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VIRAL HEPATITIS AMONG DRUG USERS IN METHADONE MAINTENANCE: ASSOCIATED FACTORS, VACCINATION OUTCOMES, AND INTERVENTIONS

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Drug users are at high risk of viral Hepatitis A, B, and C. The prevalence of Hepatitis A, Hepatitis B, and Hepatitis C, associated factors, and vaccine seroconversion among drug treatment program participants in a randomized controlled trial of hepatitis care coordination were examined. Of 489 participants, 44 and 47% required Hepatitis A/Hepatitis B vaccinations, respectively; 59% were Hepatitis C positive requiring linkage to care. Factors associated with serologic statuses, and vaccine seroconversion are reported; implications for strategies in drug treatment settings are discussed. Results suggest generalizable strategies for drug treatment programs to expand viral hepatitis screening, prevention, vaccination, and linkage to care.

KEYWORDS. Viral hepatitis, Hepatitis C, methadone maintenance treatment program, vaccination

INTRODUCTION

Viral hepatitis is a major public health problem in the United States.[1,2] Drug users (DUs), particularly people who inject drugs, are at high risk for infection with Hepatitis A (HAV), Hepatitis B (HBV), and Hepatitis C (HCV) viruses through unsterile injection practices, as well as through high risk sexual activity.[3–6] Chronic HBV and HCV infections cause substantial morbidity, including cirrhosis and hepatocellular carcinoma, potential need for liver transplant, and mortality.[7–9] While HAV and HBV are preventable by vaccination, and HAV and HBV vaccines are now included among the recommended childhood vaccines in the United States, significant proportions of DUs remain at risk for these infections.[10–12] Treatment options for both HBV and HCV are rapidly improving, and new HCV treatments with all oral direct acting anti-viral regimens have the potential to cure chronic HCV infection.[13–16]

Drug treatment programs are important settings for engaging DUs in needed disease prevention and health care.[17,18] Most drug treatment programs routinely test participants for HBV infection and many are required to do so. Few drug treatment programs however, routinely test for HAV susceptibility and even fewer provide on-site HAV/HBV vaccination to susceptible participants.[12] Drug treatment programs vary widely in the extent of HCV services offered on-site; a very small proportion provide HCV care on-site, and some provide HCV testing although the proportion doing so has declined.[19,20] For DUs with HCV infection, there are substantial gaps in the continuum of care, particularly in the early steps in the care continuum including screening, identifying

infected persons, and engaging infected persons in clinical evaluations and care.[5,21–23] There is a need for the broadened implementation of demonstrably efficacious and practical interventions to engage DUs in viral hepatitis screening, vaccination, prevention, and care.[3,24,25]

The impact of a hepatitis care coordination model embedded in the methadone maintenance treatment (MMT) setting on HAV/HBV vaccination outcomes and engagement in HCV care were evaluated. This intervention, which included on-site vaccination, two-session motivational interview-enhanced education, and case management/care coordination significantly improved vaccination and engagement in HCV care.[5,26] In this article, the prevalence of prior exposure and susceptibility to HAV, HBV, and HCV among drug treatment program participants in this multi-site randomized control trial are examined, and the associated factors to inform drug treatment program testing, vaccination, prevention, and linkage to care strategies are identified.

Methods

Data were collected as part of a two-site randomized clinical trial evaluating a multi-component intervention designed to overcome barriers to hepatitis care for DUs in MMT.[5] DUs were recruited from two methadone maintenance programs in New York City (NYC) and San Francisco (SF) between January 2008 and May 2010 and followed until specified endpoints were met. The NYC study site provided opioid treatment for approximately 1,300 patients per year, and the SF study site provided treatment for more than 400 patients per year. Participants were recruited from methadone waiting rooms using random sampling methods and were considered eligible if there were at least 18 years old; self-reported as being either HCV-negative, of unknown HCV status, or if HCV-positive, or receiving no prior care or diagnostic evaluation for HCV; and willing to participate in study-related activities.

Participants in each of two study arms completed surveys at baseline and at 3, 9, and 12 months after baseline. Both arms received viral hepatitis and HIV testing and education. Study participants needing HAV/HBV vaccination were offered vaccination on-site (in the intervention arm), or off-site by referral (in the control arm).

Laboratory testing at baseline included: HAV total antibody (HAV Ab), HBV surface antibody (HBs Ab), HBV core antibody (HBc Ab), HBV surface antigen (HBsAg), and HCV antibody (HCV Ab), as well as an opt-in HIV antibody test. Serum samples were tested by licensed clinical laboratories in California and New York according to manufacturers' instructions. Participants were considered HAV immune or HCV-positive if sera were reactive for HAV Ab or HCV Ab, respectively. HBV serologic statuses were categorized as follows: HBV naïve (negative for HBsAg, HBs Ab, HBc Ab), HBV immune by natural disease (positive for HBs Ab and HBc Ab only), HBV immune by vaccination (positive for HBs Ab only), active HBV (positive for HBsAg), and isolated HBc Ab positive (positive for HBc Ab and negative for HBs Ab and HBsAg).

Participants were considered to need HAV vaccination if they were negative for HAV Ab, and were considered to need HBV vaccination if they were HBV-naïve or had isolated HBc Ab. Those needing either vaccination for HAV, HBV, or both were offered vaccination with combined HAV/HBV recombinant vaccine (TWINRIX®) at 0, 1, and 6 months.

Interviews were conducted by trained study staff using computer assisted interviewing software after informed consent was obtained. Participants were given the option to self-administer (via computer-assisted self interview software) sensitive questions regarding current and former drug use as well as risky sexual behavior. Additional questionnaire topics included demographic information, psychosocial assessment measures, mental and physical health, health care service utilization, and healthcare service measures.

Using data from the entire study cohort (NYC and SF), the following groups were compared first in univariate analyses and then in logistic regression models: (1) HAV Ab positive versus HAV Ab negative, (2) HCV Ab positive

versus HCV Ab negative, and (3) isolated HBc Ab versus HBV immune by natural disease. The first analyses were conducted to identify factors associated with being either immune or susceptible to HAV; the second set of groups were compared to identify factors associated with having been exposed to or susceptible to HCV; the third set of analyses were conducted to identify factors associated with the lack of HBs Ab among persons having demonstrated exposure to HBV. (The decision to compare those with isolated HBc Ab to those immune by natural disease [i.e., who retained HBs Ab] was made to focus on the retention of HBs Ab after disease rather than comparing those with isolated HBc Ab to a heterogeneous group that would include those immune by natural disease and those who were vaccinated).

Stored baseline sera and post-vaccination serologic tests were available only from participants enrolled in the NYC site. Of the 32 participants from the NYC site who had isolated HBc Ab at baseline, 28 (88%) had stored sera from the baseline assessment that was available for post-hoc HBV DNA testing. Of the 141 needing vaccination for HAV or HBV at the NYC site, 105 (92%) were available for post-vaccination serologic testing after at least 1 dose of HAV/HBV vaccine.

Pearson's Chi-square or Fisher's Exact Test were used for categorical variables and 2-sided t-test and Wilcoxon Scores were used for continuous variables. Factors examined in univariate analysis included those depicted in Table 1; factors that were statistically significant at the $<.1$ level were included in the logistic regression models. Analyses were done using statistical software (SAS version 9.2; SAS Institute, Cary, NC).

RESULTS

Characteristics of the 489 study participants are summarized in Table 1. Over two-thirds (70%) reported a history of injection drug use. Only 3% of men reported having sex with men. Fifty-six percent were HAV Ab positive. Seventeen percent were HBV immune through

TABLE 1. Characteristics of Study Sample

Characteristic	N (%)*
Recruitment site	
SF	239 (48%)
NYC	250 (52%)
Age (mean, +/− SD), years	45 ± 10
Female gender	155 (35%)
Race/ethnicity	
Caucasian	176 36%)
Hispanic	148 (30%)
African American	144 (29%)
Other	21 (4.3%)
High school education or above	269 (55%)
Homeless in past 6 months	199 (41%)
Employed	78 (16%)
History of injection drug use	343 (70%)
Years of heroin use (mean, +/− SD)	15.05 ± 10.65
Immune to hepatitis A	272 (56%)
Hepatitis B status	
Susceptible	157 (32%)
Chronic antigen	6 (1.2%)
Immune, vaccination	83 (17%)
Immune, disease	145 (30%)
Isolated core	66 (15%)
Hepatitis C antibody positive	286 (59%)
HIV infected	50 (10%)
Methadone dose, mg	90 (19%)
Alcohol use, number of days in the last 30 (mean, +/− SD)	5.3 ± 9.4

*N and percentage given unless otherwise noted.

vaccination; 30% were HBV immune by natural infection; 32% were either susceptible to or naïve to HBV; 15% had isolated HBc Ab; and 1% were chronically infected with HBV. Fifty-nine percent were HCV Ab positive, and 10% were HIV positive by either study testing or self-report.

In univariate analyses, those positive for HAV Ab were significantly more likely to be older (mean, 50 versus 43 years; $p < .0001$), recruited at the SF site (55% versus 45%; $p < .0001$), have a history of injection drug use (77% versus 61%; $p < .0001$), report more years of illicit drug use (mean, 20 versus 13 years; $p < .0001$), be HCV Ab positive (75% versus 40%; $p < .0001$), and be HIV positive (17% versus 2%; $p < .0001$).

Those with isolated HBc Ab were significantly more likely than those immune by natural disease to be older (mean, 51 versus 44 years; $p < .0001$), report more years of illicit drug use (mean, 24 versus 17 years; $p < .0001$), have a history of injection drug use (83% versus 67%;

$p = .006$), be HCV Ab positive (95% versus 53%; $p < .0001$), and be HIV positive (19% versus 8%; $p = .006$).

Those with HCV Ab were significantly more likely to be older (mean, 49 versus 41 years; $p < .0001$), recruited at the SF site (60% versus 40%; $p < .0001$), have a history of injection drug use (92% versus 37%; $p < .0001$), report more years of illicit drug use (mean, 20 versus 12 years; $p < .0001$), be HAV Ab positive (71% versus 36%; $p < .0001$), and have isolated HBc Ab (23% versus 2%; $p < .0001$).

All of the factors found to be significant in each of the sets of univariate analyses were included in the respective multiple logistic regression analyses. Factors found to be independently associated with being HAV Ab positive, HCV Ab positive, or with having isolated HBc Ab are depicted in Table 2. HAV Ab positive status was independently associated with being HIV positive ($OR = 5.59$; 95% CI: 2.09–14.9), HCV Ab positive ($OR = 3.32$; 95% CI: 2.17–5.08), and reporting more years of illicit drug use ($OR = 1.04$; 95% CI: 1.02–1.06). Isolated HBc Ab was independently associated with: HCV Ab positivity ($OR = 21.3$; 95% CI: 5.09–89.1) and more years of illicit drug use ($OR = 1.05$; 95% CI: 1.02–1.08). HCV Ab positive status was independently associated with: the presence of isolated HBc Ab ($OR = 42.7$; 95% CI: 7.94–230), a history of injection drug use ($OR = 27.8$; 95% CI: 14.0–54.2), the presence of HAV Ab ($OR = 4.41$; 95% CI: 2.53–7.68), and more years of illicit drug use ($OR = 1.05$; 95% CI: 1.02–1.09).

Sixty-one percent (300/489; 95% CI: 57–66%) of participants were susceptible to HAV or HBV or both. Fifty-four percent (154/289; 95% CI: 48–59%) of HCV Ab positive participants were susceptible to HAV or HBV or both.

Of the 66 participants with isolated HBc Ab, baseline sera were available for 28 from the NYC site. Twenty-seven of the 28 (96%; 95% CI: 82–99%) were HBV DNA negative. One participant (4%) with isolated HBc Ab was HBV DNA positive (174 IU/mL; reference range less than or equal to 19) and was HIV and HCV Ab positive.

TABLE 2. Multivariate Factors Associated with Positive Antibody Test

	Adjusted odds ratio (95% CI)	p-Value
HAV antibody (positive versus negative)		
HIV+	5.59 (2.09–14.9)	.0006
HCV+	3.32 (2.17–5.08)	<.0001
Years of drug use	1.04 (1.02–1.06)	.0006
Isolated HBV core antibody (positive versus HBV immune by natural disease)		
HCV+	21.3 (5.09–89.1)	<.0001
Years of drug use	1.04 (1.02–1.08)	.0009
HCV antibody (positive versus negative)		
Isolated HBV core AB	42.7 (7.94–230)	<.0001
History of IDU (ever)	27.5 (14.0–54.2)	<.0001
HAV+	4.41 (2.53–7.68)	<.0001
Years of drug use	1.05 (1.02–1.09)	.0008

One hundred five participants at the NYC site who were vaccinated with at least 1 dose of HAV/HBV vaccine were available for post-vaccination serologic testing. The seroconversion rate for HAV immunity post-vaccination was 96% (71/74; 95% CI: 89–99%) and the seroconversion rate for HBV immunity post-vaccination was 84% (69/82; 95% CI: 75–90%).

Of the three participants who did not seroconvert to HAV Ab positive after HAV/HBV vaccination, one completed the vaccine series on schedule, one did not receive the third dose in the vaccine series, and one completed the vaccine series on schedule but was both HCV Ab positive and was positive for HBs Ag. Of the 13 participants who did not seroconvert to HBs Ab positive after HAV/HBV vaccination, all 13 completed all 3 doses in the vaccine series, 9 were HCV-positive, 6 were vaccinated for isolated HBc Ab positivity. Those vaccinated for HBV who were naïve to HBV more frequently seroconverted after vaccination than those vaccinated for isolated HBc Ab but not significantly so (89% [56/63] versus 68% [13/19], $p = .07$, $OR = 3.7$; 95% CI: .9–15.2). Those vaccinated for HBV who were also HCV Ab positive were significantly less likely to seroconvert than those who were HCV Ab negative (70% [21/30] versus 92% [48/52], $p = .012$, $OR = .19$; 95% CI: .04–.80).

DISCUSSION

A high prevalence of HBV and HCV seropositivity was found in this cohort. Overall, 46% had evidence of natural HBV infection and 59% had evidence of HCV exposure. Fifty-six percent were positive for HAV Ab; however, since seropositivity does not distinguish between immunity from prior cleared infection and immunity by vaccination, it remains uncertain what proportion was immune due to prior vaccination or prior natural disease. Surprisingly only 17% of participants demonstrated HBV immunity through previous vaccination despite there having been more extensive public health efforts at HBV vaccination of DUs than at HAV vaccination.

While high proportions of study participants had evidence of prior exposure to HAV, HBV, and HCV, many remained susceptible to viral hepatitis infection (44% to HAV, 32% to HBV, 41% to HCV) indicating the need for preventive interventions. The factors found to be associated with viral hepatitis can be used to inform prevention efforts in drug treatment programs. Both age and years of drug use were associated with prior viral hepatitis infection emphasizing the importance of providing vaccination and prevention efforts to DUs as early as possible in their drug use careers; screening at entry to drug treatment can serve as an important means of doing so.

Prior uncontrolled studies have shown on-site HBV vaccination in MMT to be feasible and to result in high rates of vaccine series completion.[27,28] In this clinical trial, HAV/HBV vaccination on-site in MMT was shown to significantly increase vaccine series initiation and completion compared with referral for free off-site vaccination.[5] Further, financial incentives have been shown to increase adherence to on-site HBV vaccination at MMT.[29,30]

While HAV Ab seropositivity does not distinguish between vaccine induced- and natural disease induced-immunity, HAV Ab seronegativity is a clear indicator of susceptibility and need for vaccination. HBV serologic testing identifies active HBV infection, immunity due to natural disease or vaccine induced immunity,

susceptibility to HBV infection, and a status in which persons only have isolated HBc Ab. Isolated HBc Ab may be due to several conditions including: very early HBV infection (if the anti-HBV core Ab is an IgM antibody), remote natural HBV infection where HBs Ab levels have dropped below detection over time, low-level chronic active HBV infection (with detectable HBV DNA in the absence of HBsAg), and a biologic false positive HBc Ab.[31,32] Remote natural HBV infection is the most common cause for isolated HBc Ab identified in most series.[32–34]

An association between isolated HBc Ab and HCV Ab positivity was identified, and has been observed by some others.[33] It was found that this association was seemingly independent of both age and years of drug use suggesting a possible role of HCV on HBV Ab responses. In the present series, the vast majority of those with isolated HBc Ab did not have chronic HBV infection but rather that isolated core status reflected remote HBV infection with loss of HBs Ab over time; this has been the case in most, but not all, series.[32,34,35] The vast majority of those with isolated HBc Ab, therefore, needed HBV vaccination, as loss of adequate HBs Ab has been associated with susceptibility to re-infection.[31,36] Those with HCV Ab seropositivity had poorer responses to HBV vaccination as has been seen in some series, but in other series the association lost significance when smoking, which is associated with poorer responses to HBV vaccination, was included in analyses.[37] HBV vaccination is recommended specifically for those with HCV and further, non-responders may respond to double dose vaccination.[15,37]

Clinically, the important distinction to be made in those with isolated HBc Ab is between low-level chronic HBV infection which may require precautions, clinical monitoring, and potential treatment, and very remote natural HBV infection where protection against recurrent infection may be diminished and revaccination may be indicated. While HBV DNA testing could be performed in all persons with isolated HBc Ab to identify those with chronic infection and inform decisions about vaccination or referral for HBV care and treatment, the fact that the vast majority with isolated HBc Ab did

not have chronic infection suggests that routine vaccination of those isolated HBc Ab may be an appropriate strategy. Post-vaccination serologic testing could then be performed to document vaccine-induced immunity, with HBV DNA testing performed on non-responders to identify low level active infection and initiate engagement in care and treatment interventions.

Vaccines against HAV and HBV are available separately (as a two-dose HAV vaccine given at 0 and 6–12 months and as a three-dose HBV vaccine series given at 0, 1, and 6 months) or as a combined HAV/HBV vaccine (given at 0, 1, and 6 months). Clinical settings could opt to stock all three vaccines (HAV, HBV, and combined HAV/HBV) and administer appropriate vaccines to those susceptible for either or both viruses as needed. Alternatively, as it is safe to administer HAV or HBV vaccine to someone either already immune, clinical settings might opt to stock only combined vaccine for administration to those susceptible to either or both viruses. This strategy may allow clinical settings to stock only one vaccine and more easily operationalize and track vaccination schedules. This strategy was employed in this study and resulted in high rates of vaccine series completion and vaccine induced seroconversion.

HCV Ab testing can be performed using blood tests sent to clinical laboratories and rapid point of care tests that are clinical laboratory improvement amendments (CLIA) waived. Both tests identify prior exposure to HCV but neither confirms chronic infection; currently chronic infection can only be confirmed by HCV polymerase chain reaction (PCR) viral load testing of blood. No vaccine is currently available for HCV. Participation in MMT has been found to be modestly efficacious at reducing HCV risk but additional prevention measures are needed.[24,38,39] All DUs found to be HCV Ab positive need PCR HCV confirmatory testing to determine the need for clinical evaluation for treatment or additional prevention counseling. Whether confirmatory testing is done on-site or off-site by referral may depend on site-specific resources, logistics, and ultimately on budget impact and cost-effectiveness analyses.

Regardless of where HCV viral load testing is performed, DUs with HCV need to be linked to care. A two-session motivational-enhanced education and counseling intervention with case management/patient navigation services demonstrated a significant increase in the proportion of HCV-positive DUs engaged in HCV clinical evaluation.[5] A demonstration project conducted at a range of sites in NYC, including drug treatment programs, found an analogous model to be effective at engaging HCV-positive DUs in HCV clinical care.[40,41]

Limitations of the study include that HBV DNA testing and post-vaccination serologic testing was only done on patients from the NYC site for whom sera were available, although the frequency of occult HBV detected and the seroconversion rates identified are consistent with those previously seen. Further, HCV testing was by antibody only, and HIV testing was offered but not required as part of the study and some participants who reported HIV infection declined confirmatory testing. Another limitation is that data was not available on patient smoking status to include in the examinations of vaccine seroconversion. Further, the ultimate feasibility of instituting the studied interventions widely among drug-treatment programs would depend on budget impact and cost-effectiveness analyses; data for these analyses have been collected and results are pending.

Nonetheless, these data suggest possible generalizable strategies for drug treatment programs to expand coordinated viral hepatitis screening, prevention, vaccination, and linkage to care strategies (Figure 1). DUs could be screened on-site for HAV, HBV, and HCV Ab, offered on-site HAV/HBV vaccination if susceptible to HAV and/or HBV, vaccinated if found to have isolated HBc Ab, and prevention efforts could be focused on those susceptible to HCV. Post-vaccination HBV testing could be done to identify those who did not develop vaccine-induced immunity and need HBV DNA testing. Those persons found to be HCV Ab positive could have HCV viral load testing done on-site if resources and systems allow, or otherwise have viral load testing done through linkages to medical care settings. Those found to have
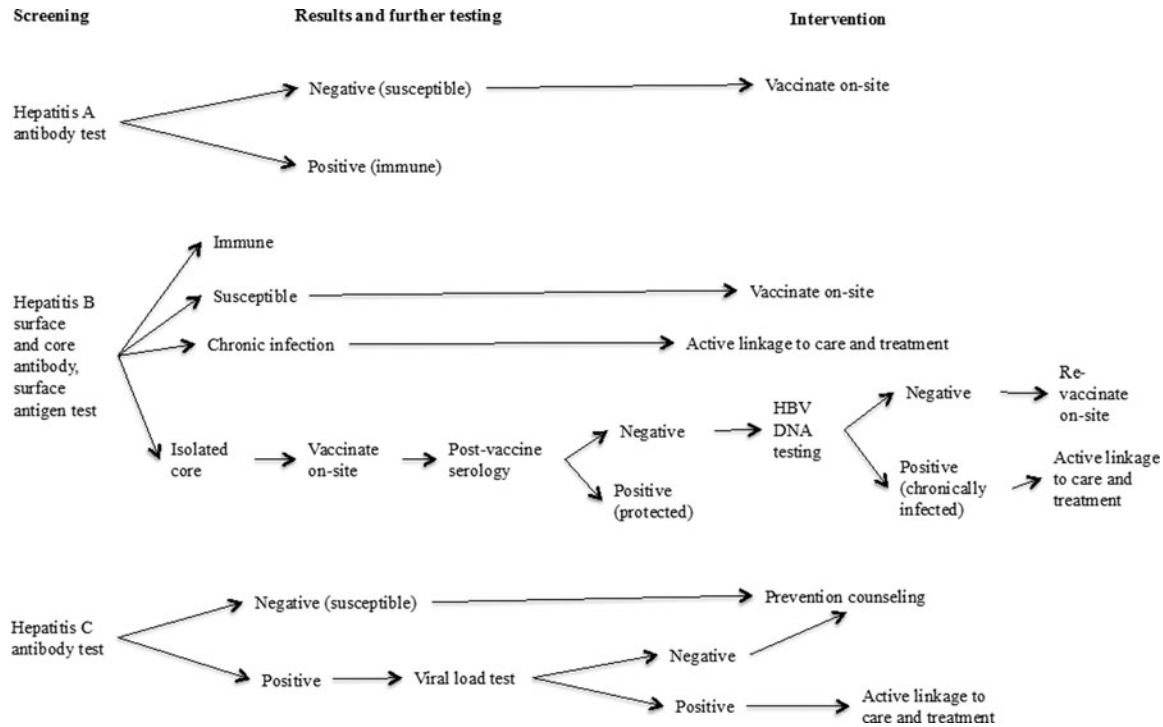
Screening   **Results and further testing**   **Intervention**

FIGURE 1. Viral hepatitis care coordination in methadone maintenance.

chronic HBV infection and those found to be HCV infected, could be treated on-site in programs with the infrastructure to do so, or linked to HCV care using demonstrably effective and efficacious linkage strategies, such as the hepatitis care coordination model.[5,42,43]

These data show that on-site testing, on-site vaccination, and coordinated linkage to care strategies are both feasible and efficacious, and there are some analogous data suggesting that these interventions can be implemented wide scale.[40] For drug-treatment programs to implement this model of coordinated HCV care, would require personnel to conduct HCV Ab testing, to perform phlebotomy for HCV viral load testing or to coordinate referral for off-site viral load testing, to stock and administer combined HAV/HBV vaccine, and to have access to HCV treatment services to which they can provide linkage to care. Further data on the budget impact and cost effectiveness of these interventions, and the availability of sustainable funding streams to support them, would be necessary for their wider implementation and dissemination and could have substantial public health benefit.

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