



Factors associated with HCV RNA levels in early acute and early chronic infection: the InC3 study

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Background

► In ~25% of individuals, acute HCV infection is followed by spontaneous viral clearance, with the remaining 75% progressing to chronic infection. *Micallef, et al. J Viral Hepatitis 2006*

► Higher HCV RNA levels during the first month of acute infection have been associated with spontaneous clearance. *Liu, et al. Hepatology 2012*

► Among individuals with chronic HCV infection, pre-treatment high HCV RNA levels have been associated with lower SVR following interferon-based therapy including direct acting antiviral agents. *Zeuzem, et al. J Viral Hepatitis 2012; Poordad, et al. NEJM 2011; McHutchison, et al. NEJM 2002*

► A better understanding of the factors associated with HCV RNA levels during early acute and chronic infection provides insights into HCV immunopathogenesis and has implications for the clinical management of chronic HCV infection with interferon-based regimens



Objectives

- To assess the factors associated with HCV RNA levels during early acute infection (the first two months following infection)
- To assess the factors associated with HCV RNA levels during early chronic infection (one year following infection)



InC3 study

The International Collaboration of Incident HIV and HCV in Injecting Cohorts
InC3 Study



<https://inc3.epi-ucsf.org>

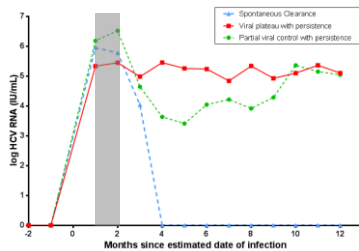
Grebely J International Journal of Epidemiology 2013



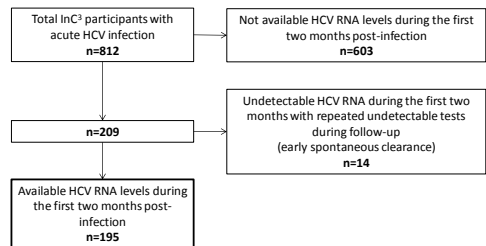
HCV RNA levels in early acute HCV

Objective 1

To assess the factors associated with HCV RNA levels during early acute infection (two months following infection)



HCV RNA levels in early acute HCV



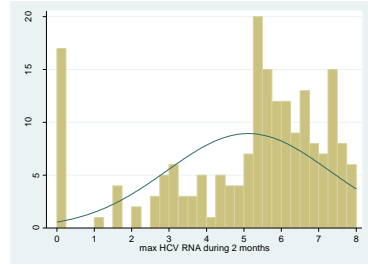


HCV RNA levels in early acute HCV

Overall (n=195)	
Median age, yrs (IQR)	24 (21-28)
Female Sex	64 (36%)
Caucasian ethnicity	155 (79%)
History of injecting drug use	195 (100%)
IFNL3 genotype (rs12979860)	
TT/CT	83 (42%)
CC	78 (40%)
Unknown	34 (17%)
HIV infection	
No	182 (93%)
Yes	6 (3%)
Unknown	7 (4%)
HCV genotype	
Genotype 1	102 (52%)
Genotype 2	15 (8%)
Genotype 3	49 (25%)
Other Genotypes	6 (3%)
Unknown genotype	23 (12%)



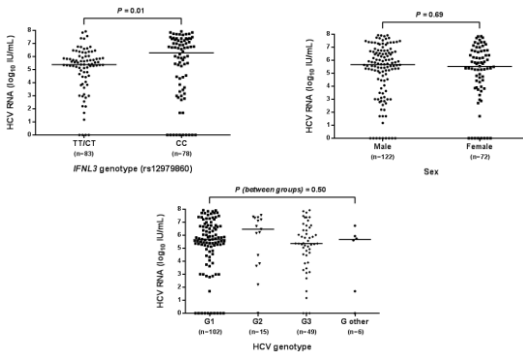
HCV RNA levels in early acute HCV



Distribution of HCV RNA in the first two months following infection (n=195)



HCV RNA levels in early acute HCV



HCV RNA levels in early acute HCV

Median HCV RNA levels in month two following infection by selected demographic and virologic variables (n=195)

	Number	Median HCV RNA levels	P
Age at the time of HCV infection			0.31
<30 years	135	5.65	
30-39 years	23	4.55	
≥40 years	8	5.68	
Gender			0.69
Female	72	5.52	
Male	122	5.67	
Ethnicity			0.38
Caucasian	155	5.72	
Black	12	5.54	
Indigenous	7	5.74	
Other	17	4.81	
IFNL3 genotype			0.01
TT/CT	83	5.39	
CC	78	6.28	
HIV status at the time of HCV infection			0.85
Negative	182	5.59	
Positive	6	5.14	
HCV genotype			0.50
Genotype 1	102	5.67	
Genotype 2	15	6.46	
Genotype 3	49	5.36	
Other	5	5.68	



HCV RNA levels in early acute HCV

Factors associated with HCV RNA levels ≥6.3 log IU/mL (top tertile) in early acute infection

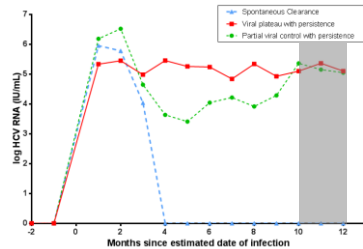
	Logistic regression model		
	OR (95% CI)	P	P overall
Age			0.75
<30years	1.00		
30-39 years	0.79 (0.30, 2.06)	0.63	
≥40 years	1.60 (0.12, 3.11)	0.55	
Sex			
Female	1.00		
Male	1.12 (1.60, 2.08)	0.72	
Ethnicity			0.58
Indigenous	1.00		
Caucasian	3.69 (0.43, 31.39)	0.23	
Black	1.20 (0.09, 16.23)	0.89	
Other	1.28 (0.11, 15.00)	0.84	
IFNL3 genotype			<0.01
TT/CT	1.00		
CC	3.88 (1.94, 7.77)		
HIV status			0.36
Negative	1.00		
Positive	2.14 (0.42, 10.92)		
HCV genotype			0.26
Genotype 3	1.00		
Genotype 1	1.30 (0.62, 2.74)	0.48	
Genotype 2	2.86 (0.87, 9.38)	0.08	
Other	0.50 (0.05, 4.67)	0.54	



HCV RNA levels in early chronic HCV

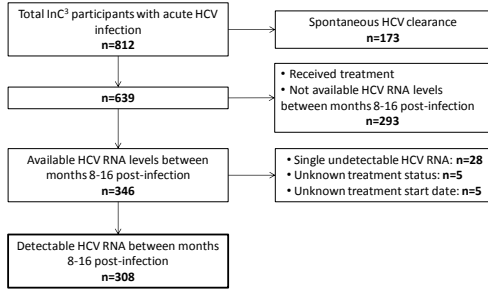
Objective 2

To assess the factors associated with HCV RNA levels during early chronic infection (12 ± 4 months following infection)





HCV RNA levels in early chronic HCV

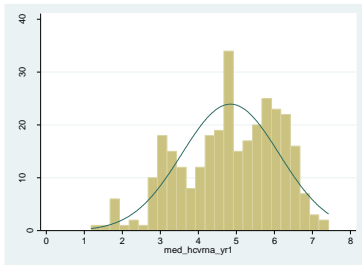


HCV RNA levels in early chronic HCV

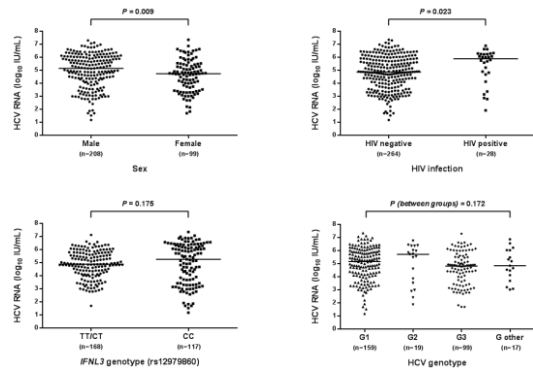
Overall (n=308)	
Median age, yrs (IQR)	26 (23-33)
Female Sex	99 (32%)
Caucasian ethnicity	243 (79%)
History of injecting drug use	292 (95%)
IFNL3 genotype (rs12979860)	
TT/CT	168 (55%)
CC	117 (38%)
Unknown	23 (7%)
HIV infection	
No	264 (86%)
Yes	28 (9%)
Unknown	16 (5%)
HCV genotype	
Genotype 1	159 (52%)
Genotype 2	19 (6%)
Genotype 3	99 (32%)
Other Genotypes	19 (6%)
Unknown genotype	14 (4%)



HCV RNA levels in early chronic HCV



HCV RNA levels in early chronic HCV



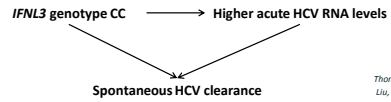
HCV RNA levels in early chronic HCV

Factors associated with high HCV RNA levels [≥5.6 log IU/mL [400,000 IU/mL]] in early chronic infection

		Unadjusted model		P overall
		OR (95% CI)	P	
Age	<30years	1.00		0.33
	30-39 years	0.87 (0.45, 1.68)	0.67	
	≥40 years	1.70 (0.79, 3.66)	0.18	
Sex	Female	1.00		
	Male	2.47 (1.40, 4.34)	<0.01	
Ethnicity	Caucasian	1.00		0.60
	Black	0.50 (0.14, 1.82)	0.29	
	Indigenous	0.77 (0.26, 2.23)	0.63	
	Other	1.28 (0.53, 3.10)	0.57	
IFNL3 genotype	TT/CT	1.00		<0.01
	CC	2.19 (1.33, 3.60)		
HIV status	Negative	1.00		<0.01
	Positive	3.55 (1.59, 7.93)		
HCV genotype	Genotype 3	1.00		0.07
	Genotype 1	1.70 (0.98, 2.98)	0.06	
	Genotype 2	3.47 (1.26, 9.54)	0.02	
	Other	1.30 (0.42, 4.07)	0.65	



Discussion: IFNL3 genotype in acute HCV

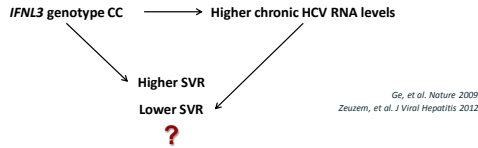


Thomas, et al. Nature 2009
Liu, et al. Hepatology 2012

- ▶ The mechanisms behind this triangular link remain to be elucidated.
- ▶ IFNL3 CC genotype is associated with innate immune function of natural killer cells to interfere with interferon-based therapy in chronic infection. Naggie, et al. Hepatology 2012
- ▶ IFNL3 regulates the interferon stimulated genes (ISGs) in chronic HCV infection. Honda, et al. Gastroenterology 2010
Urban, et al. Hepatology 2010



Discussion: *IFNL3* genotype in chronic HCV



Ge, et al. *Nature* 2009
Zeuzem, et al. *J Viral Hepatitis* 2012

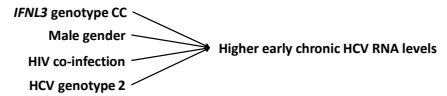
► *IFNL3* CC genotype was associated with high HCV RNA levels during both acute and chronic infection. One hypothesis is that individuals with *IFNL3* CC genotype who fail to clear virus during acute infection carry higher viraemia into chronic infection.

► *IFNL3* regulates the interferon stimulated genes (ISGs) in chronic HCV infection which is crucial to response to treatment.

Honda, et al. *Gastroenterology* 2010
Urban, et al. *Hepatology* 2010



Discussion: HCV RNA levels in chronic HCV



► Several other studies investigated the factors associated with HCV RNA levels in chronic infection.

Uccellini, et al. *Hepatology* 2012; Labarga, et al. *AIDS* 2011; Fishbein, et al. *JAIDS* 2006; Thomas, et al. *JID* 2000; Rauch, et al. *Antiviral Therapy* 2008; Yoo, *JID* 2005; Grady, et al. *J Viral Hepatitis* 2014

► There is uncertainty and heterogeneity with the timing of HCV RNA levels post-infection, given the cross-sectional nature of studies, making it difficult to measure the longitudinal effect of various factors on HCV RNA levels in chronic infection.

► Our data suggest that during chronic infection, factors associated with HCV RNA levels exert their roles as early as one year following infection.



Conclusion

► *IFNL3* CC genotype was associated with higher HCV RNA levels during the first two months following infection.

► Among participants with persistence, male sex, *IFNL3* CC genotype, HIV co-infection, and HCV genotype 2 were associated with higher HCV RNA levels at one year post-infection.

► These data suggest that during chronic infection, factors influencing HCV RNA levels exert their effects as early as one year following infection.



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