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Acute Hepatitis C Virus in an HIV Clinic: A Screening Strategy, Risk Factors, and Perception of Risk

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Abstract

Acute hepatitis C virus (HCV) infection is being acquired undetected among HIV-infected individuals. A practical way to regularly screen HIV-infected patients for acute HCV irrespective of perceived risk or symptoms is needed. We piloted implementation of an acute HCV screening strategy using routine HIV clinical care schedules and the least costly blood tests, in a Rhode Island HIV care center. Study participants had ongoing HCV risk, completed questionnaires encompassing risk behaviors and perception of risk, and were screened with quarterly alanine aminotransferase (ALT). ALT rise triggered HCV RNA testing, with pooled rather than individual specimen HCV RNA testing for underinsured participants. Participants were primarily older, college-educated men who have sex with men (MSM) with history of sexually transmitted infection other than HIV. One of 58 participants developed acute HCV in 50 person–years of observation for an annual incidence of 2.0% per year (95% confidence interval [CI] 0.05–11.1%). The majority (54%) of MSM did not perceive that traumatic sexual and drug practices they were engaging in put them at risk for HCV. Unprotected sex often occurred under the influence of drugs or alcohol. Self-reported HCV risk and participation in several risk behaviors declined during the study. It was possible to collect frequent ALTs in a busy HIV clinic with 71% of total projected ALTs obtained and 88% of participants having at least one ALT during the 9-month follow-up period. All instances of ALT rise led to reflexive HCV RNA testing. Tracking quarterly ALT for elevation to systematically prompt HCV RNA testing before seroconversion is a promising approach to screen for acute HCV in a real-world HIV clinical setting.

Introduction

Acute hepatitis C virus (HCV)—defined as the initial 6 months of infection—is an emerging sexually transmitted infection (STI)[1] among HIV-infected men who have sex with men (MSM), with increasing incidence and global significance,[2–7] in addition to being a common coprevalent pathogen among HIV-infected parenteral drug users.[8] In HIV-infected individuals, untreated acute HCV typically progresses to chronic HCV, a leading cause of non-AIDS–related morbidity and mortality for HIV-infected persons in the highly active antiretroviral therapy (HAART) era.[9] In addition to classic risk factors for acute HCV among HIV-infected women and heterosexual men, reported risk factors among HIV-infected MSM include traumatic sexual practices (e.g., unprotected anal intercourse, use of sex toys, digital–manual insertion), and having a history of or concurrent STI.[10–13] Acute HCV outbreaks have been linked to core groups of MSM who are more likely to have multiple partners, and use recreational drugs such as methylenedioxymethamphetamine (ecstasy) and other noninjection stimulants, and erectile dysfunction medications.[11] Whether most HIV-infected MSM who engage in risk behavior are aware of these nonclassic risks for acute HCV is unclear. Acute HCV is a silent epidemic due to the fact that most individuals are asymptomatic, or have symptoms that are mild and nonspecific. Early diagnosis is rare, and the extent of this epidemic unknown because most at-risk individuals are not tested for acute HCV.

HCV treatment leading to viral eradication (sustained virologic response [SVR], defined as undetectable HCV RNA 24 weeks posttreatment) reduces liver-related morbidity and mortality.[14–17] Treatment of HCV in the acute phase results in overall SVR rates up to 74% in HIV-coinfected patients[18,19]

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with 24 weeks of interferon-based therapy, dramatically higher than the 27–40% overall SVR rates achieved for chronic HCV with 48 treatment weeks.[20–23] Thus, diagnosis of acute HCV provides opportunity for HCV treatment during the stage when treatment is most effective, and permits an abbreviated therapy course, thereby reducing adverse events and cost. Acute HCV identification may also permit intervention to reduce disease transmission.

Acute HCV outbreaks have prompted a call for ongoing screening of at-risk persons.[10] How to best implement this enhanced screening remains unclear. Identifying HCV seroconversion in serial samples is suboptimal because antibody development may be delayed in HIV-infected persons, more than 1 year after the initial infection.[24] To diagnose acute HCV, HCV RNA testing is recommended since HCV RNA appears before anti-HCV antibodies may be detectable.[25] Frequent serum HCV RNA testing is thus a possible screening strategy. New viremia denotes acute HCV, as HCV RNA is detectable in the blood 1–2 weeks after HCV exposure followed by a rise in alanine aminotransferase (ALT), before subsequent seroconversion.[25,26] This approach has been validated to detect acute HIV infection among high-risk individuals in some settings, identifying individuals who would have been missed by antibody testing.[27] RNA testing involves amplification of the virus's genetic material and is thus time-consuming and more expensive than antibody testing. Combining individual samples into a single pool for RNA testing may decrease costs. Pooled testing of blood donors for HIV and HCV RNA by means of nucleic acid amplification was introduced in the United States in 1999 to identify early infections during the window period before seroconversion.[28,29]

The expense of nucleic acid testing has led to consideration of screening based on rise in ALT, a test 100-fold less costly than HCV RNA. Checking ALT at routine visits with subsequent HCV RNA testing in suspected cases identifies 90% of those with acute HCV.[24] In a recent study of HIV-infected MSM, the sensitivity of ALT testing 3 months after HCV acquisition was 74%.[24] Combining this approach with annual HCV antibody screening ensures no missed incident cases in the event that captured ALTs do not rise sufficiently to trigger nucleic acid testing.[26]

Acute HCV in the HIV clinic setting is typically diagnosed through case finding by astute providers due to nonspecific symptoms or unexplained ALT elevations rather than via a systematic approach.[26,30] In this pilot project, the primary objective was to develop, implement, and evaluate an acute HCV screening strategy based on risk alone, using routine HIV clinical care schedules and the least expensive blood tests, so that a scalable algorithm could be developed. We utilized HCV RNA testing only for patients with rise in ALT. We used pooled rather than individual specimen HCV RNA testing for underinsured patients given limited resources for individual nucleic acid testing, as an exploratory approach in the context of a study. A secondary objective was to explore risk behaviors, and perception and knowledge of risk, among at-risk patients engaged in HIV care.

Methods

HIV-infected patients of the Miriam Hospital Immunology Center in Providence, Rhode Island, with sexual and/or drug-related HCV risk factors were enrolled in a prospective, longitudinal, 9-month study to detect acute HCV by systematically reviewing standard of care blood tests at routine quarterly clinic visits. Of 1200 Immunology Center patients, one third are coinfected with chronic HCV and receive care at our dedicated coinfection clinic. Among all patients, 34% report MSM sexual transmission as their primary HIV risk factor, 25% report injection drug use (IDU), and 2% report both MSM sexual transmission and IDU as their primary HIV risk factor.

To be eligible for enrollment, individuals had to be at least 18 years of age, with no evidence of chronic HCV (HCV Ab-negative and HCV RNA-negative), able to provide informed consent and endorse any one of the following: (1) male same sex behavior involving any of the following within the prior 6 months: traumatic sex (unprotected anal intercourse/fisting, bleeding during sex), STI, unprotected oral sex,[3] stimulant or club drug use (amphetamine, crystal methamphetamine, ecstasy, cocaine, amyl nitrite [poppers], gamma-hydroxybutyrate [GHB], ketamine), having more than 5 sexual partners; (2) being an MSM with HCV-infected sexual partner; (3) injecting drugs or using drugs intranasally (any gender); (4) unprotected traumatic sex/anal sex within prior 6 months (any gender).[31]

At entry, all participants had HCV RNA testing, as well as serologic testing if the negative antibody was documented more than 1 year prior. At months 0, 3, 6, and 9, coinciding with routine clinic visit schedules, blood was drawn for ALT and a second specimen drawn and held. Development of an ALT elevation prompted HCV RNA nucleic acid testing (Siemens Versant bDNA quantitative, cutoff <650 IU/mL; Siemens Healthcare Diagnostics, Deerfield, IL). For a normal ALT at baseline, elevated ALT was defined as greater than 45 IU/mL or an increase by at least 20 IU/mL. For an abnormal ALT at baseline, elevated ALT was defined as more than 1.5 times increase from baseline.

We used HCV RNA pooling for underinsured participants to screen plasma in batches. Pooling was performed with no more than five sets of individual blood samples to create a master pool specimen (MPS) approximately once per week.[32] HCV RNA testing was then performed on the MPS. If HCV RNA for the MPS was less than 615 IU/mL, the lower limit of detection for the individual samples based on the bDNA assay, all specimens were considered to be HCV RNA-negative. If HCV RNA was greater than 615 IU/mL for the MPS, each specimen was individually tested for HCV RNA. For any found to be positive, the source participant had a subsequent individual HCV RNA test within 2 weeks. All Immunology Center patients are screened annually with syphilis serology (positive RPRs confirmed by fluorescence treponemal antibody absorption [FTA-ABS]), and urine nucleic acid amplification tests for gonorrhea and chlamydia (Aptima, Inc., Woburn, MA), with additional testing as clinically indicated. If during the study HCV RNA became detectable or signs or symptoms of STIs arose, STI testing was repeated.

A Behavioral Risk Questionnaire (BRQ) utilized in an HIV testing study among MSM at a gay bathhouse[33] was modified to include questions about injection and noninjection drug-related HCV risk behaviors, and sexual behaviors previously reported to be associated with acute HCV among HIV-infected MSM. The BRQ was completed at each visit. Participants were compensated $10 for completing each BRQ. Brief individualized risk reduction counseling was provided based on the Centers for Disease Control and Prevention model.[34]

Participants newly HCV RNA-positive were seen by a physician within 2 weeks. Persons remaining viremic 12 weeks after diagnosis without contraindications were offered genotyping and 6 months of pegylated interferon plus ribavirin (RBV) as part of their onsite clinical care. [35]

Statistical methods

The annual incidence of acute HCV [and 95% Poisson confidence interval (CI)] was estimated by dividing the number of acute HCV cases by the total amount of time participants were screened for acute HCV. The screening period included the 3 months prior to study entry, since the baseline RNA test would detect acute HCV during this period.

Within the MSM subgroup, demographics, perception of personal HCV risk, and engagement in selected risk behaviors were compared among those who attended 1 or 0 follow-up visits versus those who attended 2 or 3 follow-up visits. Comparisons were made using Fisher exact tests for categorical outcomes and row mean score tests for ordinal outcomes. The selected risks were addressed by the questionnaire responses in the "past 3 months," and included the number of sexual partners, unprotected insertive and receptive anal intercourse, fisting without gloves, group sex, meeting a sexual partner over the Internet, seeing blood on his or his partner's genitals or anus during sex, engaging in unprotected sex while high on drugs or alcohol, and taking erectile dysfunction medications.

To determine whether the odds of self-reported participation in the above selected risks or the perception of personal HCV risk changed during the course of the study, regression models for longitudinal binary or ordinal data were fitted to each risk behavior as a function of the visit number, with adjustments for age, race (white/non-white), and education. All models were fit using generalized estimating equations. For binary outcomes, an exchangeable within-subject correlation structure was assumed and 95% CI and p values were calculated using robust standard errors. For ordinal outcomes, 95% CI were estimated as the 2.5 and 97.5 percentiles of parameter estimates from 2000 bootstrapped samples using patient as the primary re-sampling unit. Models were fit using ordinal logistic regression with independent correlation structure. As an exploratory analysis, logistic regression was used to examine whether the recent use of erectile dysfunction medication at baseline (yes/no) was associated with age and three selected risk behaviors: recent number of sexual partners, insertive anal intercourse, and group sex.

Feasibility of the testing strategy was assessed using two outcomes: (1) whether we were able to readily identify acute HCV and (2) whether we were able to, in a busy clinic setting, utilize ALT elevations to trigger HCV RNA testing, assessed by considering the percent of study visits for ALT blood draws attended by participants, and whether RNA was simultaneously assessed for every ALT elevation. We calculated the percentage of participants who had at least two ALTs drawn during the study period (i.e., during at least one follow-up visit) and therefore had at least two ALTs measured per year.

Results

The Miriam Hospital Institutional Review Board approved the study in October 2007. Recruitment and enrollment began in November 2007 and participant follow-up lasted for 9 months. In 28 recruitment weeks, 194 persons were screened and 58 enrolled. Participants were primarily college-educated MSM with history of STI other than HIV, with 88% of the male sample reporting only other male partners and 9% being bisexual (Table 1). The two women who met entry criteria did so because of unprotected anal intercourse, and the male participant who had sex only with women met criteria because he reported intranasal drug use and unprotected anal intercourse. For MSM mean age was 42 (range, 21–58 years) with 65% older than 40, while overall mean age was 42 (range, 21–65 years) with 66% older than 40.

Among MSM, at baseline, most reported that in the prior 3 months they had engaged in high-risk sexual transmission behaviors, including unprotected anal intercourse, participation in group sex, meeting a sex partner via the Internet, and/or having sex with multiple partners. Stimulant and club drug use via the oral or intranasal route in the prior 3 months were common, while heroin and IDU were rare. Unprotected sex often occurred under the influence of drugs or alcohol. Despite these risks, over half (54%) of the MSM rated their HCV risk as not high.

Self-reported HCV risk and participation in several risk behaviors declined during the study (Table 2), including the odds of participating in unprotected receptive or insertive anal intercourse and engaging in unprotected sex while high on drugs or alcohol. The number of sexual partners decreased with each successive study visit. No differences were found for changes in other risk factors. Changes in two outcomes—unprotected fisting and seeing blood during sex—were not evaluated further due to their low baseline prevalence (less than 20%). Although participation in several risk behaviors declined during the study, these behaviors continued to occur at the third follow-up visit. For example, 31% of participants were still engaging in unprotected receptive anal intercourse, 17% in unprotected insertive intercourse, and 17% in group sex. Baseline reported recent use of erectile dysfunction medications was found to be significantly associated with recent participation in group sex (odds ratio [OR] = 4.98, 95% CI 1.20 to 20.60) and marginally associated with the number of sexual partners (OR = 1.45 for each successive higher ordinal partner group, 95% CI 0.99 to 2.12, $p = 0.06$) and age group (OR = 2.41 for each higher age group, 95% CI 0.85, 6.80, $p = 0.10$). Engaging in insertive anal intercourse was not found to be significantly associated with the use of erectile dysfunction medications (OR = 2.10, 95% CI 0.52, 8.53, $p = 0.29$).

At baseline, eight participants had a recent syphilis diagnosis. These patients were either being treated or had recently completed treatment for syphilis. Four of these eight participants were reinfected with syphilis during the study period. One additional participant without a recent syphilis history was newly infected with syphilis during the study follow-up period. One participant acquired chlamydia during the study period.

There was one newly diagnosed case of acute HCV over a screening period of 50 person–years. The annual incidence of acute HCV in the study cohort was estimated to be 2.0% per year (95% CI 0.05% to 11.1%). The case was a 56-year-old MSM who was not sexually active. He was injecting heroin and cocaine while being prescribed buprenorphine, with a recent change in injection practices with a period of syringe sharing. He was a binge alcohol user. HCV antibody was negative upon entry into HIV care 7 years prior, with several subsequent negative antibody tests including at study entry. For 7 years, his ALT had been within normal limits. At baseline, in November 2007, his ALT was 144 IU/mL and his HCV RNA

Table 1. Baseline Characteristics (at Enrollment) of 58 HIV-Infected Acute Hepatitis C Virus Study Participants

	n (%)
All	
Male	56 (97)
Sex with men only	49 (88)
Sex with men and women	5 (9)
Sex with women only	1 (2)
Gender of sexual partners unknown	1 (2)
Female	2 (3)
Sex with men only	2 (100)
Age, years	
18–30	7 (12)
31–40	13 (22)
41–50	30 (52)
51–60	7 (12)
≥61	1 (2)
Race/ethnicity	
Black	4 (7)
White	40 (69)
Hispanic	10 (17)
Other/unknown	4 (7)
Education	
College education	40 (69)
High school graduate	10 (17)
Did not graduate high school	4 (7)
Trade/technical school	3 (5)
Unknown	1 (2)
STI history[a,b]	41 (71)
MSM	
Age, years	
18–30	7 (13)
31–40	12 (22)
41–50	28 (52)
51–60	7 (13)
Race/ethnicity	
Black	4 (7)
White	39 (72)
Hispanic	7 (13)
Other/unknown	4 (7)
Education	
College education	40 (74)
High school graduate	8 (15)
Did not graduate high school	3 (6)
Trade/technical school	3 (6)
Sexual risk behavior, prior 3 months	
Unprotected insertive anal intercourse	28 (52)
Unprotected receptive anal intercourse	28 (52)
Participated in group sex	16 (30)
Met a sex partner over the internet	13 (24)
Unprotected fisting[c]	7 (13)
Saw blood on self/partners' genitals/anus during sex[d]	4 (8)
Shared sex toys	4 (7)
Used erectile dysfunction medications[c,e]	12 (23)
Number of sexual partners	
0	3 (6)
1	13 (24)
2–3	17 (31)
4–10	13 (24)
>10	8 (15)
Unprotected sex under influence of drugs or alcohol[c]	14 (26)
Drug use, prior 3 months	
Alcohol	30 (56)
Poppers	24 (44)
Cocaine	12 (22)
Amphetamines	6 (11)
Ecstasy	4 (7)
GHB	3 (6)
Marijuana	21 (39)
Heroin	0 (0)
Snorted or inhaled drugs	14 (26)
Shared straws while snorting	7 (13)
Injected drugs	1 (2)
Perception of risk for HCV or any STI[d]	
High	24 (46)
Not high	28 (54)

[a]Other than HIV.
[b]5 unknown/no answer.
[c]1 unknown/no answer.
[d]2 unknown/no answer.
[e]Prescribed by a physician or not.
STI, sexually transmitted infection; GHB, gamma-hydroxybutyrate; HCV, hepatitis C virus.

529,000 IU/mL. The peak ALT was 336 IU/mL with HCV seroconversion 4 weeks later. ALT declined to 21 IU/mL 8 weeks after RNA detection. At acute HCV diagnosis, his $CD4^+$ cell count was 579 cells/μL, with undetectable HIV RNA on tenofovir, emtricitabine, darunavir, ritonavir, and raltegravir. His elevated ALT and total bilirubin (8.0 mg/dL) were attributed to HAART-induced hepatotoxicity despite hospitalization with an injection-related abscess and jaundice, until it was appreciated that he was an acute HCV study participant and that his study HCV RNA was detectable. The participant declined therapy for acute HCV genotype 2 infection despite recommendation to accept treatment, and developed chronic HCV. However, the participant discontinued alcohol use, and began attending a coinfection support group and HCV clinic visits.

For the whole study sample, ALTs were collected at 164 study visits, 71% of total projected ALTs. Of 58 participants, 88% had at least 1 ALT during the 9-month follow-up period. Seventeen had blood drawn and ALT data collected for all 4 study visits (29%), 21 participants completed 3 study visits (36%), 13 completed 2 study visits (23%), and 7 attended the baseline visit only (12%). In all 170 of 232 (73%) BRQs were completed and 64% of possible follow-up BRQs were completed.

During 106 follow-up visits, there were 7 instances (6.6%) in which a rise in ALT prompted HCV RNA testing. Pooling was utilized for 5 of these 7 while 2 participants had individual samples tested. A total of 47 individual samples were pooled and a total of 21 pooled tests were performed. Different study visits (baseline and months 3, 6 and 9) were represented in each pool. Per protocol, all participants had HCV RNA testing at entry; 34 participants utilized pooling at baseline.

Discussion

We were able to implement an acute HCV screening strategy in an HIV clinical care setting. Tracking quarterly ALT for

Table 2. Estimated Change in Risk Behavior and Perceived Risk of HCV for Each Successive Study Visit in the Men Who Have Sex with Men Cohort

	Visit 1 versus baseline		*Visit 2 versus baseline*		*Visit 3 versus baseline*	
	OR (95% CI)	p *Value*	*OR (95% CI)*	p *Value*	*OR (95% CI)*	p *Value*
Number of sexual partners[a]	0.65 (0.30, 1.28)	0.126[b]	0.54 (0.22, 1.13)	0.054[b]	0.35 (0.12, 0.83)	0.012[b]
Unprotected insertive anal sex	0.33 (0.18, 0.60)	<0.001	0.33 (0.14, 0.73)	0.006	0.26 (0.12, 0.58)	<0.001
Unprotected receptive anal sex	0.27 (0.13, 0.54)	<0.001	0.42 (0.23, 0.74)	0.002	0.45 (0.28, 0.71)	<0.001
Group sex	0.64 (0.30, 1.40)	0.256	0.37 (0.13, 1.09)	0.066	0.43 (0.17, 1.11)	0.075
Meeting a sexual partner over the internet	1.09 (0.48, 2.47)	0.84	1.27 (0.56, 2.88)	0.558	0.98 (0.42, 2.30)	0.962
Unprotected sex while high on drugs or alcohol	0.57 (0.23, 1.45)	0.231	0.66 (0.31, 1.41)	0.279	0.35 (0.13, 0.93)	0.031
Taking erectile dysfunction medication	1.12 (0.61, 2.05)	0.714	0.81 (0.32, 2.07)	0.66	1.32 (0.46, 3.77)	0.603
Increased perceived risk of HCV acquisition[c]	7.29 (2.52, 25.8)	<0.001[b]	5.39 (2.00, 17.19)	<0.001[b]	4.92 (1.67, 18.9)	0.001[b]

The binary (yes/no) and ordinal risk factors are presented as odds ratios (OR) and 95% confidence intervals (CI). Each risk is evaluated in a separate model and all comparisons are with respect to the baseline visit.

Notes: unprotected means either no condom or no glove. Models are adjusted for age, race (white/non-white), education.

[a]Ordinal response: (1) 0–1 partner, (2) 2–6 partners, (3) 7 or more partners.

[b]Proportion of bootstrap runs with OR above 1 for # partners and below 1 for risk of HCV acquisition.

[c]Ordinal response: (1) Not really high or not high at all, (2) Somewhat high, (3) Very high.

HCV, hepatitis C virus.

elevation to systematically prompt HCV RNA testing before seroconversion is a promising approach that should be confirmed in larger studies. While the optimal ALT threshold triggering HCV RNA requires further investigation, in a study of 43 HIV-infected MSM with acute HCV, 65 IU/mL was the median ALT at time of first positive HCV RNA.[24] HCV RNA pooling may permit a more cost-effective approach than HCV RNA testing of individual specimens if the HCV incidence is not so high that too many pools require retesting of individual specimens. Pooled HCV RNA testing to identify patients with acute HCV was found to be feasible and relatively inexpensive among HIV-uninfected patients in England.[36] In December 2009, the U.S. Food and Drug Administration approved an additional intended use of Roche's licensed nucleic acid test to screen source plasma for HCV in pools.[37] Novel testing techniques to directly detect HCV RNA in a single reaction, without amplifying viral RNA, are under study to diminish costs. This may make HCV antibody testing unnecessary in the future, and our approach more feasible with an alternative to pooling to contain costs.[38]

The screening algorithm easily identified at-risk patients in this Rhode Island HIV care center. While we intentionally enrolled high-risk patients, and thus the associations noted in Table 1 are not surprising, we found additional risk behaviors beyond inclusion criteria including participating in group sex and meeting a sex partner over the Internet. Traumatic sexual and drug practices that may transmit HCV were prevalent and not appreciated by the well-educated, older cohort engaged in HIV care. Knowledge of nonclassic risk factors for HCV is not widespread; in an investigation of 8 HIV clinics in the United States, less that 50% of 1607 HIV-infected MSM were screened for HCV antibody.[39] Incident HCV infections may be missed among patients who rely on their physicians to care for them, without prospective surveillance.[26]

Participants had recent syphilis and chlamydial infections, which have been previously associated with acute HCV among HIV-infected MSM, while[13] heroin and IDU were rare. Having sex in a group of more than 2 people is a strong predictor of acute HCV among HIV-infected MSM[10]; we found recent use of erectile dysfunction medications to be associated with group sex.[40]

Participation in several risk behaviors declined during the study. This may be in part because of the risk reduction counseling provided, underreporting because of social desirability, or diminished memory of behaviors during substance use. Mitigating risk through proactive educational and counseling interventions merits consideration. Earlier diagnosis may impact transmitting behaviors; among injection drug users, those aware of their HCV infection engaged in fewer risk behaviors than those who were unaware of their positive status.[41]

Several limitations should be noted. We identified only one acute HCV case in 50 person-years of screening, and his likely risk was parenteral. However, the screening duration was short and the number of participants small since this was a feasibility study. Parenteral transmission highlights that this screening approach is applicable irrespective of mode of transmission. Incident cases without captured rises in ALT could have been missed, and 12% ($n=7$) of participants only attended the baseline visit. In our HIV clinic, HCV antibody-negative patients receive annual HCV antibody testing. Annual HCV antibody testing provides assurance that incident HCV, missed by an acute HCV screening strategy based on captured ALT elevation, is identified, albeit the acute period of infection may have passed. This "safety net" of annual antibody testing combined with more frequent RNA-based screening is supported by the European AIDS Treatment Network Acute Hepatitis C in HIV-infected Individuals Consensus Panel guidelines.[26] The optimal number of individual samples to include within each testing pool to achieve the most accurate result is unclear. Pooling may fail to detect specimens from patients with a low level of viremia, some of

whom may be antibody-negative and infectious.[42] The BRQ did not include questions about serosorting—the practice of engaging in unprotected sex with others of the same HIV status—which has been proposed as an explanation for the disproportionate rise in acute HCV rates among HIV-infected MSM compared to HIV-uninfected men,[12] although enhanced susceptibility or increased subgroup risk could explain this. Future studies should also gather data about intrarectal drug delivery, which may traumatize mucosa and promote HCV transmission. We did not systematically collect data on reasons for nonenrollment among screened patients. Many interested patients, particularly those with IDU history, already had chronic HCV infection and were excluded on this basis.

Finally, a cost analysis was not performed as part of this pilot study. Future larger studies should consider costs of quarterly ALT testing; individual versus pooled HCV RNA testing and the level of infection in a community that would make pooling less cost effective than individual specimen testing; hospital charges versus the true costs of tests; overhead in the laboratory; personnel; and that screening generates physician visits and more testing. These costs may be less than the additional 24 weeks of pegylated interferon/RBV therapy needed for diagnoses made in the chronic phase of infection, and the costs of the sequelae of chronic HCV including decompensated cirrhosis and hepatocellular carcinoma for the patients who will not achieve SVR in chronic HCV. This analysis will change if and when directly acting antiviral agents are approved for use in coinfection.

Acute HCV is emerging as a STI among HIV-infected MSM. International collaborative public health efforts to mitigate HCV transmission among this population, and additional research concerning precise modes of transmission, are necessary. In the interim, systematic, prompt diagnosis may lead to more successful treatment, and intervention to prevent disease spread. The European AIDS Clinical Society's Coinfection Guidelines endorse an approach that should be considered, with serologic testing for HCV for all patients upon entry into HIV care and annually thereafter for HCV-uninfected individuals, with HCV RNA testing for all HCV antibody-negative persons with unexplained increase in ALT and HCV risk (IDU, mucosal traumatic sex).[43] Additionally, the European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel's recommendations[26] include screening HIV-infected MSM at risk for acute HCV every 6 months with ALT, and screening HIV-infected patients with continued IDU and MSM with newly diagnosed STI, 3 months after diagnosis/last exposure. In the United States, national guidelines for the care HIV-infected persons recommend asymptomatic routine screening for STIs.[44] Extending these guidelines to include our newest STI, acute HCV among HIV-infected MSM, ensures diagnosis in settings in which patients and providers may not appreciate or adequately discuss nonclassic HCV risk factors. HIV-infected persons should have access to ongoing HCV screening for this disease that is clinically silent in most infected individuals until late stages.

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