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Hepatitis C Incidence and Spontaneous Viral Clearance in a Cohort of Human Immunodeficiency Virus and Hepatitis B Virus Negative Drug Users

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Abstract

Estimating HCV incidence and viral clearance in other than young, White, injection drug users (IDUs), negative for HBV and HIV has not been undertaken. We enrolled 1,260 mostly African American injecting and non-injecting drug users negative for HIV and HBV prospectively from urban areas in Houston, TX, from 2005-2009, to determine HCV incidence and spontaneous viral clearance. Socio demographic and high risk behavioral data and blood samples were collected every 6 months for two years. Serum was tested for antibodies to HCV by enzyme immunoassay (EIA), and confirmed for HCV RNA by polymerase chain reaction (PCR). Kaplan-Meier failure curves and Cox proportional hazard regression analyses were performed to identify factors for HCV incidence. A follow-up HCV RNA PCR test was used to determine viral clearance in HCV incident cases. We followed 840 anti-HCV negative participants resulting in 19 HCV seroconversions per 1436.67 person years for an HCV incidence of 13.2/1000 PY (95% Confidence Interval [CI], 8.4-20.7). IDU's risk of contracting HCV compared to non-injecting drug users (62.5 per 1000PY, 95% CI, 33.6-116.2, *vs*. 7.1 per 1000PY, 95% CI 3.7-13.6) was significantly higher. White/Hispanic race, injecting drugs at least daily, and being 40 years of age or older were significant risk factors for HCV seroconversion. Spontaneous viral clearance was observed in 42% of HCV incident cases. HCV incidence remains high among HB vaccinated drug users. Daily injecting drug use is a predictor for new HCV infection. An HCV vaccine is urgently needed, especially in high risk populations.

Keywords: HCV; HIV; HBV; Substance abuse; Infection; Disparity

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Introduction

Hepatitis C Virus (HCV) is the most common blood-borne pathogen in the U.S. An estimated 3 million Americansharbor chronic HCV infection, and up to 70% of them do not experience any symptoms during acute infection [1,2]. They may not seek medical attention, and go undetected for years, thus becoming at risk for chronic liver disease, cirrhosis or hepatocellular carcinoma, requiring liver transplantation or dying of HCV-related complications. During this long, undetected, asymptomatic stage, they continue to serve as a source of transmission to others.

The most common route of transmission for HCV is percutaneous exposure resulting from injection drug use (IDU) or needle-stick injuries [3]. The virus can also be transmitted, although much less often, through sexual contact with an HIV-infected partner [4] or from an HCV-infected mother to her infant [5]. Several cohort incidence studies have found injection drug use and related behaviors, such as trading sex for money or drugs, sharing injection equipment, and having sex with an IDU, as risk factors for acquiring HCV [6-11]. In contrast, data on risk factors associated with HCV incidence and transmission in non-injecting drug users (NIDU) are limited.

Among published cohort studies, 16-42% [12-18] of HCV infected individuals spontaneously cleared the virus (failure to detect HCV RNA, despite positive anti-HCV). Factors reportedly associated with spontaneous clearance are age, sex, race or ethnicity, level of viraemia, alcohol intake and HCV genotype; however, these results have been inconsistent, possibly due to lack of control for co-infections with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) [14,19-25]. Our previous cross-sectional study of HCV clearance in HIV and HBV negative drug users showed African American drug users were three times less likely to clear HCV compared to White drug users [26].

Table 1: Hepatitis C Incidence in 840 Drug Users.

	Total	PY[a]	HCV+	Incidence (per 1000/py)	RR (95% CI)	P Value
Total	840	1436.67	19	13.2		
Age in years						0.099
<40	359	569.01	4	7.03 (2.64-18.73)	1	
>=40	481	867.66	15	17.29 (10.42-28.68)	2.46 (0.78- 10.18)	
Sex						0.646
Male	632	1060.91	15	14.14 (8.52-23.45)	1	
Female	208	375.76	4	10.65 (4.00-28.36)	0.75 (0.18-2.36)	
Race						0.004
Black	745	1316.97	13	9.87 (5.73-17.00)	1	
White/Hispanic	95	119.7	6	50.12 (22.52-111.57)	5.08 (1.58- 14.32)	
MSM[b]						0.028
No	772	1350.56	15	11.11(6.70-18.42)	1	
Yes	66	85.32	4	46.88 (17.60-124.92)	4.22 (1.02-13.25)	
Traded money/drugs for sex[b]						0.583
No	715	1210.81	17	14.04 (8.73-22.59)	1	
Yes	125	225.86	2	8.85 (2.21-35.41)	0.63 (0.07-2.67)	
Ever IDU						0
No	735	1276.69	9	7.00 (3.67-13.55)	1	
Yes	105	159.98	10	62.5 (33.63-116.17)	8.58 (3.49-21.13)	
Injection frequency						0
Less than daily	789	1375	11	8.00 (4.43-14.45)	1	
At least daily	32	61.67	8	129.72 (64.87-259.40)	16.21 (5.66- 44.26)	
Powder cocaine use[b]						0.078
No	700	1215.93	13	10.69 (6.21-18.41)	1	
Yes	140	220.74	6	27.18 (12.21-60.50)	2.54 (0.79-7.17)	
Methamphetamine use[b]						0.025
No	806	1390.01	16	11.51 (7.05-18.79)	1	
Yes	34	46.6	3	64.37 (20.76-199.59)	5.59 (1.04-19.54)	
Heroin use[b]						0.041
No	822	1413.31	17	12.03 (7.48-19.35)	1	
Yes	18	23.37	2	85.60 (21.41-342.25)	7.12 (0.80- 29.98)	
Polydruguse[c]						0.031
1-2 drugs	473	831.09	6	7.22 (3.24-16.07)	1	
3 or more drugs	344	572.88	12	20.95 (11.90-36.88)	2.9 (1.01-9.42)	

A Person-Years; b In the past 30 days; c One missing .

Co-infection with HIV and HBV is commonly observed in HCV infected drug users, not allowing for the observation of the natural history of HCV infection in an HIV and HBV negative cohort. We are able to study the natural history of HCV infection in the absence of HIV and HBV in our cohort. Most of the HCV incidence cohort studies have mainly focused on White, injecting drug users under the age of 30 [6,7,9,10,27]. To the best of our knowledge, this is the first prospective cohort study to examine HCV incidence and viral clearance in HIV and HBV negative, mainly African American, injecting and non-injecting drug users.

Materials and Methods

Study design and population

The current study was part of a large behavioral and vaccine schedule intervention trial (DASH; Drug, AIDs, STDs, Hepatitis project) which was conducted to administer the hepatitis B vaccine to not-in-treatment current drug users while testing two interventions, an accelerated vaccine schedule and a self-motivating behavioral intervention [28]. During this trial, 1,260 injecting and non-injecting drug users, negative for HIV and HBV, were enrolled from two drug endemic urban neighborhoods in Houston, Texas, from February 2004 to November 2006. They were followed for two

Table 2: Predictors of Hepatitis C Incidence in a Cohort of Drug Users (Multivariable Cox Proportional Hazards Regression Model).

		Adjusted Hazard Ratio	P Value
Age			0.035
	<40	1	
	>=40	3.41 (1.09-10.67)	
Race			0.039
	Black	1	
	White/Hispanic	3.11 (1.06-9.14)	
Injection frequency			0
	Less than daily	1	
	At least daily	3.44 (2.10-5.62)	

Adjusted for sex, HBV vaccine completion, MSM in the past 30 days, injection frequency, HBV status at enrollment, syphilis infection (ever), cocaine use in the past 30 days, methamphetamine use in the past 30 days, heroin use in the past 30 days, speedball use in the past 30 days, and poly drug use.

years to assess adherence to hepatitis B vaccine, immune response after administration of hepatitis B vaccine, and incidence of HIV and HCV infection [28,29]. In order to examine HCV incidence in this cohort, all enrolled drug users were tested for antibodies to HCV (anti-HCV) every 6 months during the two-year follow-up period. A questionnaire was also administered at these 6-month visits to assess risk factors for HCV acquisition. Two-thirds (840/1260) of drug users were HCV negative at enrollment and included in the current study to determine HCV incidence. Each participant provided written informed consent to participate in the DASH project, and this study was approved by the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects.

Data collection and laboratory method

Previous instruments were used to create the enrollment and follow-up questionnaires utilized in this study [28]. All questionnaires asked questions regarding socio-demographic measures such as age, sex, race or ethnicity, living arrangement, jail history of more than 24 hours; drug use history including lifetime IDU, frequency of injected drugs in past 30 days, lifetime and number of times shared needles in past 30 days, duration of IDU, types and frequency of cocaine, heroin, methamphetamine, marijuana and alcohol in past 48 hours and 30 days; history of blood transfusion, occupational exposure to blood; drug treatment; sexually transmitted disease occurrence; and sexual behavior, such as number and type of partner in the past 30 days,

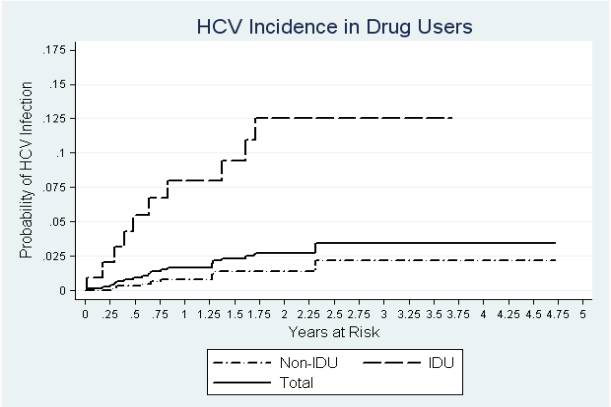

Figure: Kaplan Meier Failure Curves for HCV Incidence in Drug Users, stratified by Injecting Drug Use.

condom use, trading sex for money or drugs in the past 30 days, and sexual orientation. The enrollment questionnaire included additional questions on drug binging and HBV perception scales. All interviews were verbally administered and recorded electronically via computer administered personal interview (CAPI, Questionnaire Development System, Bethesda, Maryland).

Blood specimens collected at enrollment and follow-up were tested for anti-HCV performed on the Abbott AxSYM (MEIA; microparticle enzyme immunoassay) system (Abbott Laboratories, Chicago, IL). All quality control measures were followed, as recommended by the manufacturer, including running controls and repeat testing when advised. Polymerase chain reaction (PCR; Roche Cobas Amplicor) was used to detect HCV RNA qualitatively to confirm incident cases of HCV infection and evaluate spontaneous HCV clearance.

Definitions

HCV incidence was defined as a positive anti-HCV test, with or without a positive HCV RNA test, with at least one follow-up sample also testing positive for anti-HCV. HCV viral clearance was defined as a positive anti-HCV test with a negative HCV RNA test at seroconversion or at least 6 months post seroconversion.

Statistical analyses

Questionnaire data were exported from QDS into SAS 9.1 (Cary, NC), and laboratory results were entered into a Microsoft Access database. Data analyses were performed using STATA 9.1 (STATA Corp., College Station, TX). For univariate analysis, incidence rates and 95% confidence intervals were used to measure the strength of association between each dependent variable and independent variables. White and Hispanic races were combined because of small numbers. For the multivariable analyses, variables with a p-value <0.2 in the univariate analysis and age, sex and race were entered into the multivariable cox proportional hazards regression model. Independent variables were eliminated based on backward stepwise regression according to Hosmer and Lemeshow [30]. Hazard ratios and 95% confidence intervals were calculated for the variables with a p-value less than or equal to 0.05, and adjusted for sex, HBV vaccination completion, MSM status in the past 30 days, injection frequency, HBV status at enrollment, syphilis infection (ever), cocaine use in the past 30 days, methamphetamine use in the past 30 days, heroin use in the past 30 days, speedball use in the past 30 days, and polydrug use. Kaplan-Meier failure curves were generated for HCV incidence to demonstrate probabilities for seroconvert ing to HCV among injecting and non-injecting drug users. A log-rank test was performed to assess the difference in their probabilities for seroconversion. Due to small number of HCV incident cases, only univariate analysis was performed to identify the differences between those who spontaneously cleared HCV and those who did not clear HCV, using Fisher's exact tests and Wilcoxon rank-sum tests for categorical and continuous variables, respectively.

Results

A total of 840 anti-HCV negative current drug users were followed for 1436.67 person-years and assessed for incidence of HCV infection. Majority of these participants were male (75%), aged 40 years or older (57%), and African American (89%). Thirteen percent were injecting drug users at some point in their lifetime. Crack cocaine (90%), followed by powder cocaine (16%), and methamphetamines or heroin (4%, 2%, respectively) were the primary drugs of choice

Table 3: Characteristics of Drug users Achieving Spontaneous HCV Viral Clearance.

	Total	Clearance[#]	Non-clearance	p value
Number of drug users	19	8 (42)	10 (53)	-
Mean age (range)	42 (22-56)	44 (22-54)	42 (31-56)	0.265[†]
Age, years				1.00[*]
<40	4 (21)	1 (12.5)	2 (20)	
≥40	15 (79)	7 (87.5)	8 (80)	
Sex				0.275[*]
Male	15 (79)	5 (62.5)	9 (90)	
Female	4 (21)	3 (37.5)	1 (10)	
Race				0.314[*]
African-American	13 (68)	7 (87.5)	6 (60)	
Non-African	6 (32)	1 (12.5)	4 (40)	
Past 30 days				
IDU	4 (21)	0	4 (40)	0.092[*]
MSM	4 (21)	1 (12.5)	3 (30)	0.588[*]
Crack	18 (95)	8 (100)	9 (90)	1.00[*]
Cocaine	6 (32)	2 (25)	4 (40)	0.638[*]
Methamphetamine	3 (16)	0	3 (30)	0.216[*]
Fry	1 (5)	1 (12.5)	0	0.444[*]
Marijuana	11 (58)	5 (62.5)	5 (50)	0.664[*]
Alcohol	15 (79)	7 (87.5)	7 (70)	0.588[*]
Heroin	2 (11)	0	2 (20)	0.477[*]
Speedball	1 (5)	0	1 (10)	1.00[*]
Number of drugs				0.335[*]
1-2 drugs	6 (32)	4 (50)	2 (20)	
3 or more drugs	11(58)	4 (50)	7 (70)	
Ever used injecting drugs	10 (53)	5 (62.5)	5 (50)	0.664[*]

[#]Inconclusive HCV RNA with no subsequent follow-up: 27 year old, White, male with history of crack, marijuana and alcohol use in the past 30 days
[*]Fisher's Exact Test; † Wilcoxon Rank-Sum Test

for this cohort. Eight percent of the male participants had a male sex partner in the past 30 days. Fifteen percent of the study participants had traded sex for money or drugs in the past 30 days.

Out of 840 participants, 19 had evidence of HCV seroconversion by becoming anti-HCV positive for an incidence of HCV infection rate of 13.2 per 1,000 person years (95% Confidence Interval [CI], 8.4-20.7). There were 13 African Americans and 15 males among the 19 seroconverts. Ten participants were injecting drug users. Only 2 study participants had shared injecting equipment. Four of the 19 were men having sex with men (MSM), and 3 MSMs were also IDUs. Six participants had traded sex for money or drugs at enrollment. A majority of them, 14 out of 19, had spent at least 24 hours in jail at enrollment. Two participants had no identifiable risk factors from the questionnaire data used in this study.

Univariate analysis and incidence rates of exposure variables are presented in (Table 1). The incidence rate for injecting drug users was 62.5 per 1000 PY (95% CI, 33.6-116.2) versus 7.1 per 1000PY (95% CI 3.7-13.6) for non-IDUs resulting in a significant difference (p<0.000).

To avoid collinearity issues in the multivariable model, injection frequency instead of lifetime of injection drug use was used in the univariable and multivariable analyses. Significant risk factors for HCV seroconversion in the univariable analysis were White or Hispanic race (versus African-American race), MSM, injecting drugs at least daily (versus less than daily), use of methamphetamines (or heroin) in the past 30 days, and poly drug user (3 or more drugs versus 1-2 drugs). Two other variables with p values <0.1 were age (40 years or older versus less than 40) and use of powder cocaine in past 30 days. These variables, along with sex, hepatitis B vaccine completion (did not complete versus completed), hepatitis B status at enrollment (positive versus negative), syphilis infection, and speedball use in the past 30 days were included in the multivariable cox regression model. After adjustment for the above-mentioned exposures, significant risk factors for HCV seroconversion were White or Hispanic race (RR 3.11, 95% CI 1.06-9.14), injecting drugs at least daily (RR 3.44, 95% CI 2.10-5.62), and being 40 years of age or older (RR 3.41, 95% CI 1.09-10.67) (Table 2). Kaplan-Meier failure curves demonstrated that injecting drug users had a higher HCV incidence compared to non-injecting drug users (12.5% versus 2.4%; over 2 years) (Figure 1). This was a significant difference as demonstrated by the log-rank test (p<0.000).

Out of the 19 HCV incident cases, 1 case had an inconclusive HCV RNA result, and the participant did not have any subsequent follow-up visits. From the remaining 18 with HCV RNA results, 8 individuals (42%) spontaneously cleared HCV in a period of 6-24 months after initial infection. Out of the 10 non-clearance individuals,

6 cases had evidence of HCV persistence (confirmed HCV RNA via PCR) during the 6- 24 month follow-up period and 4 cases had HCV RNA at conversion without a confirmatory follow up sample. (Table 3) compares characteristics between these two groups. None of these factors were statistically significant, probably because of small sample size.

Discussion

This is the first prospective cohort study to determine HCV incidence and viral clearance in HIV and HBV negative, mainly African American, injecting and non-injecting drug users. The overall incidence of HCV infection in current drug users in this study was 13.2 per 1,000 PY. The HCV incidence was significantly higher in IDUs (62.5/1,000 PY) compared to non-IDUs (7.1/ 1,000PY). Significant risk factors for HCV seroconversion were White or Hispanic race, injecting drugs at least daily, and being 40 years of age or older.

The incidence rate for IDUs in this study was substantially lower than most studies, 25.1-41.3 per 100 PY [6-8,31], but comparable to other studies ranging from 6.4-11.0 cases per 100 PY [9,10,27]. White IDUs under the age of 30 were recruited for many of these studies whereas our study sample included 89% African American drug users, and out of the entire population, 12% were IDUs, and 57% were over the age of 40. The cohort in this study was derived from a hepatitis B vaccination intervention study, therefore, the lower HCV incidence could be a result of the interventions conducted in the study who were HIV and HBV negative, as well. HCV incidence in non-IDU was comparable to one other study, at 0.4 per 100 PY [8]. This study shows that participants aged 40 years or older had the highest risk of acquiring HCV compared to those younger than 40. This finding was different from two other reports [6,7].

Frequency of injecting drugs was significantly related to HCV seroconversion in this study. We used this measure instead of IDU status because of the intermittent nature of IDUs in this study. The answers to the IDU question would vary from visit to visit throughout the follow-up period. A possible explanation for intermittent injecting drug use is the lack of availability and/or high cost of heroin and cocaine whereas crack cocaine is cheap and readily available, and the favored drug of choice in our population. Another possibility may be a failure by the drug users to be honest on the questionnaire. Several studies have shown that the more frequently one injects, the more likely the drug user is to have HCV infection, whether it is injecting daily, or injecting for many years [7-10]. The linear relationship that is involved in number of unprotected sexual acts and HIV acquisition is also observed with the frequency of injecting drugs and HCV acquisition.

Even if the person is an intermittent injector, there are several ways to be exposed to HCV. These include sharing needles or other preparation paraphernalia or having unprotected sex with an HCV positive IDU, especially in a highly prevalent HCV positive group, such as injecting drug users. Two out of the 10 HCV positive IDUs in our study shared needles. Although power is an issue, reasons why we did not find this association may be underreporting or collinearity (with injection status). Other studies, except one [7], have shown significant associations with sharing paraphernalia and equipment with HCV seroconversion [6,9,10,27].

Another important factor in the majority of these incidence cases was a history of incarceration at enrollment. We had 2 participants with a documented history of being in jail at least 6 months prior to seroconversion, one 1 of these participants was an IDU. Tattooing and sharing injection equipment in jail most likely occurs with dirty needles or paraphernalia [32-35]. In this study, we had limited incarceration history data to evaluate the risk of incarceration for incidence. However, we can speculate being in jail or prison would limit access to clean needles, for injecting a drug or tattooing, and could be a plausible explanation for HCV infection. Tattooing in jail may have occurred with one of our NIDUs, who had a jail history prior to seroconversion to HCV. Low numbers of non-IDUs in this study prevented us from assessing risk factors for seroconversion in that subgroup. Lastly, there is conflicting incidence and prevalence data linking sexual transmission to HCV [36-40]. NIDU populations may be saturated with former IDUs, therefore, a pure NIDU population may be hard to find, and thus analyze for HCV infection, as one incidence study showed that 62% of their NIDUs were former IDUs [39]. But, NIDU have lower incidence rates versus self-reported IDUs, as shown by our study and others.

Spontaneous clearance occurred in 42% of our HCV incident cases. This is at the high end of the range of spontaneous clearance observed in other studies, 16-42% [12-18]. This rate was higher than our previous report of 15% in our cross-sectional study [26]. In general, the viral clearance rate would be higher in cohort studies than cross-sectional studies because cohort studies are a better design to examine the natural history of HCV infection. Although we could not perform further analyses to identify predictors, our descriptive results shared what has been seen in other studies, such as females appear to clear HCV better than males [12,14,17,18]. Being female and having the favorable genetic variation of IL-28 causes a synergy, and increases the likelihood of HCV viral clearance [17]. Alone, the IL-28B locus was found to be associated with increased natural HCV clearance [41]. Race or Ethnicity is an identified predictor for HCV viral clearance. Studies have found persons of African American race to be less likely to clear HCV [12,15,21]. Since our study consisted of 89% African Americans, our lack of diversity may not have allowed us to detect this finding. No studies to date have found age to be a significant factor in the clearance of HCV. Our data also suggest that recent illicit drug use may hinder the ability of the body to clear HCV, like two other studies have reported [12,16]. Immune dysfunction, co-morbidities and reinfection are hypothesized reasons for this effect [16]. In this cohort, we enrolled drug users that were HIV and HBV negative, therefore mechanisms related to other possible host genetic susceptibility other than co-infections may exist.

There are some limitations to this study. Underreporting in the drug using population may have occurred, which could have affected our power and contributed to collinearity with some variables, such as sharing equipment and being an injecting drug user. Despite these limitations, our study demonstrates the need to infiltrate minority groups with innovative interventions to curb high-risk behaviors.

As demonstrated in our study, HCV incidence remains high amongst drug users, including those vaccinated for hepatitis B. The need for vigilant surveillance and active interventions to prevent HCV transmission is needed, especially in injecting drug users. The surveillance and interventions can provide a better understanding of prevention and control of HCV. Studying natural history of HCV infection among drug users without HIV and HBV co-infections can help us estimate the willingness and effectiveness of future HCV vaccine trials. Even though the HB vaccine is a multi-dose vaccine, we

successfully vaccinated enrolled drug users with a 75% adherence rate to 3 doses of the HB vaccine, and 65% achieved HBV seroprotection by 12 months [28,29]. An HCV vaccine is urgently needed, especially for this high-risk group.

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