UCLA
UCLA Previously Published Works

Title

Differences in hepatitis C virus prevalence and clearance by mode of acquisition among men who have sex with men

Permalink

https://escholarship.org/uc/item/1q83q9mv

Journal

Journal of Viral Hepatitis, 21(10)

ISSN

1352-0504

Authors

Seaberg, EC
Witt, MD
Jacobson, LP
et al.

Publication Date

2014-10-01

DOI

10.1111/jvh.12198

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

NIH Public Access
Author Manuscript
J Viral Hepat. Author manuscript; available in PMC 2015 October 01.

Published in final edited form as:
J Viral Hepat. 2014 October ; 21(10): 696–705. doi:10.1111/jvh.12198.

Differences in hepatitis C virus (HCV) prevalence and clearance by mode of acquisition among men who have sex with men (MSM)

Eric C Seaberg[1], **Mallory D Witt**[2], **Lisa P Jacobson**[1], **Roger Detels**[3], **Charles R Rinaldo**[4], **Steve Young**[5], **John P Phair**[6], and **Chloe L Thio**[7]

[1]Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, 21205 USA.

[2]David Geffen School of Medicine, University of California, Los Angeles, CA and Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California, 90509 USA.

[3]Department of Epidemiology, UCLA School of Public Health, Los Angeles, California, 90095 USA.

[4]Department of Infectious Diseases and Microbiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, 15261 USA.

[5]TriCore Reference Laboratory, Albuquerque, New Mexico, 87131 USA.

[6]Howard Brown Health Center and Department of Medicine, Northwestern University, Chicago, Illinois, 60611 USA.

[7]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, 21205 USA.

Abstract

Objective—To compare the characteristics associated with hepatitis C virus (HCV) antibody (anti-HCV) prevalence and HCV clearance between injection drug using (IDU) and non-IDU men who have sex with men (MSM).

Methods—Stored serum and plasma samples were tested for anti-HCV and HCV RNA to determine the HCV status of 6925 MSM at enrollment into the Multicenter AIDS Cohort Study (MACS). Prevalence and clearance ratios (PR and CR) were calculated to determine the characteristics associated with HCV prevalence and clearance. Multivariable analyses were performed using Poisson regression methods with robust variance estimation.

Results—Anti-HCV prevalence was significantly higher among IDU than non-IDU MSM (42.9% vs. 4.0%) while clearance was significantly lower among IDU MSM (11.5% vs. 34.5% among non-IDU MSM). HIV infection, Black race, and older age were independently associated with higher prevalence in both groups while smoking, transfusion history, and syphilis were

Corresponding author: Eric C. Seaberg, PhD, MPH Department of Epidemiology Johns Hopkins Bloomberg School of Public Health 615 North Wolfe Street, Room E-7634 Baltimore, MD 21205 USA Telephone: 410-955-4320 Fax: 410-955-7587 eseaberg@jhu.edu.

Statement of interests: SY is on the advisory board for Roche Molecular Systems and Quidel. All other authors report no potential financial or personal conflicts of interest.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

significantly associated with prevalence only among non-IDU MSM. The rs12979860-C/C genotype was the only characteristic independently associated with HCV clearance in both groups, but the effects of both rs12979860-C/C genotype (CR=4.16 IDUs vs. 1.71 non-IDUs; p=0.03) and HBsAg positivity (CR=5.06 IDUs vs. 1.62 non-IDUs; p=0.03) were significantly larger among IDU MSM. HIV infection was independently associated with lower HCV clearance only among non-IDU MSM (CR=0.59, 95% CI=0.40–0.87).

Conclusions—IDU MSM have higher anti-HCV prevalence and lower HCV clearance than non-IDU MSM. Differences in the factors associated with HCV clearance suggest that the mechanisms driving the response to HCV may differ according to the mode of acquisition.

Keywords

Hepatitis C; HIV; IFNL4; IL28B; Injection Drug Use; MSM

The hepatitis C virus (HCV) is most effectively transmitted via parenteral exposures including injection drug use (IDU) and blood transfusions (1). Although heterosexual transmission of HCV is uncommon (2), sexual transmission has been recognized among men who have sex with men (MSM) (3).

During the past decade, increasing HCV infection rates among human immunodeficiency virus (HIV)-infected MSM have been reported around the world (4-7). Host characteristics that have been linked to HCV infection among MSM include HIV infection (8;9), lower CD4+ cell count (10), unsafe sex practices including unprotected anal intercourse and fisting (4;11-13), the presence of certain sexually transmitted infections including syphilis (2;14), and recreational drug use (8). However, it is unknown whether each of these characteristics might differentially affect the risk of HCV acquisition via sexual versus parenteral exposures.

It is also unclear whether spontaneous HCV clearance differs by mode of acquisition. Overall, spontaneous clearance occurs in about 25% of people (15;16), but individual reports have ranged from 11% to 49% (17-21) demonstrating substantial heterogeneity for successful immune responses to acute HCV infection. Lower spontaneous clearance has been associated with IDU (18;22), Black race (17), male gender (16), HIV-infection (23), and age>40 years (24). Two characteristics linked to higher HCV clearance are infection with the hepatitis B virus (HBV)(18;22;25;26) and homozygosity for the C allele of the single nucleotide polymorphism (SNP) rs12979860 (24) which is also referred to as '*IL28B*' and is located within intron 1 of the interferon lambda 4 (*IFNL4*) gene (27). Because the majority of previously published HCV studies have included predominantly IDU study populations, generalizations to MSM who do not use injection drugs may be problematic.

The objective of this study was to determine whether the factors associated with HCV prevalence and spontaneous clearance among MSM differ by mode of acquisition. We examined these outcomes in a large cohort of MSM that included both injection drug users (IDUs) and non-IDUs as well as HIV-infected and HIV-uninfected men.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Methods

Study population

The MACS is an ongoing observational study of MSM in four metropolitan areas of the United States (US) (Baltimore MD, Chicago IL, Pittsburgh PA, and Los Angeles CA) that enrolled 6972 participants during three periods; 1984-1985, 1987-1995, and 2001-2003 (28-30). Data were collected at study entry and during semi-annual study visits via interviewer-administered questionnaires and physical examinations. Biological specimens were obtained for laboratory determinations of HIV/AIDS disease biomarkers and for repository storage. Baseline HIV status was determined using enzyme-linked immunosorbent assays (ELISA) and confirmed with Western blot (28). The MACS protocol and data collection forms (available at http://statepi.jhsph.edu/macs/macs.html) were approved by the institutional review board at each site. This study has been performed according to the World Medical Association Declaration of Helsinki and all study participants provided written informed consent.

The MACS instituted a prospective HCV testing protocol in 2001. All men enrolled in 2001 or later had HCV antibody (anti-HCV) tested at study entry, and those who were anti-HCV positive had an additional baseline sample tested for HCV RNA. These participants were then classified as HCV negative (anti-HCV negative), chronic HCV (CHC) infection (HCV RNA positive), or cleared HCV infection (anti-HCV positive and HCV RNA negative). For men enrolled prior to 2001, we retrospectively tested stored blood specimens to determine HCV status at study entry using the following algorithm which was designed to minimize the number of samples required for HCV testing. First, anti-HCV was tested in the earliest available stored specimen obtained within two years of study entry (baseline). Anti-HCV negative men were classified as being uninfected, while those who were anti-HCV positive had HCV RNA tested at their last study visit (LSV). Men who were HCV RNA positive at the LSV were classified as having CHC infection and no further testing was performed. Those who were HCV RNA negative at the LSV had HCV RNA tested in an additional baseline sample and were classified accordingly.

In total, HCV status was determined at study entry for 6925 (99.3%) of the 6972 MACS participants. Only one MACS participant received anti-HCV therapy prior to enrollment; he tested positive for HCV RNA at study entry and was classified as CHC. Because all men who previously cleared HCV had done so without anti-HCV therapy, they all cleared HCV spontaneously.

Laboratory testing

Anti-HCV status was assessed by EIA (ADVIA Centaur HCV assay, Siemens). HCV RNA was quantified with a quantitative real-time PCR assay (COBAS AmpliPrep COBAS TaqMan HCV assay, Roche). When a sufficient amount of specimen was available, we determined HCV genotype for men with CHC using a line probe assay (Inno-LiPA HCV II, Innogenetics). Genotyping for rs12979860 was performed in men who were anti-HCV positive using the ABI TaqMan allelic discrimination kit and the ABI7900HT sequence Detection System (Applied Biosystems) (24).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Statistical Analysis

In this cross-sectional study, we investigated the factors associated with two different measures of HCV status at enrollment: anti-HCV prevalence and spontaneous HCV clearance. The participant characteristics, behaviors, and exposures included in this study were recruitment period, MACS site, race/ethnicity, age, cigarette use, history of IDU, lifetime number of male sex (intercourse) partners, history of syphilis, history of blood transfusions, HIV infection status, and hepatitis B surface antigen (HBsAg) status. For spontaneous HCV clearance we also examined rs12979860 genotype. All exposure measures were ascertained by participant self-report at enrollment except for HIV status, HBsAg status, HCV RNA level and genotype, and rs12979860 genotype.

The primary analyses were stratified by IDU history to identify HCV risk factors separately for MSM who had and had not ever injected recreational drugs. Univariate analyses of HCV prevalence and clearance were performed using chi-square tests for association or trend, and HCV RNA levels were compared using the Wilcoxon Rank Sum Test. In the multivariate analyses we estimated the prevalence ratio (PR) and clearance ratio (CR) which, respectively, provide direct estimates of the relative risk of prevalence and clearance with binomial data, using the Poisson regression approximation to the log-binomial model with robust variance estimates (31;32). Additional models were fit to data from all participants to directly compare anti-HCV prevalence and spontaneous HCV clearance by IDU history. Interaction terms were used to compare the magnitudes of the effects of selected characteristics between IDUs and non-IDUs. 95% confidence intervals (CI) were calculated for both the PR and CR, and a two-sided p-value <0.05 indicated statistical significance. All analyses were performed using SAS version 9.3 (SAS Institute, Cary NC).

Results

Among the 6925 men in the study cohort, 71.4% were enrolled during the initial MACS recruitment period (1984-85), the median age was 33.5 years (range: 17-70 years), 72.7% were Caucasian, and 42.1% were HIV-infected. Thirty-five (0.5%) men did not respond to the IDU history questions and were excluded from further analysis. Among the 6890 men who did respond, 652 (9.5%) reported that they had used injection drugs at some point during their lives. The characteristics of IDUs and non-IDUs are shown in Table 1, and these two groups differed significantly on all characteristics except for HBsAg status.

Overall, 532 (7.7%) men were anti-HCV positive at study entry with the prevalence differing significantly by IDU history (4.0% among non-IDUs and 42.9% among IDUs; $p<0.001$) (Table 1). In univariate analysis, characteristics that were significantly associated with anti-HCV prevalence regardless of IDU status included enrollment during a later recruitment wave, older age, non-Hispanic Black race, history of cigarette smoking, and the lifetime number of male intercourse partners. Prevalent HIV infection, blood transfusion during the prior 5 years, and prior infection with syphilis were associated with anti-HCV prevalence only among non-IDUs. Although anti-HCV prevalence was similar in the four MACS sites among non-IDUs, it varied significantly across the sites among IDUs from 27.2% to 68.6%.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In the multivariable analysis among non-IDUs (Table 2), the participant characteristics that were independently associated with higher anti-HCV prevalence were older age, Black race, current cigarette smoking, recent blood transfusion, prior syphilis infection, no prior intercourse with another man, and HIV infection. A smaller set of risk factors was identified among IDUs where older age, Black race, having fewer than 50 lifetime male intercourse partners, and HIV infection were independently associated with being anti-HCV positive. When we included both IDUs and non-IDUs in a single multiple regression analysis (data not shown), men with an IDU history were more than 6 times as likely to be anti-HCV positive (PR: 6.80, 95% CI: 5.63-8.23) compared to their non-IDU counterparts after adjusting for all cofactors listed in Table 2. Furthermore, the magnitudes of the associations of HIV infection, Black race, and age with anti-HCV prevalence were each significantly lower among IDUs compared to non-IDUs (p-values for interaction; 0.002, <0.001, and <0.001, respectively).

Sufficient specimen was available to determine HCV RNA status (clearance versus persistence) for 528 (99.2%) of the 532 men who were anti-HCV positive at enrollment. These men included 279 (53%) IDUs and 249 (47%) non-IDUs, and the two groups differed significantly by recruitment period, age, smoking history, and lifetime number of male intercourse partners (Table 3). Overall, 22.3% of these men were HCV RNA negative at enrollment, but significantly fewer IDUs were HCV RNA negative compared to non-IDUs (11.5% vs. 34.5%, respectively, p<0.001). Among those with detectable HCV RNA, the $\log_{10}$ HCV RNA levels did not differ by IDU status; median=6.39 (interquartile range (IQR): 5.61-6.85) among IDUs vs. median=6.42 (IQR: 5.72-6.83) among non-IDUs, p=0.68. We were able to determine the HCV genotype for 413 (99.5%) of the 415 HCV RNA positive men and nearly 82% had a genotype 1 virus, 13% had genotype 2, and 4% had genotype 3. As expected, HCV genotype varied significantly by race with only 3.9% of Blacks having a genotype 2 virus compared to over 20% of men in the White and Other groups, and this race difference existed among both IDUs and non-IDUs (data not shown).

The characteristics that were significantly associated with HCV clearance among both IDUs and non-IDUs in univariate analyses were non-Black race and the rs12979860-C/C genotype (Table 3). Additionally, recruitment prior to 2001, younger age, a larger number of male intercourse partners, and being HIV negative were significantly associated with HCV clearance among non-IDUs while HBsAg positivity was significantly associated with HCV clearance among IDUs.

In the multivariable analysis (Table 4), rs12979860-C/C genotype was the only participant characteristic that was independently associated with increased HCV clearance among both IDUs and non-IDUs. Notably, the CR for the rs12979860-C/C genotype was significantly higher among men with a history of IDU compared to that among men who had never injected drugs (CR=4.16 and 1.71, respectively; p=0.03). HBsAg positivity was significantly associated with HCV clearance among IDUs, but among non-IDUs the association with HCV clearance was only borderline significant (p=0.0503). As observed for rs12979860 genotype, the CR for HBsAg positivity was significantly higher among IDUs than among non-IDUs (CR=5.06 and 1.62, respectively; p=0.03). HIV-infected men were less likely to have cleared HCV in both groups, but the difference was statistically significant only among

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

non-IDUs. A similar effect was observed among men who were current smokers at enrollment, but this difference was statistically significant only among IDUs. When we included both IDUs and non-IDUs in a single multiple regression analysis (data not shown), HCV clearance was significantly less common among men with an IDU history compared to their non-IDU counterparts (CR: 0.40, 95% CI: 0.28-0.58).

Discussion

This is the first study to comprehensively examine HCV prevalence and spontaneous clearance in MSM with and without a history of IDU. Although it was not surprising that MSM with a history of IDU were more than 6 times as likely to be anti-HCV positive compared to non-IDU MSM, it was notable that the likelihood of spontaneous HCV clearance among IDUs was less than half of that observed among non-IDUs. Several participant characteristics were associated with these HCV outcomes regardless of IDU history, but the magnitudes of the associations differed significantly by IDU status. One example of this is that the magnitude of the association of rs12979860-C/C genotype with HCV clearance was larger among IDUs. Taken together, the results from this study support the hypothesis that the characteristics associated with HCV infection and the mechanisms involved in spontaneous HCV clearance differ according to the mode of HCV acquisition.

Consistent with other study groups that observed an increase in HCV incidence among MSM during the past decade (4-7), our univariate analysis demonstrated a higher HCV prevalence among men recruited after versus before 2000. However, this difference was not present after accounting for recognized HCV risk factors including IDU. Therefore, in the US cities represented in the MACS, the observed marginal increase in anti-HCV prevalence among men enrolled after 2000 was most likely due to the higher HCV risk profile in this group of men that included more IDUs. Whether the increases observed among MSM in other geographic locations is solely due to an increase in risky sex practices or is also due to changes in IDU deserves further study.

HIV infection (33;34), Black race (35-37), and older age (33;38;39) have been linked with HCV infection in other studies. Our finding that these characteristics were associated with higher anti-HCV prevalence among both IDUs and non-IDUs supports the view that these are common risk factors for HCV exposure regardless of route of infection. The magnitudes of the associations of these characteristics, however, were significantly larger among non-IDUs suggesting that their role in HCV acquisition may differ according to the underlying exposure mechanism. It is also unclear whether these characteristics are causally related to HCV acquisition or are simply markers of other HCV risk factors that were not included in our analysis. Older age, for example, may be a marker of cumulative lifetime exposure to HCV which, in turn, may be more important for less efficient sexual exposures.

Several factors including cigarette smoking, prior transfusion, and a history of syphilis were independently associated with anti-HCV prevalence only among non-IDUs. The higher transmission efficiency of HCV through percutaneous exposure compared to sexual exposure may overwhelm the effects of these factors among IDUs providing an explanation for the lack of association in this group. For example, syphilis, which has also been linked to

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

HCV infection (14;40), may facilitate sexual transmission of HCV by disrupting mucosal immunity (3) while having no impact on transmission from percutaneous exposures.

The association of lifetime number of male intercourse partners with anti-HCV prevalence differed by IDU history. Among MSM with a history of IDU, anti-HCV prevalence was significantly lower in those with at least 50 lifetime male intercourse partners compared to men with fewer partners. This finding suggests that the number of partners may be inversely correlated with IDU intensity which would be consistent with prior research showing an increased degree of impotence and decreased interest in sex among chronic opiate users (41;42). Under this hypothesis, men with many lifetime partners might have injected drugs less frequently compared to men with fewer partners who injected drugs more frequently and accumulated a higher lifetime risk of exposure to HCV. Unfortunately, we did not assess the frequency of IDU prior to enrollment into the MACS. An alternative hypothesis is that those with more partners might be more inclined to use condoms, thereby reducing their exposure to HCV.

Among MSM without a history of IDU, we were surprised to observe a significantly higher HCV prevalence in those who reported never having had intercourse with any men. These 200 participants reported a history of sexual activity with men that included oral sex or genital touching without sexual intercourse. We speculate that this unique subgroup of MSM who acknowledged having had some form of sex with men other than intercourse either were less inclined to admit to their prior use of injection drugs or had some other unmeasured HCV risk factor. Similar to findings in the US population (36), we did observe a higher albeit non-significant HCV prevalence among those with at least 50 lifetime partners. It is likely that our adjustment for age, which is positively correlated with number of lifetime partners, accounted for some of the effect that had been attributed to the number of lifetime partners by other investigators (36).

Spontaneous HCV clearance was documented in 22.3% of the MSM in our study group which is close to the population-based estimate of 25% (16). Importantly, spontaneous HCV clearance was significantly lower among MSM with a history of IDU, and these results are consistent with the findings from previous studies that examined IDUs (17) and HIV-infected men and women (22). Lower spontaneous clearance among IDU MSM may reflect repeated HCV exposure and reinfection in this group since the likelihood of a given individual developing chronic infection increases following each exposure (43). As Shores, et al, (22) have discussed, it is also possible that the inoculum size with percutaneous exposure is larger than with sexual exposure, making it more difficult to mount a successful immune response after percutaneous exposure. Additionally, mucosal immunity may contribute to increased spontaneous clearance among those who acquire HCV sexually.

Although our finding that rs12979860 genotype was associated with spontaneous HCV clearance is known (24), our finding is novel because it suggests that the protective effect of the C/C genotype might be significantly larger among IDUs than among non-IDUs. One possible explanation for this finding is that the IFN-lambdas may differentially impact the immune response to HCV according to the mode of acquisition. In the case of sexual HCV acquisition, mucosal immunity and lower viral inoculums may play a role in achieving

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

spontaneous clearance before the immunologic mechanisms involving IFN-lambdas are initiated. However, it is also possible that this difference is the result of IDUs having been reinfected with HCV more often than non-IDUs such that the IDUs who remained HCV RNA negative at the time of enrollment into the MACS may have been enriched for characteristics such as rs12979860 C/C genotype that are associated with spontaneous HCV clearance.

The association between HBsAg positivity and HCV clearance has also been documented previously (18;22;25;26), but we found that the protective effect of active HBV infection was significantly stronger among IDUs. This difference might occur if the mechanisms leading to a higher likelihood of spontaneous HCV clearance among non-IDUs can overcome the strong protective effect of chronic hepatitis B infection that we observed among IDUs.

HIV infection was significantly associated with lower spontaneous clearance only among non-IDUs in this study. The differential effect of HIV infection is consistent with the understanding that HIV usually precedes HCV among non-IDUs while HCV usually precedes HIV among IDUs (44). Thus, among IDUs, HCV clearance or persistence is usually determined prior to HIV infection.

Our results must be interpreted in light of the primary limitation of our study design that is shared with nearly all HCV prevalence and clearance studies; these cross-sectional data do not provide any insight regarding the temporal relationship between the exposure measures and the outcomes. Misclassification is another potential limitation of our study. We classified men who were anti-HCV positive at baseline and RNA positive at their last study visit as having chronic HCV infection at enrollment, but some men might have cleared HCV prior to enrollment and then been reinfected during follow-up. On the other hand, men who had been infected with HCV and then seroreverted, i.e., became anti-HCV negative, prior to enrollment would have been incorrectly classified as being HCV negative at baseline. We expect that few participants would have been misclassified in this manner since the overall prevalence of anti-HCV in this cohort was just 7.7% and seroreversion occurs in fewer than 10% of those who clear HCV (37). Other limitations include the fact that MACS did not ascertain duration or frequency of injecting prior to enrollment and did not ascertain sufficient details about rough sex practices for us to evaluate the impact of these high risk behaviors on HCV prevalence and clearance. Finally, this study was not designed to evaluate the effect of HCV reinfection on HCV prevalence or clearance.

The primary strength of this study is that we examined a well-defined multicenter MSM cohort which allowed us to compare and contrast the effects of selected HCV risk factors among men with and without a history of IDU. Second, the MACS is the largest population-based MSM cohort in which HCV prevalence and clearance have been studied which increases the generalizability of our results to all MSM. Lastly, our study period began during the early HIV epidemic in the US and covers 20 years.

In this study of MSM, we demonstrated that IDUs had significantly higher anti-HCV prevalence and lower spontaneous HCV clearance compared to non-IDUs. The

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

characteristics found to be associated with anti-HCV prevalence and spontaneous HCV clearance differed in important ways between these two groups, suggesting that the mechanisms that drive the HCV response may differ according to the mode of acquisition. Given the cross-sectional design of this study, these findings need to be confirmed in a longitudinal study.

Acknowledgments

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) with centers (Principal Investigators) at: Johns Hopkins University Bloomberg School of Public Health (Joseph Margolick), U01-AI35042; Northwestern University (Steven Wolinsky), U01-AI35039; University of California, Los Angeles (Roger Detels), U01-AI35040; University of Pittsburgh (Charles Rinaldo), U01-AI35041; the Center for Analysis and Management of MACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson), UM1-AI35043. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the National Cancer Institute (NCI). Targeted supplemental funding for specific projects was also provided by the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Deafness and Communication Disorders (NIDCD). MACS data collection is also supported by UL1-TR000424 (JHU CTSA). Website located at http://www.statepi.jhsph.edu/macs/macs.html. Additional funding for this work was provided by the National Institute on Drug Abuse [grant number DA013324] and the National Center for Advancing Translational Science [grant number UL1TR000124]. The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH).

Reference List

(1). Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. Am J Public Health. May; 1996 86(5):655–61. [PubMed: 8629715]

(2). Tohme RA, Holmberg SD. Is sexual contact a major mode of hepatitis C virus transmission? Hepatology. Oct; 2010 52(4):1497–505. [PubMed: 20635398]

(3). Bradshaw D, Matthews G, Danta M. Sexually transmitted hepatitis C infection: the new epidemic in MSM? Curr Opin Infect Dis. Feb; 2013 26(1):66–72. [PubMed: 23242342]

(4). van de Laar TJ, van der Bij AK, Prins M, Bruisten SM, Brinkman K, Ruys TA, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis. Jul 15; 2007 196(2):230–8. [PubMed: 17570110]

(5). Fox J, Nastouli E, Thomson E, Muir D, McClure M, Weber J, et al. Increasing incidence of acute hepatitis C in individuals diagnosed with primary HIV in the United Kingdom. AIDS. Mar 12; 2008 22(5):666–8. [PubMed: 18317014]

(6). Fierer DS, Uriel AJ, Carriero DC, Klepper A, Dieterich DT, Mullen MP, et al. Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study. J Infect Dis. Sep 1; 2008 198(5):683–6. [PubMed: 18627270]

(7). Matthews GV, Hellard M, Kaldor J, Lloyd A, Dore GJ. Further evidence of HCV sexual transmission among HIV-positive men who have sex with men: response to Danta et al. AIDS. Oct 1; 2007 21(15):2112–3. [PubMed: 17885306]

(8). Urbanus AT, van de Laar TJ, Stolte IG, Schinkel J, Heijman T, Coutinho RA, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS. Jul 31; 2009 23(12):F1–F7. [PubMed: 19542864]

(9). Jin F, Prestage GP, Matthews G, Zablotska I, Rawstorne P, Kippax SC, et al. Prevalence, incidence and risk factors for hepatitis C in homosexual men: data from two cohorts of HIV-negative and HIV-positive men in Sydney, Australia. Sex Transm Infect. Feb; 2010 86(1):25–8. [PubMed: 19841001]

(10). Witt MD, Seaberg EC, Darilay A, Young S, Badri S, Rinaldo CR, et al. Incident hepatitis C virus infection in men who have sex with men: a prospective cohort analysis from 1984 to 2011. Clin Infect Dis. Mar 26; 2013 57(1):77–84. [PubMed: 23532480]

(11). Rauch A, Rickenbach M, Weber R, Hirschel B, Tarr PE, Bucher HC, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

men: the Swiss HIV Cohort Study. Clin Infect Dis. Aug 1; 2005 41(3):395–402. [PubMed: 16007539]

(12). Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men--New York City, 2005-2010. MMWR Morb Mortal Wkly Rep. Jul 22; 2011 60(28):945–50. [PubMed: 21775948]

(13). Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, et al. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. AIDS. May 11; 2007 21(8):983–91. [PubMed: 17457092]

(14). Ndimbie OK, Kingsley LA, Nedjar S, Rinaldo CR. Hepatitis C virus infection in a male homosexual cohort: risk factor analysis. Genitourin Med. Jun; 1996 72(3):213–6. [PubMed: 8707327]

(15). Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. May 16; 2006 144(10):705–14. [PubMed: 16702586]

(16). Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. Jan; 2006 13(1):34–41. [PubMed: 16364080]

(17). Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA. Jul 26; 2000 284(4): 450–6. [PubMed: 10904508]

(18). Soriano V, Mocroft A, Rockstroh J, Ledergerber B, Knysz B, Chaplinskas S, et al. Spontaneous viral clearance, viral load, and genotype distribution of hepatitis C virus (HCV) in HIV-infected patients with anti-HCV antibodies in Europe. J Infect Dis. Nov 1; 2008 198(9):1337–44. [PubMed: 18767985]

(19). Danta M, Semmo N, Fabris P, Brown D, Pybus OG, Sabin CA, et al. Impact of HIV on host-virus interactions during early hepatitis C virus infection. J Infect Dis. Jun 1; 2008 197(11):1558–66. [PubMed: 18419344]

(20). Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med. Apr 22; 1999 340(16):1228–33.

(21). Wiese M, Grungreiff K, Guthoff W, Lafrenz M, Oesen U, Porst H. Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany--a 25-year multicenter study. J Hepatol. Oct; 2005 43(4):590–8. [PubMed: 16237783]

(22). Shores NJ, Maida I, Soriano V, Nunez M. Sexual transmission is associated with spontaneous HCV clearance in HIV-infected patients. J Hepatol. Sep; 2008 49(3):323–8. [PubMed: 18486266]

(23). Sulkowski MS. Viral hepatitis and HIV coinfection. J Hepatol. Feb; 2008 48(2):353–67. [PubMed: 18155314]

(24). Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. Oct 8; 2009 461(7265):798–801. [PubMed: 19759533]

(25). Zhang MD, Rosenberg PS, Brown DL, Preiss L, Konkle BA, Eyster ME, et al. Correlates of spontaneous clearance of hepatitis C virus among people with hemophilia. Blood. Feb 1; 2006 107(3):892–7. [PubMed: 16204310]

(26). van den Berg CHBS, Grady BPX, Schinkel J, van de Laar T, Molenkamp R, van Houdt R, et al. Female Sex and IL28B, a Synergism for Spontaneous Viral Clearance in Hepatitis C Virus (HCV) Seroconverters from a Community-Based Cohort. Plos One. Nov 15.2011 6(11):e27555. [PubMed: 22110669]

(27). Prokunina-Olsson L, Muchmore B, Tang W, Pfeiffer RM, Park H, Dickensheets H, et al. A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. Nature Genetics. Feb; 2013 45(2):164–71. [PubMed: 23291588]

(28). Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol. Aug; 1987 126(2):310–8. [PubMed: 3300281]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

(29). Silvestre AJ, Hylton JB, Johnson LM, Houston C, Witt M, Jacobson L, et al. Recruiting minority men who have sex with men for HIV research: results from a 4-city campaign. Am J Public Health. Jun; 2006 96(6):1020–7. [PubMed: 16670218]

(30). Detels R, Jacobson L, Margolick J, Martinez-Maza O, Munoz A, Phair J, et al. The multicenter AIDS Cohort Study, 1983 to …. Public Health. Mar; 2012 126(3):196–8. [PubMed: 22206985]

(31). Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. Apr 1; 2004 159(7):702–6. [PubMed: 15033648]

(32). Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol. Aug 1; 2005 162(3):199–200. [PubMed: 15987728]

(33). Choy Y, Gittens-Williams L, Apuzzio J, Skurnick J, Zollicoffer C, McGovern PG. Risk factors for hepatitis C infection among sexually transmitted disease-infected, inner city obstetric patients. Infect Dis Obstet Gynecol. 2003; 11(4):191–8. [PubMed: 15108864]

(34). Frederick T, Burian P, Terrault N, Cohen M, Augenbraun M, Young M, et al. Factors associated with prevalent hepatitis C infection among HIV-infected women with no reported history of injection drug use: the Women's Interagency HIV Study (WIHS). AIDS Patient Care STDS. Nov; 2009 23(11):915–23. [PubMed: 19877800]

(35). Kelen GD, Green GB, Purcell RH, Chan DW, Qaqish BF, Sivertson KT, et al. Hepatitis B and hepatitis C in emergency department patients. N Engl J Med. May 21; 1992 326(21):1399–404. [PubMed: 1373867]

(36). Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med. Aug 19; 1999 341(8):556–62. [PubMed: 10451460]

(37). Seeff LB, Miller RN, Rabkin CS, Buskell-Bales Z, Straley-Eason KD, Smoak BL, et al. 45-year follow-up of hepatitis C virus infection in healthy young adults. Ann Intern Med. Jan 18; 2000 132(2):105–11. [PubMed: 10644270]

(38). Nyamathi AM, Dixon EL, Robbins W, Smith C, Wiley D, Leake B, et al. Risk factors for hepatitis C virus infection among homeless adults. J Gen Intern Med. Feb; 2002 17(2):134–43. [PubMed: 11841529]

(39). van B I, Buckley R, Stewart M, MacDonald M, Kaldor J. Risk factors for hepatitis C virus infection among injecting drug users in Sydney. Genitourin Med. Oct; 1994 70(5):321–4. [PubMed: 8001943]

(40). Wandeler G, Gsponer T, Bregenzer A, Gunthard HF, Clerc O, Calmy A, et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. Clin Infect Dis. Nov 15; 2012 55(10):1408–16. [PubMed: 22893583]

(41). Mirin SM, Meyer RE, Mendelson JH, Ellingboe J. Opiate Use and Sexual Function. American Journal of Psychiatry. 1980; 137(8):909–15. [PubMed: 6774622]

(42). Bang-Ping J. Sexual Dysfunction in Men Who Abuse Illicit Drugs: A Preliminary Report. Journal of Sexual Medicine. Apr; 2009 6(4):1072–80. [PubMed: 18093094]

(43). Matthews GV, Grebely J, Dore GJ. The role of re-infection in determining rates of spontaneous clearance after hepatitis C exposure. J Hepatol. Sep; 2008 49(3):305–7. [PubMed: 18644647]

(44). Kim AY, Chung RT. Coinfection with HIV-1 and HCV--a one-two punch. Gastroenterology. Sep; 2009 137(3):795–814. [PubMed: 19549523]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Comparison of participant characteristics by injection drug use history at enrollment and univariate analyses of anti-HCV prevalence.

	Non-IDUs			IDUs		
		Anti-HCV Positive			Anti-HCV Positive	
Participant Characteristics [a]	**N (%)**	**%** [b]	**P** [c]	**N (%)**	**%** [b]	**P** [c]
All	6238 (100.0)	4.0		652 (100.0)	42.9	
Recruitment period (p<0.001)			<0.001			<0.001
1984-1985	4520 (72.5)	3.1		420 (64.4)	28.8	
1987-1995	609 (9.8)	5.9		23 (3.5)	52.2	
2001-2003	1109 (17.8)	6.8		209 (32.1)	70.3	
MACS site (p<0.001)			0.31			<0.001
Baltimore	1603 (25.7)	4.8		137 (21.0)	68.6	
Chicago	1487 (23.8)	3.8		125 (19.2)	42.4	
Pittsburgh	1445 (23.2)	3.5		100 (15.3)	54.0	
Los Angeles	1703 (27.3)	3.9		290 (44.5)	27.2	
Age (years) (p<0.001)			<0.001 [d]			<0.001 [d]
<30	2056 (33.0)	2.1		184 (28.2)	28.3	
30-39	2824 (45.3)	4.4		266 (40.8)	36.1	
40-49	1095 (17.6)	5.9		159 (24.4)	60.4	
≥50	263 (4.2)	8.0		43 (6.6)	83.7	
Race/ethnicity (p<0.001)			<0.001			<0.001
Non-Hispanic Black	1022 (16.4)	10.0		171 (26.7)	78.7	
Non-Hispanic White	4617 (74.1)	2.8		408 (62.6)	27.9	
All Others	595 (9.5)	3.9		70 (10.7)	41.4	
Smoking history (p<0.001)			<0.001			0.01
Never smoked	2506 (40.4)	2.9		108 (16.6)	30.6	
Former smoker	1237 (19.9)	3.9		103 (15.8)	41.7	
Current smoker	2467 (39.7)	5.3		441 (67.6)	46.3	
Transfusion past 5 years (p<0.001)			<0.001			0.10
No	5952 (96.9)	3.8		593 (92.2)	42.0	
Yes	189 (3.1)	11.3		50 (7.8)	54.0	
Syphilis history (p<0.001)			<0.001			0.78
No	4992 (80.1)	3.2		423 (65.0)	43.3	
Yes	1237 (19.9)	7.5		228 (35.0)	42.1	
Lifetime number male intercourse partners (p<0.001)			0.04 [d]			<0.001 [d]
0	200 (3.2)	14.5		94 (14.5)	87.2	
1-9	434 (7.0)	3.0		41 (6.3)	68.3	
10-49	1457 (23.5)	3.0		66 (10.2)	53.0	
50-499	2749 (44.4)	3.6		230 (35.4)	27.4	

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

	Non-IDUs			IDUs		
		Anti-HCV Positive			Anti-HCV Positive	
Participant Characteristics [a]	**N (%)**	**%** [b]	**P** [c]	**N (%)**	**%** [b]	**P** [c]
≥500	1357 (21.9)	4.6		218 (33.6)	32.1	
HIV infection (p<0.001)			<0.001			0.42
Negative	3760 (60.3)	2.6		242 (37.1)	40.9	
Positive	2478 (39.7)	6.3		410 (62.9)	44.2	
HBsAg status (p=0.21)			0.36			0.08
Negative	5628 (94.5)	3.9		597 (93.3)	43.7	
Positive	329 (5.5)	4.9		43 (6.7)	30.2	

Abbreviations: HCV, hepatitis C virus; IDUs, injection drug users; anti-HCV, antibody to the hepatitis C virus; MACS, Multicenter AIDS Cohort Study; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen.

[a] P-values shown in parentheses are from the test of association between the indicated participant characteristic and IDU status.

[b] Percent (row %) of anti-HCV positive men who were HCV RNA negative at enrollment.

[c] Univariate p-value for test of association between participant characteristic and HCV RNA status.

[d] Test of trend.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 2

Multiple regression analysis of the association of participant characteristics with anti-HCV prevalence at enrollment stratified by history of injection drug use.

	Non-IDUs		IDUs	
Participant Characteristics	**PR**	**95% CI**	**PR**	**95% CI**
Recruited 1984-1995 vs. 2001-2003	1.27	0.89 – 1.82	1.13	0.79 – 1.60
Age (per 10 years)	**1.48**	**1.30 – 1.69**	**1.14**	**1.01 – 1.28**
Non-Hispanic Black race	**2.78**	**2.06 – 3.77**	**1.57**	**1.18 – 2.08**
Current smoker	**1.44**	**1.11 – 1.86**	1.12	0.92 – 1.36
Transfusion (past 5 years)	**2.53**	**1.68 – 3.82**	0.94	0.74 – 1.19
Syphilis	**1.53**	**1.17 – 2.02**	1.10	0.91 – 1.32
Lifetime number male intercourse partners				
0	**2.74**	**1.68 – 4.46**	1.15	0.95 – 1.40
1-49	1	(reference)	1	(reference)
≥50	1.31	0.94 – 1.85	**0.67**	**0.50 – 0.89**
HIV positive	**2.05**	**1.55 – 2.70**	**1.34**	**1.11 – 1.61**
HBsAg positive	1.10	0.69 – 1.77	0.80	0.51 – 1.25

Models are adjusted for MACS site and all characteristics listed in this table.

Confidence intervals that do not include 1 are indicated in bold.

Abbreviations: HCV, hepatitis C virus; IDUs, injection drug users; anti-HCV, antibody to the hepatitis C virus; PR, prevalence ratio; CI, confidence interval; HIV, human immunodeficiency virus; HBsAg, hepatitis

B surface antigen; MACS, Multicenter AIDS Cohort Study.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 3

Comparison of participant characteristics of anti-HCV positive men by injection drug use history and univariate analyses of spontaneous HCV clearance.

	Non-IDUs			IDUs		
		Cleared HCV			Cleared HCV	
Participant Characteristics [a]	**N (%)**	**%** [b]	**p** [c]	**N (%)**	**%** [b]	**p** [c]
All	249 (100.0)	34.5		279 (100.0)	11.5	
Recruitment period (p<0.001)			0.01			0.15
1984-1985	139 (55.8)	41.7		121 (43.4)	15.7	
1987-1995	36 (14.5)	38.9		12 (4.3)	8.3	
2001-2003	74 (29.7)	18.9		146 (52.3)	8.2	
MACS site (p=0.66)			0.36			0.54
Baltimore	77 (30.9)	32.5		94 (33.7)	9.6	
Chicago	57 (22.9)	42.1		53 (19.0)	17.0	
Pittsburgh	50 (20.1)	38.0		53 (19.0)	9.4	
Los Angeles	65 (26.1)	27.7	0.05 [d]	79 (28.3)	11.4	0.40 [d]
Age (years) (p=0.004)						
<30	41 (16.5)	48.8		52 (18.6)	13.5	
30-39	123 (49.4)	35.0		96 (34.4)	13.5	
40-49	65 (26.1)	24.6		95 (34.1)	8.4	
≥50	20 (8.0)	35.0		36 (12.9)	11.1	
Race/ethnicity (p=0.10)			0.01			0.04
Non-Hispanic Black	101 (40.6)	23.8		136 (48.7)	6.6	
Non-Hispanic White	125 (50.2)	42.4		114 (40.9)	16.7	
All Others	23 (9.2)	39.1		29 (10.4)	13.8	
Smoking history (p<0.001)			0.59			0.58
Never smoked	72 (28.9)	30.6		32 (11.5)	15.6	
Former smoker	48 (19.3)	39.6		43 (15.4)	14.0	
Current smoker	129 (51.8)	34.9		204 (73.1)	10.3	
Transfusion past 5 years (p=0.77)			0.46			0.54
No	221 (90.9)	33.0		248 (90.2)	10.9	
Yes	22 (9.1)	40.9		27 (9.8)	14.8	
Syphilis history (p=0.52)			0.16			0.44
No	155 (62.8)	38.1		182 (65.5)	10.4	
Yes	92 (37.2)	29.4		96 (34.5)	13.5	
Lifetime number of male intercourse partners (p<0.001)			0.03 [d]			0.43 [d]
0	28 (11.4)	17.9		82 (29.6)	11.0	
1-9	13 (5.3)	23.1		27 (9.7)	11.1	
10-49	44 (18.0)	20.5		35 (12.6)	8.6	
50-499	99 (40.4)	41.4		63 (22.7)	7.9	
≥500	61 (24.9)	36.1		70 (25.3)	17.1	

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

	Non-IDUs			IDUs		
		Cleared HCV			Cleared HCV	
Participant Characteristics [a]	**N (%)**	**%** [b]	**P** [c]	**N (%)**	**%** [b]	**P** [c]
HIV infection (p=0.47)			0.01			0.92
Negative	95 (38.2)	44.2		98 (35.1)	11.2	
Positive	154 (61.8)	28.6		181 (64.9)	11.6	
HBsAg status (p=0.39)			0.12			<0.001
Negative	215 (93.5)	33.5		260 (95.2)	10.0	
Positive	15 (6.5)	53.3		13 (4.8)	46.2	
rs12979860 genotype (p=0.78)			<0.001			<0.001
CC	76 (32.5)	51.3		92 (35.2)	23.9	
CT	104 (44.4)	30.8		109 (42.8)	8.3	
TT	54 (23.2)	20.4		60 (23.0)	1.7	

Abbreviations: HCV, hepatitis C virus; IDUs, injection drug users; anti-HCV, antibody to the hepatitis C virus; MACS, Multicenter AIDS Cohort Study; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen.

[a] P-values shown in parentheses are from the test of association between the indicated participant characteristic and IDU status

[b] Percent (row %) of anti-HCV positive men who were HCV RNA negative at enrollment.

[c] Univariate p-value for test of association between participant characteristic and HCV RNA status.

[d] Test of trend.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 4

Multiple regression analysis of the association of participant characteristics with spontaneous HCV clearance stratified by history of injection drug use.

	Non-IDUs		IDUs	
Characteristics	**CR**	**95% CI**	**CR**	**95% CI**
Recruited 1984-1995 vs. 2001-2003	1.79	0.90 – 3.58	1.97	0.48 – 8.06
Age (per 10 years)	0.80	0.61 – 1.15	0.95	0.59 – 1.52
Non-Hispanic Black race	1.09	0.62 – 1.93	0.38	0.13 – 1.15
Current smoker	0.80	0.57 – 1.20	**0.45**	**0.23 – 0.88**
Transfusion (past 5 years)	1.25	0.66 – 2.35	1.36	0.53 – 3.50
Syphilis	0.94	0.60 – 1.46	1.98	0.95 – 4.12
Lifetime number male intercourse partners				
0	1.15	0.42 – 3.16	2.54	0.70 – 9.17
1-49	1	(reference)	1	(reference)
≥50	1.24	0.73 – 2.10	0.45	0.17 – 1.20
HIV positive	**0.59**	**0.40 – 0.87**	0.70	0.33 – 1.47
HBsAg positive	1.62	1.00 – 2.63	**5.06**	**2.25 – 11.37**
rs12979860 genotype CC vs. CT/TT	**1.71**	**1.17 – 2.49**	**4.16**	**1.99 – 8.72**

Models are adjusted for MACS site and all characteristics listed in this table.

Confidence intervals that do not include 1 are indicated in bold.

Abbreviations: HCV, hepatitis C virus; IDUs, injection drug users; CR, clearance ratio; CI, confidence interval; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; MACS, Multicenter AIDS Cohort Study.