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Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution and reinfection

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Abstract

Background—Hepatitis C virus (HCV) infection, clearance and reinfection are best studied in injection drug users (IDU) who have the highest incidence and are representative of most infections.

Methods—A prospective cohort of HCV negative young IDU was followed from 2000 to 2007, to identify acute and incident HCV and prospectively study infection outcomes.

Results—Among 1,191 young IDU screened, 731 (61.4%) were HCV negative, and 520 (71.1%) were enrolled into follow-up. Cumulative HCV incidence was 26.7 per 100 person years of observation (PYO) (95% CI, 21.5, 31.6). 95 (70.4%) of 135 acute/incident HCV infections were followed; 21% cleared HCV. Women had a significantly higher incidence of viral clearance compared to men (age-adjusted relative hazard 2.91, 95% CI, 1.68, 5.03) and also showed a significantly faster rate of early HCV viremia decline. Estimated reinfection rate was 24.6 per 100 PYO (95% CI, 11.7, 51.6). Among seven individuals, multiple episodes of HCV reinfection and re-clearance were observed.

Conclusions—In this large sample of young IDU, females show demonstrative differences in their rates of viral clearance and kinetics of early viral decline. Recurring reinfection and re-clearance suggest possible protection against persistent infection. These results should inform HCV clinical care and vaccine development.

Keywords

hepatitis C virus; HCV; injection drug use; acute HCV infection; clearance; viral load; reinfection; female

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Dedication: This paper is dedicated to the memory of Pete Morse (1970–2007), who committed himself unselfishly to the health and welfare of young injectors in San Francisco and the U.S. and who continues to inspire us.

Introduction

Hepatitis C virus (HCV) is the most common blood borne viral infection in the U.S, and a major etiological agent of liver disease [1]. Overall, about one in four (26%) infected persons spontaneously resolves infection, but there is significant variation (0% to 80%) between different studies [2]. As viral resolution occurs principally in acute infection [3], understanding correlates and mechanisms underlying successful resolution will contribute to clinical decisions regarding early treatment as well as potential vaccine development.

Acute HCV infection has been principally studied in small heterogeneous groups identified opportunistically [4–6], including recipients of plasma-derived blood products [7], transfusion donors and recipients [8,9], and health care workers [10]. Multiple host factors (reviewed in [11]), especially immune responses [12–14], but also age, sex, race/ethnicity, and route of infection [2,14–17] have been associated with clearance. Reinfection and re-clearance of HCV infection are less well studied. Acute HCV infection is important to study in IDU [18], as they have the highest incidence of HCV [19] and are likely to be representative of most infections [20]. We present results of a prospective study of HCV infection among young IDU, followed to measure incident HCV, acute infection, clearance and reinfection rates.

Methods

Population

HCV negative IDU were enrolled and followed in three waves between January 2000 and September 2007 in a prospective cohort named the UFO-3 Study in San Francisco, California. Recruitment and follow up details for the first wave of participants (2000 and 2001) were previously published [19], subsequent waves were recruited in 2003 through 2004, and again starting in 2006 and followed through September 2007. Cohort eligibility was restricted to those under age 30, who reported injecting drugs in the prior month, who spoke English as their primary language, and if recruited in 2003 or later, did not plan to travel outside of San Francisco within the next three months.

Cohort screening, enrollment and follow-up—At a baseline eligibility visit, IDU were screened for age and injecting history, and since 2005, knowledge of HCV status. Eligible consenting participants were interviewed, counseled, and tested for antibodies to HCV (anti-HCV) and HCV RNA. Each was remunerated $10 at screening, and $20 at results visits. HCV negatives and those with indicators of previously resolved HCV infection (negative HCV RNA and positive anti-HCV) were offered enrollment into the prospective cohort (UFO-3 Study). Follow-up included monthly “check-ins” and quarterly study visits which included structured interviews to assess exposures, HCV testing, and risk reduction counseling and referrals. Voluntary anonymous HIV screening was offered to participants.

Participants with newly detected HCV (HCV RNA and or anti-HCV) were offered enrollment in the prospective study *UFO Acute HCV* cohort which included monthly visits to document and study the natural history of acute HCV infection. All were provided with referrals for follow-up care, and after 2005 offered enrollment into a study of early HCV treatment candidacy (to be described elsewhere).

Procedures

Laboratory tests—Serum samples were tested for anti-HCV, HCV RNA, and HCV genotype. At baseline, anti-HCV testing was conducted using HCV EIA 2.0 (Abbott Laboratories, Abbott Park, IL). Sera was tested in parallel or retrospectively for anti-HCV using EIA-3 (Ortho Clinical Diagnostics, Raritan NJ), and reactive samples were confirmed

using HCV RIBA™3.0 Test System (Novartis Vaccines & Diagnostics, Emeryville, CA). In April, 2007, all anti-HCV testing was shifted to EIA-3 testing. HCV RNA testing was conducted using the discriminatory HCV TMA (dHCV TMA) assay component of the Procleix® HIV-1/HCV assay, developed and manufactured by Gen-Probe Inc., San Diego, CA, and marketed by Novartis Vaccines & Diagnostics, Emeryville, CA. The assay's 50% limit of detection is 12.1 (95% CI, 11.1 to 13.2) copies/mL of HCV RNA when using the recommended 0.5 mL specimen input. Samples were tested individually (i.e., non-pooled) [21]; reactive samples were re-tested and repeatedly reactive samples were assumed to be confirmed HCV RNA positive. HCV viral load was measured by either: (1) HCV Monitor (Roche Amplicor Monitor HCV 2.0, Roche Molecular Systems, USA) performed on the Cobas Amplicor semiautomatic instrument, or (2) Bayer HCV RNA bDNA assay (Versant® HCV 3.0; Bayer Diagnostics, Tarrytown NY). The lower limits of detection for these two assays are 50 IU/mL and 615 IU/mL, respectively. Samples reactive for HCV RNA by sensitive dHCV TMA (qualitative) testing but with undetectable quantitative RNA results were judged to be HCV RNA positive and quantified as half the value of the lower limit of detection based on the quantitative test used. Samples negative on both qualitative and quantitative tests were judged to be HCV RNA negative and assigned a 0 value. Genotype was determined by the LiPA Line Probe Assay (Bayer Diagnostics, Tarrytown, NY). Samples where no HCV RNA was available (principally due to follow up intervals which exceeded the RNA positive interval) were tested using Murex HCV Serotyping EIA to distinguish antibodies to type-specific epitopes in the NS4 region of HCV (Murex Biotech Limited, Dartford, U.K.; distributed in Europe by Abbott Diagnostics, Wiesbaden, Germany)[22].

HCV infection case definitions

i. *Acute HCV infection* was classified as follows: (1) *baseline incident* acute infection, those persons who were anti-HCV negative but positive for HCV RNA (by TMA) at baseline testing visit; (2) *prospective incident* acute infection, HCV negative participants followed prospectively who presented with either a new positive HCV RNA and/or positive anti-HCV result.

ii. *HCV viral clearance* was defined as two consecutive negative HCV RNA results after confirmed acute or incident infection. The interval during which HCV infection occurred was defined by the date of the last documented anti-HCV and HCV RNA negative results, and the date of the first positive HCV RNA result. The interval during which viral clearance occurred was defined by the date of the last test with detectable HCV RNA and the first of two consecutive samples with undetectable RNA.

iii. *Reinfection* was considered in participants followed longitudinally who demonstrated viral clearance; a new positive HCV RNA test was considered indicative of reinfection. Reinfection was considered *confirmed* if the recurring infection was a different HCV genotype/serotype compared to the previous infection [23] and, *potential* if the participant had the same or no genotype result.

Statistical analyses

We compared those with two or more follow up visits to those who had less or no follow up to assess potential biases associated with loss to follow-up. Cumulative HCV infection rates were calculated using person-time of observation, and confidence intervals (CI) for the rates were calculated assuming a Poisson distribution. Occurrence dates of infection or seroconversion were imputed as the midpoint of the interval between the dates of the last observed HCV negative and either the first HCV RNA positive or first anti-HCV positive test result (with or without a concurrent HCV RNA detection). Baseline incident acute infections with no follow up were not counted in the incidence estimates.

We estimated the distribution of time to clearance using semiparametric methods for doubly interval-censored event times that avoid the potential bias associated with imputation based on interval midpoints [24]. Participants who did not clear HCV infection, including those who developed chronic infection and those who did not have two consecutive HCV RNA negative test results during follow-up, were treated as right-censored on the date of the last sample. Estimates of the clearance hazard and distribution were smoothed using a penalized likelihood approach [25]. Separate estimates of the clearance distribution for sub-groups of interest (e.g. by gender) were also made.

We fit Cox proportional hazards regression models applied to midpoint-imputed event times to assess variables independently associated with viral clearance. (These results were similar to those found using regression models for interval censored outcomes.) Variables considered included sociodemographic characteristics, risk exposures, and viral load data. Covariate effects were summarized as estimated incidence rate ratios with corresponding approximate 95% confidence intervals. Covariates observed to be associated with clearance in bivariate analyses at a significance level of 0.15 or less were included in the models. The validity of the proportional hazards assumption was evaluated by graphical comparison of estimated cumulative hazards between groups defined by the covariates of interest.

Quantitative viremia measures, including initial and peak viral loads detected in the first 6 months after estimated date of infection, were compared between those clearers and non-clearers using logged IU/mL values by Kruskal Wallis tests and a non-parametric equality of median test. We examined changes in viremia using various methods to account for dependent observations, including linear regression of log-transformed values with variances estimated accounting for clustering (i.e. robust variance) as well as generalized linear mixed models of transformed values with random intercepts and slopes. As results were similar using the different analyses, and our main interest is in a marginal interpretation of slope coefficient reflecting change over time, we present results of the linear regression. Differences in slope between clearers and non-clearers, and between males and females within those groups were examined by testing main effects and interaction terms in the regression models.

Incidence of reinfection was estimated among participants with resolved HCV infection; dates were estimated to occur at the midpoint between last RNA negative (clearance) date and the first RNA reactive (reinfection) date. Time to first reinfection (2^{nd} HCV infection) was calculated as the number of days elapsed from estimated date of clearance (midpoint between last RNA reactive and first RNA negative) to the reinfection date. We did not have enough cases to examine predictors of reinfection.

Results

Cohort enrollment and characteristics

Between January, 2000 and September, 2007, 1,191 young IDU were screened for anti-HCV; 731 (61.4%) were seronegative of whom 520 (71.1%) were enrolled into the UFO-3 cohort. Non-enrollment was principally due to participants not returning for results (~50%); the remainder for other (planning to travel out of San Francisco and refusals) reasons. Twenty-two (4.3%) enrolled anti-HCV negative participants were found to be RNA positive and were classified as *baseline incident* acute HCV infections. Thirteen participants were enrolled who had evidence of previously resolved infection (anti-HCV positive/HCV RNA negative) for a total of 533 cohort participants (Figure 1). The median age was 22 years (Interquartile Range (IQR) 20, 25), under half (45.9%) had completed high-school, two-thirds (65.2%) were male, and most (76.8%) were white. The reported median number of years injecting was 3.7 (IQR 1.3, 6.0), and median number of days injected in the past month was 20 (IQR 7,30).

Acute HCV infections

Cumulatively, 132 new HCV infections were detected in over 495 person-years of observation (PYO) yielding an HCV incidence of 26.7 per 100 PYO (95% CI: 21.5, 31.6). Three additional acute HCV infections were detected among participants with evidence of previously resolved infection, yielding a total of 135 acute HCV infections. Of these, 95 (70.4%) had at least two follow-up visits (Figure 1). No differences were found by sociodemographic, injecting or sexual behaviors, or incarceration history by follow-up status. Five of the 95 (5.2%) were HIV positive. Of 56 participants with acute infection identified in the acute pre-seroconversion window period, 49 (87.6%) had follow-up and 47 (95.9%) seroconverted. Two participants (one HIV positive (3.6%) did not seroconvert, but remained HCV RNA positive on serial retesting [26]. A total of 123 (91.1%) samples were genotyped or serotyped: 54% were type 1 or 1a, 14% type 2, 2a, or 2c, 31% type 3, or 3a, and one was type 4.

HCV viral clearance

Among the 95 acutely infected participants with follow-up (Figure 1), 20 (21.1%) cleared HCV infection; 68 (71.6%) showed persistent chronic viremia; 5 (5.3%) lacked two consecutive HCV RNA results; and 2 (2.1%) demonstrated intercalated viremia (intermittent positive and/or negative HCV RNA results) over the observation period, and which could not be classified as resolved or persistent. Two clearers were HIV positive. Figure 2 shows the estimated HCV viral persistence probability as a function of number of months following infection. The shaded 95% confidence intervals account for uncertainties in both the time of infection and time of clearance. Interpreted similarly to a Kaplan-Meier survival curve, the solid line gives the estimated probability of remaining infected at each time point. The corresponding probability of clearance at any time point is obtained by subtracting the estimated persistence probability from one. An estimated 20% of infected individuals clear within nine months of infection (95% CI, 14%, 27%), leveling off thereafter. Although there is some indication of a possible increase in clearance probability beginning approximately two years after infection, this is attributed to only one additional case of delayed clearance and the large uncertainty evident in this period precludes any definitive interpretation. Estimates of the median time to clearance were not feasible, as fewer than half the participants were observed to clear in the maximum observed duration of follow-up. However, to further illustrate the apparent rapid rate of clearance in the first two years following primary infection, we estimated the probability of clearance within six and 12 months among individuals observed to clear infection within 24 months: probability of 6-month clearance was 0.86 (95% CI: 0.40, 1.0), and of 12-month clearance was 0.95 (95% CI:0.42, 1.0). Thus, among individuals clearing infection within two years, we estimate that 86% will clear in the first six months, and almost all (95%) will clear within twelve months.

Table 1 shows demographic characteristics, exposures and risk behaviors and associations with HCV clearance. Viral clearance varied significantly by biological sex (p=0.01): clearance among women was 34.6/100 PYO (95% CI 19.2, 62.5) compared to 12.1/100 PYO (95% CI, 6.3, 23.3) among men. No statistically significant differences were noted in viral clearance by HCV genotype, although infection with genotype 3 showed a marginal negative association with clearance compared to genotype 1 (P=0.06). Figure 3 displays estimated HCV persistence probabilities for female and male participants. The curves reveal similar patterns of clearance in the two groups, but illustrate the higher overall rates in females.

In multivariate analyses controlling for age, the only factor found to be significantly associated with clearance was sex: women were significantly more likely to clear HCV infection than men: HR=3.51 (95% CI, 1.63, 9.70).

Viremia in early infection

We examined viremia (Log IU/mL) during the six months after detection of infection including first viral load value, maximum viral load, and the decline in viral load (Table 2). Of 20 clearers, serial samples were available for 17 (85%) participants. Participants had a median of two tests (range 1–4) in the six months following infection. The slope of viral load decline was significantly different ($p<0.01$) between male and female clearers: females who cleared infection had a log 83 IU/month decline compared to log 1 IU/month in males Figure 4).

Reinfection

Among 27 participants with resolved HCV infection (the 20 incident cleared infection cases and seven (of the13) participants who were enrolled as previous resolvers), seven showed evidence of reinfection (Figure 5). Estimated incidence of first observed reinfection was 24.6/100 PYO (95% CI, 11.7, 51.6). Overall, up to 14 potential reinfections were detected: three participants with two HCV infections (MN0018, TL0161, MN0561), one with three infections (SM0047), and three participants with four HCV infections (MN0552, MN0560, SM0051) (Figure 5). All (100%) of these participants re-cleared HCV RNA after every reinfection.

Discussion

This study provides a detailed assessment of acute HCV infection outcomes in a large cohort of young IDU with a high incidence of HCV and a significant number of acute infections. Analyses using interval censored techniques showed that an estimated 20% of infected individuals resolved infection, and that 86% of those followed cleared within six months of infection. Females were over three times more likely to resolve HCV than males, and female clearers showed a significantly steeper decline in HCV viral load during early infection compared to male clearers. Finally, reinfection and re-clearance was common.

Numerous studies have shown that women are more likely to resolve HCV infection compared to men [5,8,27]. Almost half (45%) of women who received HCV contaminated Rh immune globulin cleared infection [28,29]. Other studies have not shown gender differences including among IDU [18], or in cross-sectional population samples [30]. In cross-sectional studies, a temporal effect might be attributed to a loss of detectable antibody in women who resolved early [8] resulting in underestimation clearance among women [31]. A recent systematic review of prospective studies of HCV infection supports that clearance is significantly more likely in women compared to men[2]. Nevertheless, most studies investigating HCV clearance merely control for gender and therefore this factor remains understudied. Sex differences are also not well understood with respect to treatment outcomes [32], and progression to liver disease[33, 34], and sex hormones have been hypothesized to be involved [35]. The higher rate of clearance among women raises a number of important areas to be examined, not only with respect to controlling infection, but also to potential differences in susceptibility to infection.

For the majority of HCV infected young IDU, infection outcome was determined within six months, the period generally considered to be the defining threshold for infection outcome. However, a measureable number of clearance events occurred outside this window, as others have documented [6,8,16]. In the first two years after infection we show that the probability of clearing infection levels off nine months after infection. We acknowledge, however that these results could be underestimates of the true clearance rates due to the relatively short follow up period [36]. In a retrospective study of transfusion recipients with an overall 35% clearance rate, 27% cleared within two years, and 8% between 2–10 years later [8]. We also acknowledge that if participants with aviremia were misclassified as clearers when they were actually experiencing temporary viral suppression followed by viral rebound, we could be

overestimating rates of viral clearance. Viral interclations, however are relatively brief and we expect that with the frequent testing in our cohort, we reduced the chances of misclassification [8].

Patterns of viral load in early infection [16,37] and clearance [38] are usually examined on an individual basis, and are often limited by testing frequency. Our analyses assess patterns in aggregate and present a population perspective of viremia in early infection. Unlike Hofer et al, [39] we observed neither differences in peak viremia between clearers and non-clearers, nor in the rate of intermittent viremia prior to ramp-up [40]. Like others we saw steep declines in viremia [18,38,39], and also show significant differences among clearers by sex. These data suggest that monitoring changes in viral load in acute infection may help discriminate cases which should be considered for early HCV treatment from those who might wait for spontaneous resolution, potentially avoiding unnecessary exposure to HCV chemotherapy. HCV RNA values obtained at a single time point were not useful in discriminating between resolvers and non-resolvers, however, and the analyses limit individual inference regarding prediction of infection outcome. Nevertheless, the data are meaningful on a population level and demonstrate the need for more research on the predictive value of early viral kinetics in acute infection.

Frequent HCV viremia testing after initial infection allowed us to demonstrate that the HCV reinfection incidence was high in our young IDU sample, consistent with others [23,41–43]. Re-clearance of HCV after reinfection is not well studied. Mehta et al, [42] showed that previously infected IDU were 12 times less likely to develop chronic infection with reinfection, and that they had lower peak viral loads and a shorter duration of subsequent viremia compared to initial infection. Gerlach showed viremia generally lasted less than 12 weeks among reinfected IDU who re-cleared [44]. These and other studies of recurring infection and clearance in animals demonstrate that host genetic and/or immune responses exist that protect from chronic infection [45,46]. It is also unknown unclear whether persons who clear one viral strain have reduced infection susceptibility to the same or different HCV genotypes, as has been seen in animals [47]. Our results and others show that there is greater genetic heterogeneity in HCV among active IDU [23] than in clinical and other populations [30,48]. Reinfections were confirmed in two of the seven cases by a switch in HCV genotypes. The remaining five cases failed to yield genotype information and will require direct viral sequencing to confirm that reinfection occurred. The use of serotyping may have limitations: if it reflects the first infection, subsequent reinfections could be misclassified. Some had very short HCV negative intervals, which could indicate rapid clearance after reinfection as others have shown[42,44]. Further studies of reinfection and re-clearance are needed to shed more light mechanisms that may protect against persistent infection [47].

Despite the relatively large number of new infections and systematic follow up, we were nonetheless limited by the small number of clearance and reinfection events, indicating the need to combine data from multiple acute infection HCV cohorts to refine estimates for rates and kinetics HCV infection outcomes. The significant differences found by sex show the need for further studies of biological and immunological differences between females and males in HCV infection control. Finally, incidence of HCV remains very high in IDU, and more work is urgently needed to prepare for and develop vaccines which will offer the most important opportunity to prevent and control this common bloodborne viral infection [49,50].

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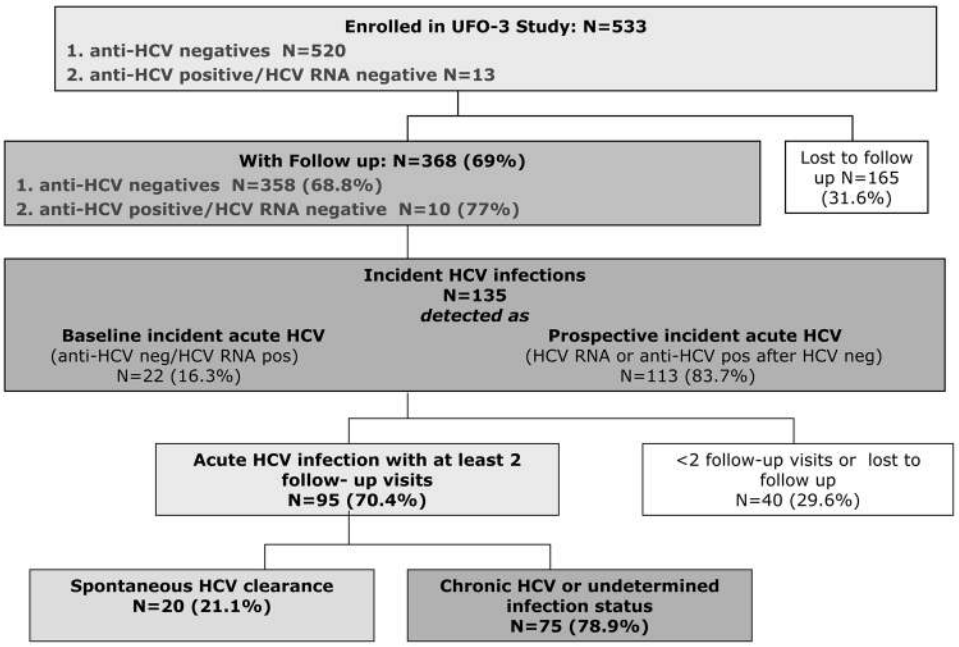


Figure 1.
Enrollment and prospective follow up of incident HCV infection, and infection outcome of young injection drug users in the UFO-3 Study

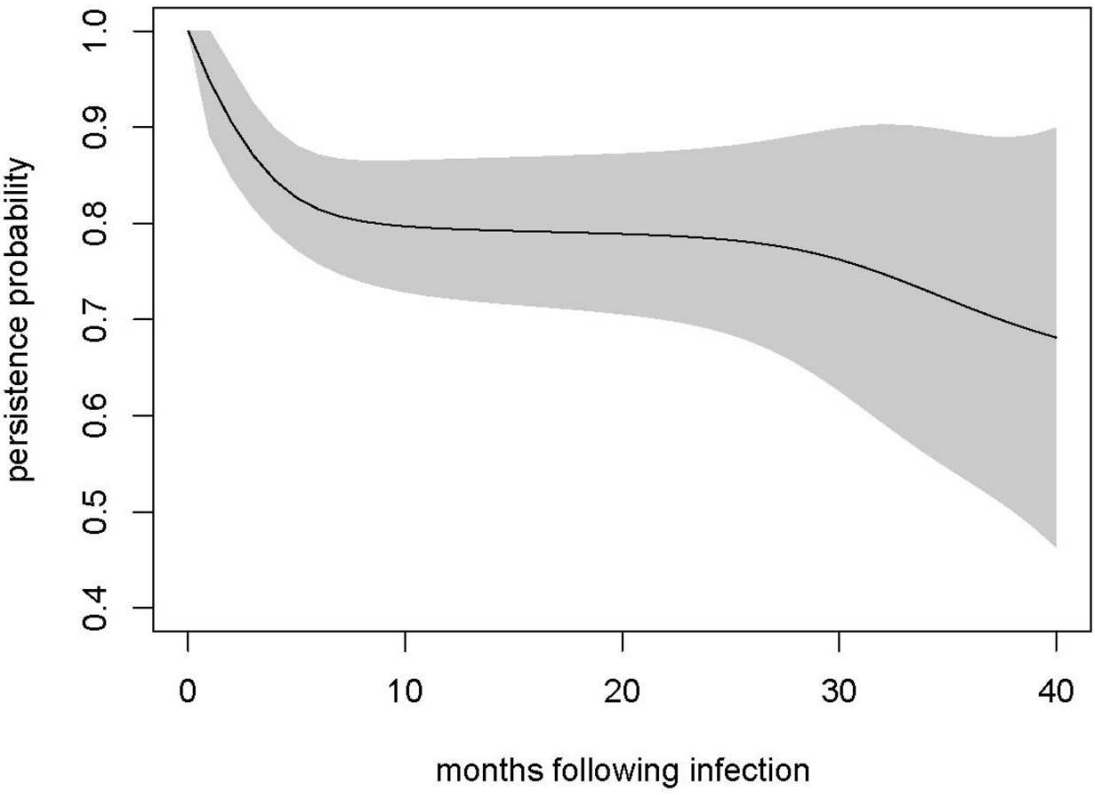


Figure 2.
Estimated HCV viral persistence probability (in months) among young injection drug users with incident HCV infection. The shaded area shows the 95% confidence interval accounting for uncertainties in both time of infection and time of clearance.

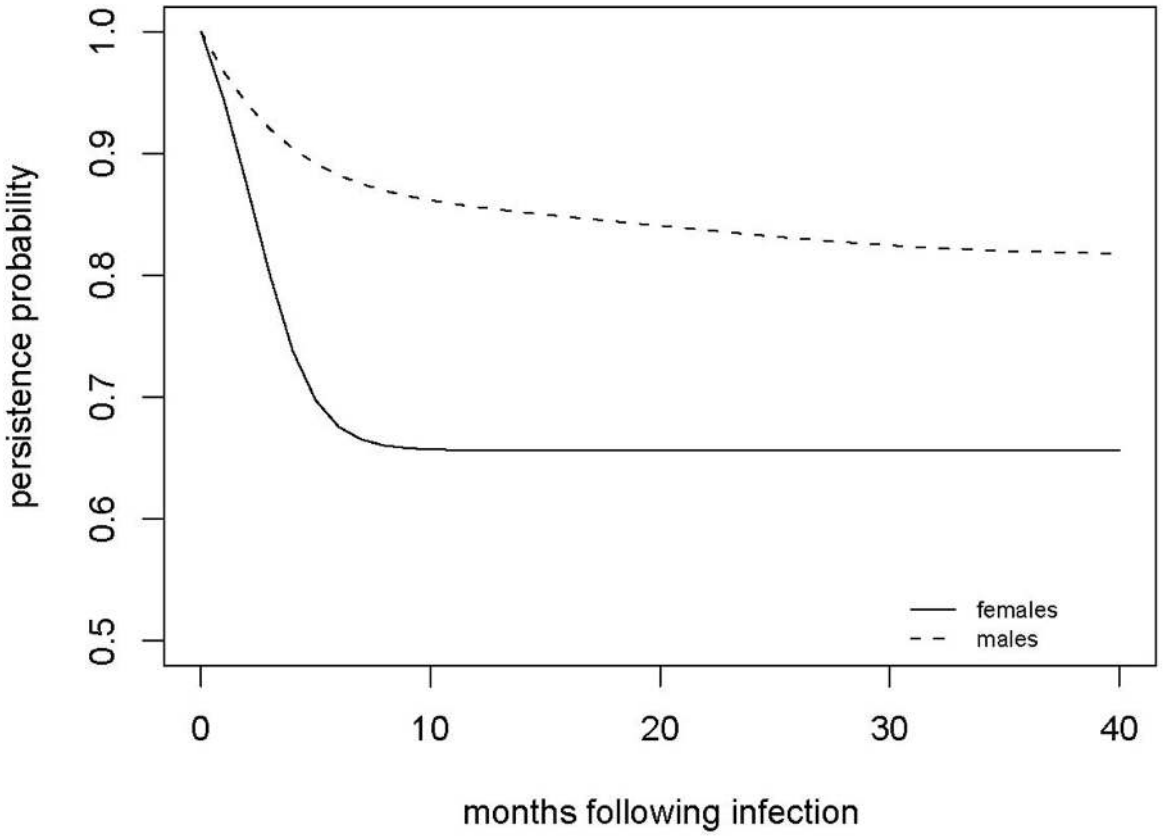


Figure 3.
Estimated HCV viral persistence probabilities (in months) among female and male young injection drug users with incident HCV infection.

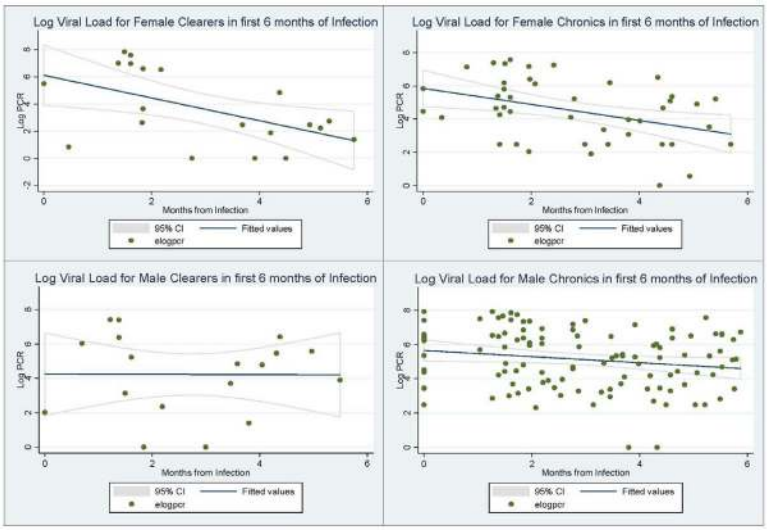
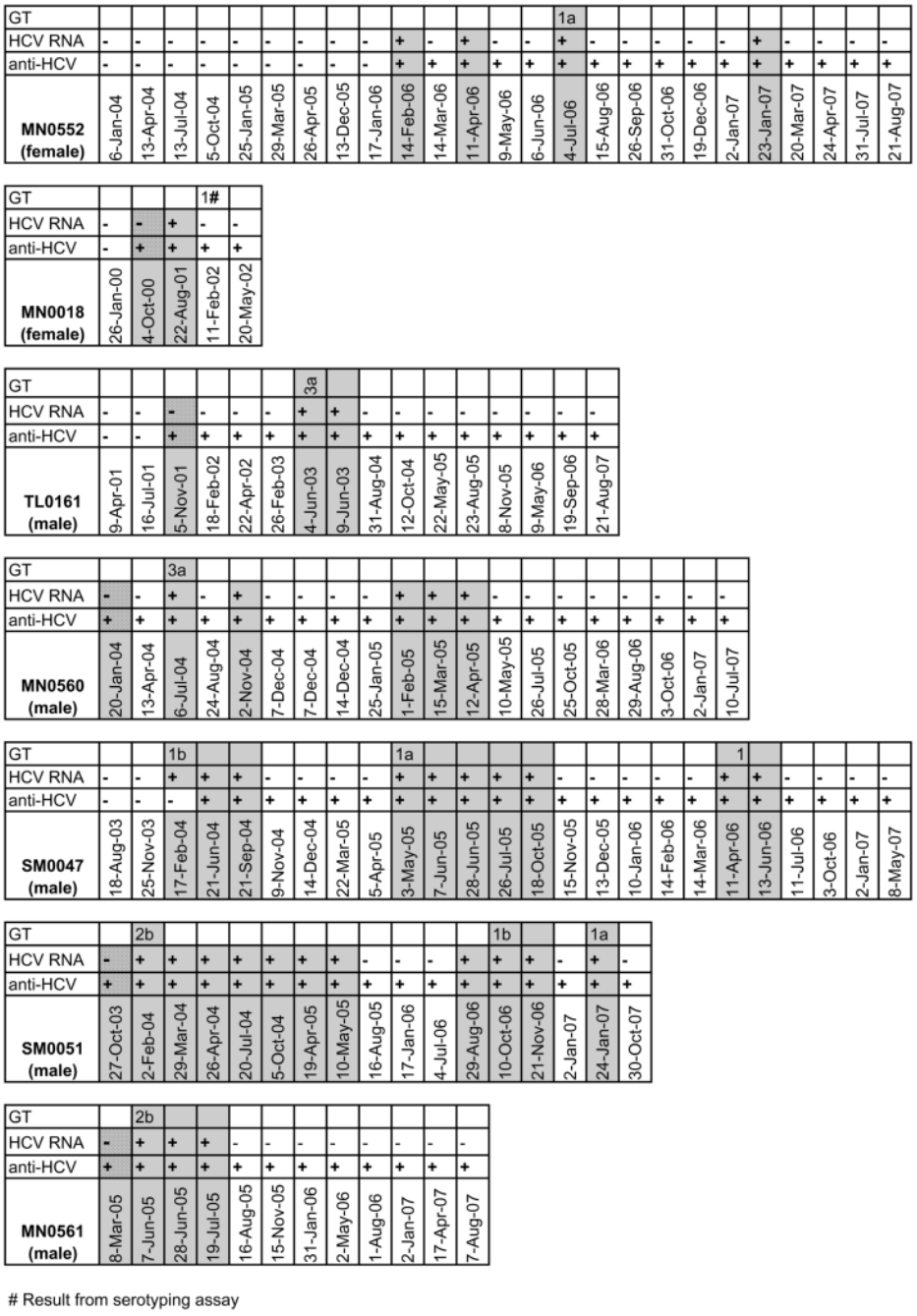


Figure 4.
HCV viral load declines (log iμ/ml/month) in the first 6 months after detection of incident HCV infection among female and male injection drug users by infection outcome (clearance or chronic infection).



GT																1a													
HCV RNA	-	-	-	-	-	-	-	-	-	-	+	-	+	-	-	+	-	-	+	+	+	+	+	-	-	-	-	-	-
anti-HCV	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MN0552 (female)	6-Jan-04	13-Apr-04	13-Jul-04	5-Oct-04	25-Jan-05	29-Mar-05	26-Apr-05	13-Dec-05	17-Jan-06	14-Feb-06	14-Mar-06	11-Apr-06	9-May-06	6-Jun-06	4-Jul-06	15-Aug-06	26-Sep-06	31-Oct-06	19-Dec-06	2-Jan-07	23-Jan-07	20-Mar-07	24-Apr-07	31-Jul-07	21-Aug-07					

GT				1#	
HCV RNA	-	-	+	-	-
anti-HCV	-	+	+	+	+
MN0018 (female)	26-Jan-00	4-Oct-00	22-Aug-01	11-Feb-02	20-May-02

GT							3a																						
HCV RNA	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
anti-HCV	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TL0161 (male)	9-Apr-01	16-Jul-01	5-Nov-01	18-Feb-02	22-Apr-02	26-Feb-03	4-Jun-03	9-Jun-03	31-Aug-04	12-Oct-04	22-May-05	23-Aug-05	8-Nov-05	9-May-06	19-Sep-06	21-Aug-07													

GT			3a																										
HCV RNA	-	-	+	-	+	-	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
anti-HCV	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MN0560 (male)	20-Jan-04	13-Apr-04	6-Jul-04	24-Aug-04	2-Nov-04	7-Dec-04	7-Dec-04	14-Dec-04	25-Jan-05	1-Feb-05	15-Mar-05	12-Apr-05	10-May-05	26-Jul-05	25-Oct-05	28-Mar-06	29-Aug-06	3-Oct-06	2-Jan-07	10-Jul-07										

GT			1b							1a											1								
HCV RNA	-	-	+	+	+	-	-	-	-	+	+	+	+	+	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-
anti-HCV	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SM0047 (male)	18-Aug-03	25-Nov-03	17-Feb-04	21-Jun-04	21-Sep-04	9-Nov-04	14-Dec-04	22-Mar-05	5-Apr-05	3-May-05	7-Jun-05	28-Jun-05	26-Jul-05	18-Oct-05	15-Nov-05	13-Dec-05	10-Jan-06	14-Feb-06	14-Mar-06	11-Apr-06	13-Jun-06	11-Jul-06	3-Oct-06	2-Jan-07	8-May-07					

GT		2b											1b			1a													
HCV RNA	-	+	+	+	+	+	+	+	-	-	-	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
anti-HCV	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SM0051 (male)	27-Oct-03	2-Feb-04	29-Mar-04	26-Apr-04	20-Jul-04	5-Oct-04	19-Apr-05	10-May-05	16-Aug-05	17-Jan-06	4-Jul-06	29-Aug-06	10-Oct-06	21-Nov-06	2-Jan-07	24-Jan-07	30-Oct-07													

GT		2b																											
HCV RNA	-	+	+	+	-	-	-	-	-	-	-	-																	
anti-HCV	+	+	+	+	+	+	+	+	+	+	+	+																	
MN0561 (male)	8-Mar-05	7-Jun-05	28-Jun-05	19-Jul-05	16-Aug-05	15-Nov-05	31-Jan-06	2-May-06	1-Aug-06	2-Jan-07	17-Apr-07	7-Aug-07																	

Result from serotyping assay

Figure 5.

Genotype (GT), HCV RNA and anti-HCV results showing acute HCV infection, reinfection and re-clearance among young injection drug users who have previously cleared HCV infection. Visit dates are shown in the lower boxes. Gray boxes (▩) show new acute HCV infections and reinfections. Participants whose first infection serology was consistent with previously resolved infection (anti-HCV positive and HCV RNA negative) are shown with gray stippled boxes (▨).

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Table 1

Characteristics, exposures and risk behaviors and association with clearance of HCV Infection in young IDU followed (N=95) in the UFO Cohort Study, San Francisco, CA, 2000–2007.

Baseline characteristic	Total N*	Proportion clearing infection N (%)	PYO	Incidence per person year (95% CI)	Rate Ratio (95% CI)	p- value
Overall	95	20 (21.1)	106.0	18.9 (12.2–29.3)		
Age						
<=22	33	8 (24.2)	35.7	22.4 (11.2–44.9)	1.00	
>22	62	12 (19.4)	70.3	17.1 (9.7–30.1)	0.76 (0.31–1.86)	0.55
Race/ethnicity						
White	70	13 (18.6)	81.4	16.0 (9.3–27.5)	1.00	
Non-white	24	7 (29.2)	23.5	29.8 (14.2–62.6)	1.87 (0.75–4.68)	0.18
Gender						
Male	61	9 (14.8)	74.2	12.1 (6.3–23.3)	**1.00**	
Female	34	11 (32.4)	31.8	34.6 (19.2–62.5)	**2.85 (1.18–6.88)**	**0.01**
HCV Genotype						
1	48	13 (27.1)	51.4	25.3 (14.7–43.6)	1.00	
2	11	3 (27.3)	14.5	14.5 (6.7–64.2)	0.83 (0.25–2.70)	0.75
3	33	3 (9.1)	37.1	8.1 (2.6–25.0)	0.62 (0.38–1.02)	0.06
4	1	0 (0)	1.0	0 (0)	--	
not available	2	1 (50.0)	1.9	52.4 (7.4–372.1)	--	
Years injecting						
<=3	41	8 (19.5)	43.3	18.5 (9.2–36.9)	1.00	
>3	54	12 (22.2)	62.6	19.2 (10.9–33.7)	1.04 (0.42–2.54)	0.94
History of drug treatment						
No	34	5 (14.7)	42.4	11.8 (4.9–28.3)	1.00	

Baseline characteristic	Total N*	Proportion clearing infection N (%)	PYO	Incidence per person year (95% CI)	Rate Ratio (95% CI)	p- value
Yes	60	15 (25.0)	61.5	24.4 (14.7–40.5)	2.07 (0.75–5.39)	0.15
Drug injected most days, last mo.						
Heroin/Heroin mixed	63	11 (17.5)	72.5	15.2 (8.4–27.4)	1.00	
Speed/Cocaine/Crack	30	8 (26.7)	31.7	25.3 (12.6–50.5)	1.66 (0.67–4.14)	0.27
Injection frequency, last mo.						
Less than daily	54	12 (22.2)	56.7	21.1 (12.0–37.2)	1.00	
Daily	39	7 (18.0)	47.4	14.8 (7.0–31.0)	1.43 (0.56–3.64)	0.45
Number of injection events, last mo.						
100+	26	4 (15.4)	29.3	13.7 (5.1–36.4)	1.00	
30–100	41	9 (22.0)	49.8	18.1 (9.4–34.8)	1.31 (0.42–4.03)	0.64
<30	26	6 (23.1)	25.1	23.9 (10.7–53.2)	1.32 (0.71–2.46)	0.38
Borrowed used needle, last 3 mo.						
No	52	10 (19.2)	55.6	18.0 (9.7–33.4)	1.00	
Yes	41	9 (22.0)	48.5	18.5 (9.7–35.6)	1.03 (0.42–2.54)	0.95
Used a shared cooker, last 3 mo.						
No	40	10 (25.0)	44.5	22.5 (12.1–41.8)	1.00	
Yes	53	9 (17.0)	59.6	15.1 (7.9–29.0)	0.67 (0.27–1.65)	0.38
Injected someone's rinse, last 3 mo.						
No	50	11 (22.0)	58.2	18.9 (10.5–34.1)	1.00	
Yes	43	8 (18.6)	45.9	17.4 (8.7–34.8)	0.92 (0.37–2.29)	0.86
Days drank alcohol, last mo.						
0	39	10 (25.6)	38.6	25.9 (14.0–48.2)	1.00	
1–14	32	4 (12.5)	38.7	10.3 (3.9–27.5)	0.42 (0.15–1.21)	0.11
>=15	21	6 (19.1)	26.3	15.2 (5.7–40.5)	0.78 (0.46–1.33)	0.36

Baseline characteristic	Total N*	Proportion clearing infection N (%)	PYO	Incidence per person year (95% CI)	Rate Ratio (95% CI)	p- value
Any sex partner, last 3 mo.						
No	19	2 (10.5)	23.8	8.4 (2.1–33.5)	1.00	
Yes	73	17 (23.3)	79.9	21.3 (13.2–34.2)	2.54 (0.59–10.98)	0.20
IDU sex partner, last 3 mo.						
No	43	6 (14.0)	52.5	11.4 (5.1–25.4)	1.00	
Yes	50	13 (26.0)	51.6	25.2 (14.6–43.4)	2.21 (0.84–5.80)	0.10
Incarceration, last 3 mo.						
No	56	9 (16.1)	62.2	14.4 (7.5–27.8)	1.00	
Yes	36	10 (27.8)	38.2	26.2 (14.1–48.6)	1.81 (0.74–4.45)	0.19

*N=95 with 2 or more visits after HCV infection

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Table 2

HCV Viremia during acute and early infection overall, by resolution, and between females and males

	N	First detected viremia (IU/ml)		Peak viremia (IU/ml)		Decline in first 6 months
						Beta coef. (95% CI) *
		Med	(IQR)	Med	(IQR)	
Overall	92	5.70	4.24; 6.52	6.31	5.32; 6.99	
Clearers	17	5.50	2.74; 7.01	6.38	3.86; 7.01	−0.49 (−1.00, 0.03)
Chronic	75	5.71	4.37; 6.49	6.27	5.33 6.93	−0.24 (−0.42, −0.06)
Female clearer	9	5.50	2.63; 7.01	6.54	3.34, 7.01	**−0.83 (−1.53, −0.14)** **
Female chronic	23	5.39	4.45; 6.17	5.83	5.09, 6.58	−0.48 (−0.80, −0.16)
Male clearer	8	5.62	3.99; 6.90	6.35	5.81, 6.92	**−0.01 (−0.67, 0.65)**
Male chronic	52	5.82	4.30; 6.51	6.35	5.65, 7.05	−0.17 (-0.37, 0.03)

* from linear regression of log-transformed viral load levels on time in months from infection

** Female clearers compared to male clearers have significant differences in slope of viral load decline; $p<0.01$