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Interferon lambda 3 genotype predicts hepatitis C virus RNA levels in early acute infection among people who inject drugs: The InC³ Study

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Abstract

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Background and Objectives—Hepatitis C virus (HCV) RNA level in acute HCV infection is predictive of spontaneous clearance. This study assessed factors associated with HCV RNA levels during early acute infection among people who inject drugs with well-defined acute HCV infection.

Study design—Data were from International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC³) Study, an international collaboration of nine prospective cohorts studying acute HCV infection. Individuals with available HCV RNA levels during early acute infection (first two months following infection) were included. The distribution of HCV RNA levels during early acute infection were compared by selected host and virological factors.

Results—A total of 195 individuals were included. Median HCV RNA levels were significantly higher among individuals with *interferon lambda 3* (*IFNL3*, formerly called *IL28B*) CC genotype compared to those with TT/CT genotype (6.28 vs. 5.39 log IU/mL, respectively; $P=0.01$). *IFNL3* CC genotype was also associated with top tertile HCV RNA levels (6.3 IU/mL; vs. TT/CT genotype; adjusted Odds Ratio: 4.28; 95%CI: 2.01, 9.10; $P<0.01$).

Conclusions—This study indicates that *IFNL3* CC genotype predicts higher HCV RNA levels in early acute HCV infection.

Keywords

Viral load; acute HCV; *IFNL3* genotype; *IL28B* genotype; Cohort study

Introduction

The dynamics of hepatitis C virus (HCV) RNA levels in acute HCV infection have been characterised as occurring in three phases: a pre-ramp-up phase with intermittent low-level HCV RNA (from exposure to initial quantifiable HCV RNA); a ramp-up phase with exponential increase in HCV RNA levels; and a high-titre viremic plateau phase¹. Then, acute HCV infection is followed by spontaneous clearance in around 25% of individuals^{2, 3} while the remaining 75% progress to chronic HCV infection.

Higher HCV RNA levels during the first month of acute infection have been shown to be associated with spontaneous clearance⁴. However, there are limited studies investigating factors associated with HCV RNA levels during acute infection^{4, 5}, and none evaluating multiple relevant factors simultaneously. A better understanding of factors associated with HCV RNA levels in early acute infection has the potential to assist in therapeutic decision making during acute HCV and also enhance our understanding of HCV immunopathogenesis and biological mechanisms for defining protective immunity, which is important for vaccine design.

This current study assessed factors associated with HCV RNA levels in early acute infection (first two months following infection) among people who inject drugs (PWID) in a large population with well-defined acute HCV infection.

Study Design

Study population

The International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC³) Study, is a collaboration of pooled data from nine prospective international cohorts prominently following PWID, consisting of a large number of well characterized participants with acute HCV infection and longitudinal follow-up⁶. All cohorts follow participants at regular intervals using standardized methods.

Documented acute HCV is defined as either: 1) HCV seroconversion with an HCV antibody (anti-HCV) or HCV RNA positive test within two years of the anti-HCV negative test; or 2) evidence of symptomatic HCV infection (defined by a positive anti-HCV/HCV RNA test, jaundice or alanine transaminase (ALT) elevation >400 IU/L, and detection of HCV RNA or history of high-risk exposure within three months of clinical manifestation of acute HCV).

HCV RNA levels in early acute infection were assessed among InC³ participants with available HCV RNA tests during the first two months following infection. This period was chosen on the basis of our initial analysis^{7, 8} and also the other data⁴ demonstrating that this is the period where peak HCV RNA levels are observed during acute infection. From the total InC³ participants with acute HCV infection (n=812), individuals with unavailable HCV RNA tests during the first two months following infection were excluded (n=603). Individuals with undetectable HCV RNA during the first two months with repeated undetectable tests during follow-up were defined as having early spontaneous clearance and also excluded (n=14). As such, 195 individuals with available HCV RNA during the first two months following infection were included in this analysis.

The estimated date of HCV infection was calculated based on a hierarchy using all serological (anti-HCV), virological (HCV RNA) and clinical (symptoms and liver function tests) data to arrive at the most precise estimate of infection date:

- a. Among individuals with HCV RNA positive and anti-HCV negative at acute HCV detection, date of infection was four weeks prior to HCV RNA detection^{9, 10}.
- b. Among individuals with symptomatic acute HCV, date of infection was six weeks prior to its onset (jaundice or ALT >400 IU/L)¹¹.
- c. Among individuals with a negative anti-HCV test followed by either a positive anti- HCV or HCV RNA test, seroconversion was assumed to occur at the mid-point between the last negative and the first positive test. HCV seroconversion generally occurs about 30-60 days following infection^{9, 10, 12}. Date of infection in this group was six weeks prior to estimated seroconversion date if the first positive test was anti- HCV test and four weeks prior to estimated seroconversion date if the first positive test was only HCV RNA test.

Laboratory testing

Choice of qualitative and quantitative HCV RNA testing varied by cohort but was consistent at each site. Qualitative HCV RNA testing was performed using the following assays:

Versant TMA [Bayer, Australia; <10 IU/ml], COBAS AmpliPrep/COBAS TaqMan (Roche, Branchburg, NJ, USA; <15 IU/ml), COBAS AMPLICOR HCV Test v2.0 (Roche Diagnostics, Mannheim, Germany; <50 IU/ml) or discriminatory HCV transcription-mediated amplification component of the Procleix HIV-1/HCV (Gen-Probe, San Diego, CA, USA; <12 copies/mL). Quantitative HCV RNA testing was performed using the Versant HCV RNA 3.0 (Bayer, Australia; <615 IU/ml), COBAS AMPLICOR HCV MONITOR 2.0 (Roche Diagnostics, Mannheim, Germany; <600 IU/ml), COBAS AmpliPrep/COBAS TaqMan (Roche, Branchburg, NJ, USA; <15 IU/ml) or an in-house PCR (<1000 IU/ml)^{13, 14}. HCV genotype was determined by line-probe assay (Versant LiPa1/LiPa2, Bayer, Australia) or HCV sequencing at acute HCV detection. Among those with undetectable HCV RNA (no genotype) and available samples, Murex HCV serotyping was performed to determine HCV genotype (Murex Biotech Limited, Dartford, UK). *Interferon lambda 3* (*IFNL3*) genotyping (formerly called *interleukin 28 B* [*IL-28B*]) was determined by sequencing of the rs12979860 single nucleotide polymorphism, as previously described in^{2, 15-17}.

Study outcomes and statistical analyses

The study outcome was HCV RNA levels during the first two months following infection (early acute infection). Nonparametric statistical tests were used for analyses, given that HCV RNA levels (IU/mL) and log₁₀ transformation of HCV RNA levels (log IU/mL) were not normally distributed. The top tertile HCV RNA levels (≥ 6.3 log IU/mL) was defined as a high HCV RNA level.

Previous data indicated that spontaneous clearance is associated with higher HCV RNA levels in early acute infection⁴. Therefore, factors hypothesized to be associated with HCV RNA levels were determined *a priori* based on the factors shown to be associated with spontaneous clearance, including age¹⁸, sex^{2, 3, 17, 19}, ethnicity²⁰, *IFNL3* genotype (SNP rs12979860; CC vs. CT/TT)^{2, 15, 16, 21}, HIV co-infection²⁰, and HCV genotype^{2, 22}.

Median HCV RNA levels were compared between groups using the Wilcoxon-Mann-Whitney (or Kruskal Wallis) test. Logistic regression models were also used to assess factors associated with high HCV RNA levels (≥ 6.3 log IU/mL). In multivariate regression analysis, initial models were adjusted for sex, *IFNL3* genotype, and HCV genotype *a priori* given our data showed independent association between these variables and spontaneous clearance². To account for potential unmeasured confounders introduced by cohort sites, multivariate regression analysis was performed using mixed modelling, with a random intercept for cohort site. Statistically significant differences were assessed at $P < 0.05$ (P -values are two-sided). All analyses were performed using Stata v12.0 (College Station, TX, United States).

Results

One hundred and ninety-five individuals were included in the analysis. The median age was 24 years, 36% were female, 79% were Caucasian, and 3% were HIV co-infected (Table 1). Among those with data on infecting HCV genotype (n=172; 88%), 59% had genotype 1. Among those with data on *IFNL3* genotype (n=161; 83%), 48% were *IFNL3* CC genotype.

One hundred and fifty individuals (77%) were anti-HCV negative/HCV RNA positive at acute HCV detection.

Median HCV RNA levels during early acute infection was 5.64 log IU/mL (Inter-quartile range [IQR]: 3.97, 6.70). Significantly higher median HCV RNA levels were observed among individuals with *IFNL3* CC genotype compared to those with TT/CT genotype (6.28 vs. 5.39 log IU/mL, respectively; $P=0.01$). There was no significant difference in median HCV RNA levels by age, sex, ethnicity, HIV co-infection and HCV genotype (Table 2 and Figure 1).

In unadjusted logistic regression analysis (Table 3), *IFNL3* CC genotype was the only factor significantly associated with high HCV RNA levels (6.3 log IU/mL). In a logistic regression model adjusting for sex, *IFNL3* genotype, HCV genotype, and the cohort sites (Table 3), *IFNL3* CC genotype remained independently associated with high HCV RNA levels (adjusted odds ratio: 4.28; 95%CI: 2.01, 9.10). Interactions between covariates were not statistically significant on the multiplicative scale.

Discussion

In this current study, *IFNL3* CC genotype was associated with higher HCV RNA levels in early acute infection, which is consistent with previous data^{4,5}. The strength of the current study was that we controlled for a range of factors potentially associated with spontaneous clearance, and the association between *IFNL3* CC genotype and high HCV RNA levels (6.3 log IU/mL) remained strong even after adjustment. Previous studies have also demonstrated that *IFNL3* CC genotype is associated with higher HCV RNA levels in chronic HCV infection²³⁻²⁵. Genetic variation in the *IFNL3* gene region is a major host factor associated with both spontaneous and treatment-induced HCV clearance (reviewed in²⁶). The exact mechanism underlying this genetic association remains to be determined. In one study of acute HCV infection, *IFNL3* CC genotype was associated with higher initial HCV RNA levels, which was correspondingly associated with a greater likelihood of spontaneous clearance⁴. The authors suggested that high-level HCV replication could trigger stronger innate immune responses, thereby activating a stronger adaptive immune response that enhanced eradication of the virus⁴. Further research is needed to better elucidate the mechanisms behind the relationship between *IFNL3* genotype, early HCV RNA levels and spontaneous clearance.

While the current study is unique given the large sample size and well-defined nature of early acute HCV infection, there are some limitations. Nine cohorts of individuals with acute HCV were combined. Participating cohorts bring a range of data types and structures presenting issues surrounding both inconsistent measurement and biological data testing protocols (e.g. HCV RNA assays differed across cohorts with different sensitivity, specificity and lower limit of detection). There were also small numbers for some categorized variables in this study (ethnicity and HIV status), limiting the statistical power of detecting associations between these variables and HCV RNA levels.

In conclusion, the current study identified that *IFNL3* genotype predicts higher HCV RNA levels during the first two months following infection. These data provide better understanding of HCV immunopathogenesis during early acute infection. Further research is needed to understand the mechanism of *IFNL3* genotype on HCV replication.

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Highlights

- Factors associated with HCV RNA levels in early acute infection were evaluated.
- *Interferon lambda 3 (IFNL3)* genotype was associated with HCV RNA levels.
- Median HCV RNA levels were higher among those with *IFNL3* CC genotype (vs. TT/CT).
- *IFNL3* CC genotype was associated with HCV RNA levels 6.3 IU/mL.
- *IFNL3* CC genotype predicts higher HCV RNA levels in early acute HCV infection.

Fig. 1.

Distribution of HCV RNA levels during the first two months following infection in participants with acute HCV infection in the InC³ study, stratified by (A) *IFNL3* genotype, (B) sex, and (C) HCV genotype. Horizontal lines represent the medians HCV RNA levels in each subgroup.

Table 1
Characteristics of participants with available HCV RNA levels during during the first two months following infection in the InC³ Study

	Number (%) <i>Total n=195</i>
Site	
ACS (the Netherlands)	21 (11)
ATAHC (Australia)	5 (3)
BAHSTION (United States)	9 (5)
BBAASH (United States)	72 (37)
HEPCO (Canada)	4 (2)
HITS-c (Australia)	2 (1)
HITS-p (Australia)	23 (12)
N2 (Australia)	0 (0)
UFO (United States)	59 (30)
Median age at the time of HCV infection, years (IQR)	24 (21, 28)
Sex	
Female	64 (36)
Male	122 (63)
Unknown	1 (1)
Ethnicity	
Caucasian	155 (79)
Black	12 (6)
Indigenous	7 (4)
Other	17 (9)
Unknown	4 (2)
History of injecting drug use	195 (100)
Symptomatic HCV infection	
No	9 (5)
Yes	15 (8)
Unknown	171 (88)
<i>IFNL3</i> genotype (rs12979860)	
TT	16 (8)
CT	67 (34)
CC	78 (40)
Unknown	34 (17)
HIV infection at the time of HCV infection	
No	182 (93)
Yes	6 (3)

	Number (%) Total n=195
Unknown	7 (4)
HCV genotype	
Genotype 1	102 (52)
Genotype 2	15 (8)
Genotype 3	49 (25)
Genotype 4	2 (1)
Mixed genotype	4 (2)
Unknown	23 (12)

ACS: Amsterdam Cohort Studies; ATAHc: Australian Trial in Acute Hepatitis C; BAHSTION: Boston Acute HCV Study: Transmission, Immunity and Outcomes Network; BBAASH: Baltimore Before and After Acute Study of Hepatitis; HEPcO: St. Luc Cohort, HEPcO; HITS-c: Hepatitis C Incidence and Transmission Study-Community; HITS-p: Hepatitis C Incidence and Transmission Study-Prison; N2: Networks 2; UFO: UFO STUDY; IQR: Inter-quartile range

Table 2
Median HCV RNA levels during the first two months following infection by selected demographic and virologic variables in participants with acute HCV infection in the InC³ study

	Number Total n=195	Median HCV RNA levels* (IQR)	P
Age			0.31
<30 years	135	5.65 (4.32, 6.76)	
30-39 years	23	4.55 (1.70, 6.75)	
40 years	8	5.68 (5.07, 6.20)	
Sex			0.69
Female	72	5.52 (3.93, 6.70)	
Male	122	5.67 (4.07, 6.66)	
Ethnicity			0.38
Caucasian	155	5.72 (3.97, 6.75)	
Black	12	5.54 (5.10, 6.17)	
Indigenous	7	5.74 (4.43, 5.83)	
Other	17	4.81 (2.69, 6.04)	
IFNL3 genotype			0.01
TT/CT	83	5.39 (4.46, 6.02)	
CC	78	6.28 (3.45, 7.28)	
HIV status			0.85
Negative	182	5.59 (3.97, 6.65)	
Positive	6	5.14 (3.17, 6.75)	
HCV genotype			0.50
Genotype 1	102	5.67 (4.74, 6.70)	
Genotype 2	15	6.46 (3.82, 7.33)	
Genotype 3	49	5.36 (4.45, 6.39)	
Other [†]	6	5.68 (1.70, 5.93)	

IQR: Inter-quartile range

* log IU/mL

[†] Included genotype 4 (n=2), and mixed genotype (n=4).

Table 3
Logistic regression models assessing factors associated with HCV RNA levels 6.3 IU/mL (top tertile) during the first two months following infection in participants with acute HCV infection in the InC3 study

HCV RNA levels		6.3 IU/mL n (%)	Unadjusted model			Adjusted model*		
			OR (95% CI)	P	P overall	AOR (95% CI)	P	
Age								
<30 years	48 (36)		1.00		0.75			
30-39 years	7 (30)		0.79 (0.30, 2.06)	0.63				
40 years	2 (25)		0.60 (0.12, 3.11)	0.55				
Sex								
Female	23 (32)		1.00			1.00		
Male	42 (34)		1.12 (0.60, 2.08)	0.72		1.15 (0.53, 2.47)	0.72	
Ethnicity								
Indigenous	1 (14)		1.00		0.58			
Caucasian	59 (38)		3.69 (0.43, 31.39)	0.23				
Black	2 (17)		1.20 (0.09, 16.23)	0.89				
Other	3 (18)		1.28 (0.11, 15.00)	0.84				
IFNL3 genotype								
TT/CT	17 (20)		1.00			1.00		
CC	39 (50)		3.88 (1.94, 7.77)	<0.01		4.28 (2.01, 9.10)	<0.01	
HIV status								
Negative	58 (32)		1.00					
Positive	3 (50)		2.14 (0.42, 10.92)	0.36				
HCV genotype								
Genotype 3	14 (29)		1.00		0.26	1.00		
Genotype 1	35 (34)		1.30 (0.62, 2.74)	0.48		1.20 (0.51, 2.81)	0.69	
Genotype 2	8 (53)		2.86 (0.87, 9.38)	0.08		2.15 (0.49, 9.36)	0.31	
Other	1 (17)		0.50 (0.05, 4.67)	0.54		0.46 (0.04, 5.05)	0.52	

OR: Odds Ratio; CI: Confidence Interval; AOR: Adjusted Odds Ratio

* Includes 149 participants in the model. The model was adjusted for site using a random intercept model