with variation between sites (35%–87%) from 2000 to 2011 [23].

Table 4. Results of a Multivariate Logistic Regression: Predicting Multiple Resting for HCVAb or Multiple Testing for RPR

		Multivariate Logistic Regression			
		HCVAb		RPR	
Associated Factors	n	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Gender/Sex Preference					
Female	70	Referent		Referent	
Male, non-MSM	78	1.88 (.96–3.72)	.07	1.19 (.54–2.65)	.67
Male, MSM	211	2.62 (1.38–5.04)	.003	5.92 (2.48–14.48)	<.001
Race					
Not white	155	Referent		Referent	
White	204	0.72 (.43–1.18)	.19	0.49 (.24–.97)	.045
Time observed (years)	359	1.06 (.97–1.16)	.16	1.21 (1.06–1.39)	.006
History of Positive RPR					
No history of +RPR	306	Referent		Referent	
History of +RPR	53	0.93 (.50–1.78)	.83	3.69 (.84–16.33)	.08
History of IV Drug Use					
No IDU	346	Referent		Referent	
IDU	13	1.69 (.52–6.58)	.41	0.42 (.11–1.64)	.20

Abbreviations: Ab, antibody; CI, confidence interval; HCV, hepatitis C virus; IDU, injection drug user; IV, intravenous; MSM, men having sex with men; OR, odds ratio; RPR, rapid plasma reagin.

Table 5. Demographics of HCVAb Seroconverters

Pt no.	Sex	Route of HIV Transmission	Age at Seroconversion	Years Between HCV Tests	Max AST	Max ALT	No. RPR Tests	No. HCVAb Tests	History of RPR +	Symptom/ Laboratory-Based Testing?
1	M	MSM	35	2.0	39	27	3	2	N	N
2	M	MSM	46	6.5	180	264	1	2	N	Y
3	M	MSM	63	1.3	149	311	12	2	Y	Y
4	M	IDU	36	3.8	49	60	1	2	N	N
5	M	IDU	40	0.13	455	527	2	5	N	Y
6	F	IDU	42	3.4	32	22	8	2	N	N[a]
7	M	Hetero sex	53	0.5	62	99	0	2	N	Y

Abbreviations: Ab, antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; HCV, hepatitis C virus; Hetero, heterosexual; HIV, human immunodeficiency virus; IDU, injection drug user; Max, maximum; MSM, men having sex with men; Pt, patient; RPR, rapid plasma reagin.

[a] HCV viral load positive, HCVAb negative in setting of CD4 count <50.

The demographics and HIV clinical characteristics of this cohort are representative of the overall US population with HIV who are not coinfected with HCV; approximately half of our patients were white and MSM, with relatively few reporting IDU [31]. The inclusion criteria for our study allowed us to focus on PLWH who were actively engaged in our clinic (observed in clinic for a median of 5 years). The multivariate analysis in this study allowed for a more comprehensive evaluation of factors contributing to repeat testing. Compared with females, MSM were more likely to have repeat HCV and RPR testing (AOR = 2.5 and 5.92, respectively); however, they were not more likely to have repeat HCV and RPR testing compared with non-MSM men. We also found that one third of the groups at highest risk for HCV infection, those with a history of syphilis and MSM, did not have evidence of repeat HCVAb testing. It is also worth noting that 9% (58 of 622) of persons in the clinic population were excluded from analysis because they had no record of HCVAb testing at all, and they did not meet the study entry criteria. People living with HIV who do not have initial or repeat HCVAb screening represent missed opportunities for diagnosis and treatment, and they also represent people who can potentially transmit infection.

The results of our study suggest that providers may still not recognize changes in the epidemiology of HCV or face systematic barrier to implementation of annual testing. There was considerable variability in providers' repeat HCVAb screening performance, with 1 provider only testing 50% of patients with repeat HCVAb. The variability in provider compliance with repeat HCV testing suggests that an intervention focusing on provider ordering habits may be successful. Education of providers is one method to overcome this barrier; however, education alone is often not sufficient to change provider practice. One proposed method to increase HCVAb screening is the institution of annual screening protocols in clinics caring for PLWH. System-level changes to facilitate easy annual ordering may also help increase screening. Electronic prompts to remind providers about HCVAb testing have been studied for initial HCVAb screening in the baby boomer cohort (people born between 1945 and 1965) [32, 33]. One clinic in Australia found that a simple modification in the process of ordering follow-up laboratory results on PLWH dramatically increased screening and diagnosis of syphilis [34]. There are also some centers interested in developing system-based practices to improve repeat HCVAb testing in PLWH [22]. At our institution, we have been working with the information systems department to modify our current electronic ordering system to facilitate ordering repeat HCVAb tests in PLWH with previously negative HCVAb. We hope this intervention will remove physician-related barriers and facilitate increases in annual HCVAb screening. Initial analysis of this process has yielded an increase in diagnosis of incident HCV cases.

The risk factors and laboratory values of the 7 people in the cohort who seroconverted are informative. Of the 7 people identified with incident HCV infection, 4 had elevated liver function tests that prompted HCV testing. Because persons with acute and chronic HCV infection can be asymptomatic, limiting repeat HCV antibody testing to people with symptoms or laboratory abnormalities will miss incident HCV cases [23, 35]. Three of 7 patients with seroconversion had a history of IDU. One of the patients with IDU did not seroconvert until the fifth time he had an HCVAb test. This case is instructive in how repeat annual testing is necessary to pick up incident HCV.

We were surprised to find that, in the multivariate analysis, IDU status was not associated with either repeat HCVAb testing or repeat RPR testing. Possible explanations for lack of repeat testing in IDU include providers' assumptions that the patient had ceased IDU-related risk behaviors, or that they were already HCVAb positive. However, this study focuses on PLWH without a history of IDU due to the exclusion criteria of a positive HCVAb at baseline (because over 80% of IDU with HIV also have HCV). The lack of association between IDU and repeat HCV testing may be explained by the small number of patients in this cohort (n = 13) reporting a history of IDU who were HCVAb negative at baseline, thus limiting our ability to analyze

discrete associations and suggesting a select population of IDU who had not been previously exposed to HCV infection.

There are several limitations to this study that should be acknowledged. This is a relatively small study limiting our ability to control for other potential confounders. As a retrospective study, we rely on medical chart review and provider documentation in order to classify people into sexual risk groups, and therefore there may be some misclassification bias. In addition, although HCVAb and RPR are similar in the amount of blood, price, and simplicity of the assay, there are differences that should be noted. Hepatitis C virus Ab is only a screening test, whereas RPR is used for screening and to follow treatment response. Therefore, repeat RPR tests, especially in the high-risk group, may have been completed in order to follow treatment response rather than to rescreen. In addition, our patients may have had other providers in the hospital system, including primary care doctors or dermatologists, who ordered laboratories and, therefore, having a repeat HCV or RPR test may reflect practices outside of the ID division. We were not able to control for this difference in our analysis.

CONCLUSIONS

Given the power and tolerability of current HIV medications, the focus of the clinician has shifted from management of symptoms of opportunistic infections and medication side effects towards preventative medicine, cancer screening, and screening for incident infections. Understanding barriers to effective screening and developing methods to increase rates of repeat HCVAb testing are an important topic to improve care for PLWH. The scope of impact from lessons learned about barriers and facilitators for HCVAb extends far beyond improving diagnosis of incident HCV infection and can be applied to several other aspects of primary care of PLWH including increasing annual screening for other infections, mental illness, drug use, and malignancy.

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