



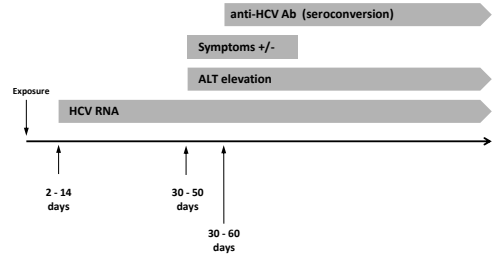
Patterns of hepatitis C virus RNA levels during acute infection: the InC³ study

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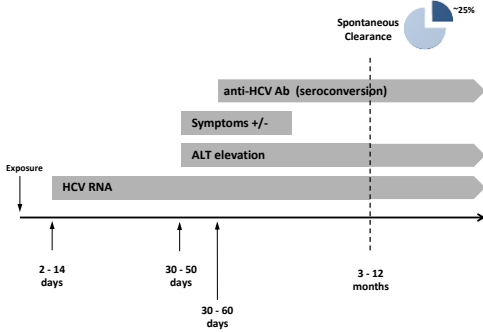
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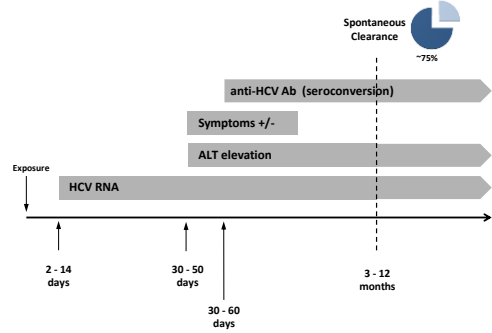
Background



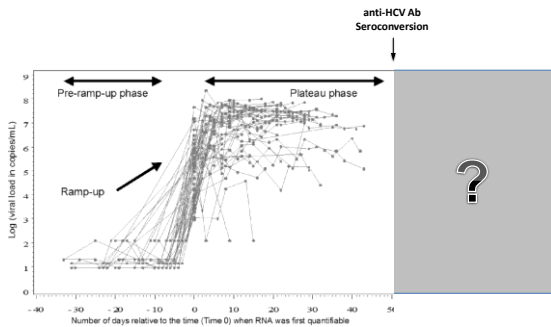
Background



Background



Background

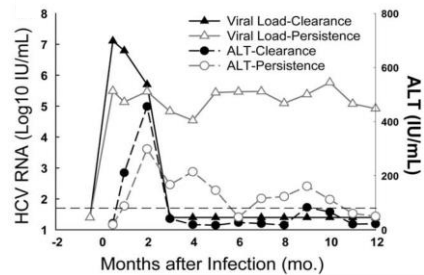


Glynn, et al. Transfusion 2005.



Limitations of studies to date

BBAASH, Baltimore, 1997-2009, n=29



Liu, et al. Hepatology 2012



Limitations of studies to date

- ▶ Few studies have regular HCV virological monitoring in acute infection
- ▶ Often small samples sizes, resulting in limited power
- ▶ No study assessed the factors associated with early HCV RNA dynamics



Objectives

- ▶ To assess the pattern of HCV RNA levels during acute HCV infection
- ▶ To define the factors associated with early HCV RNA dynamics



Nine cohorts in 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



InC3 study: Methods

Definition of acute HCV infection

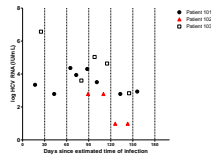
- ▶ HCV seroconversion within two years (an anti-HCV Ab negative test followed by either an anti-HCV/HCV RNA positive test within two years of the anti-HCV negative test)
- OR
- ▶ Evidence of symptomatic HCV infection (defined by a positive anti-HCV/HCV RNA test plus jaundice or ALT elevation >400 U/L).



InC3 study: Methods

- ▶ The median HCV RNA levels (log IU/mL) among all individuals were calculated in monthly intervals since the estimated date of infection and were plotted disaggregated by participant outcome.

- ▶ To calculate monthly median of HCV RNA levels, all individual measurements recorded during one month were included



- ▶ To account for within-individual clustering of data points (repeated measurements) and the natural heterogeneity of the population a random effects linear regression model was also fitted for the different patterns of HCV RNA levels.

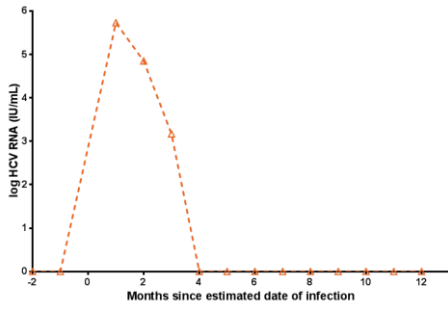


Background characteristics

	Overall (n=643)
Median age, yrs (IQR)	26 (23-33)
Female Sex	230 (36%)
Caucasian ethnicity	525 (82%)
History of injecting drug use	616 (96%)
IFNL3 genotype (rs12979860)	
TT/CT	279 (43%)
CC	272 (42%)
Unknown	92 (14%)
HIV infection	
No	574 (89%)
Yes	44 (7%)
Unknown	25 (4%)
HCV genotype	
Genotype 1	302 (47%)
Genotype 2	33 (5%)
Genotype 3	187 (29%)
Other Genotypes	25 (4%)
Unknown genotype	96 (15%)



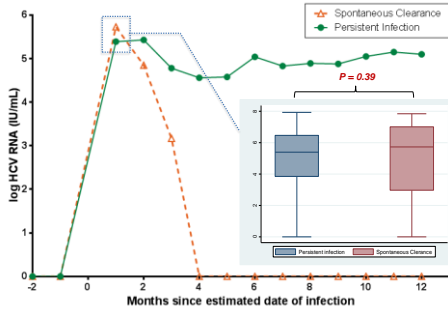
Patterns of HCV RNA levels



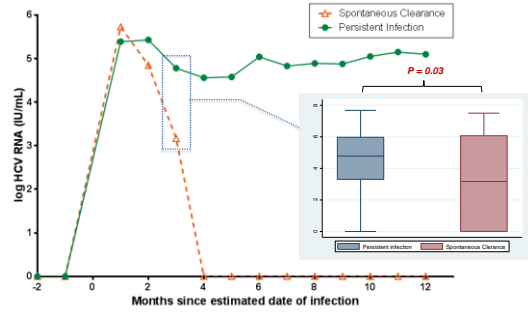
Patterns of HCV RNA levels



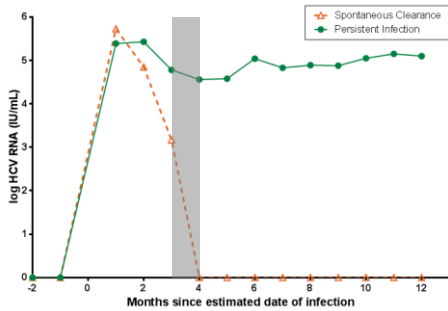
Patterns of HCV RNA levels



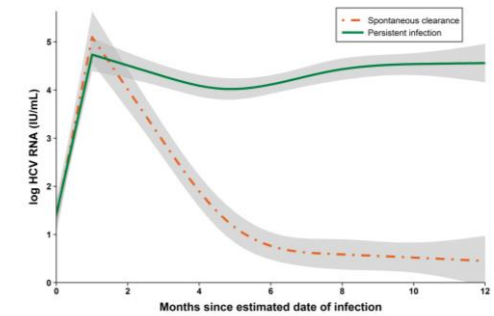
Patterns of HCV RNA levels



Patterns of HCV RNA levels

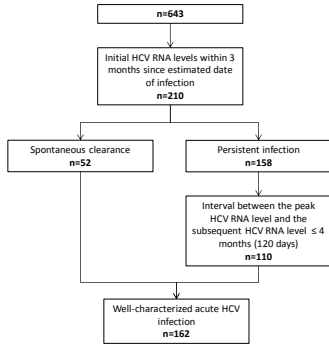


Patterns of HCV RNA levels

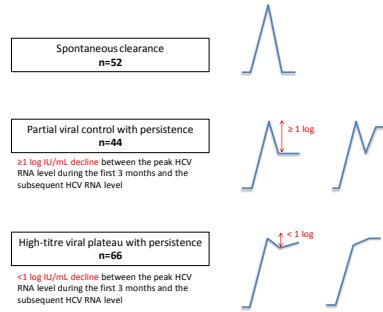




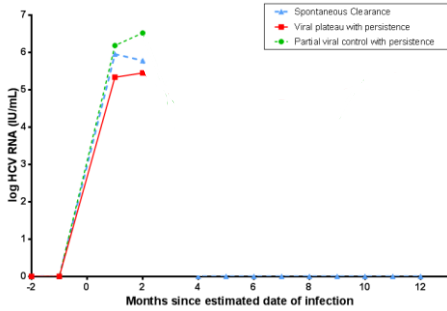
Patterns of HCV RNA levels



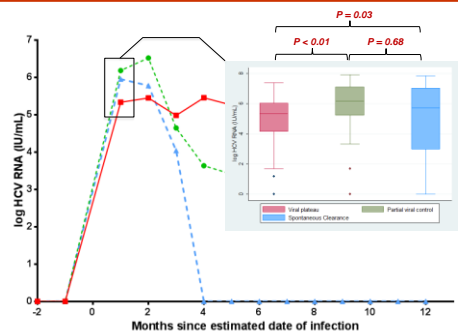
Patterns of HCV RNA levels



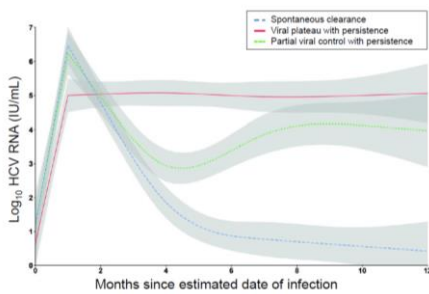
Patterns of HCV RNA levels



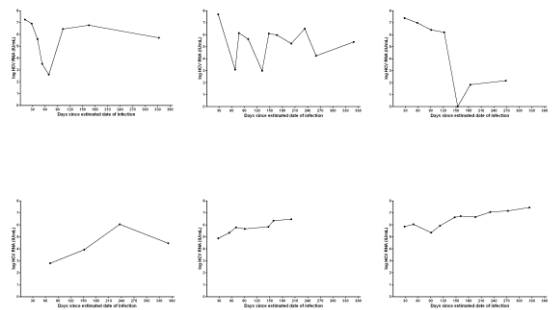
Patterns of HCV RNA levels



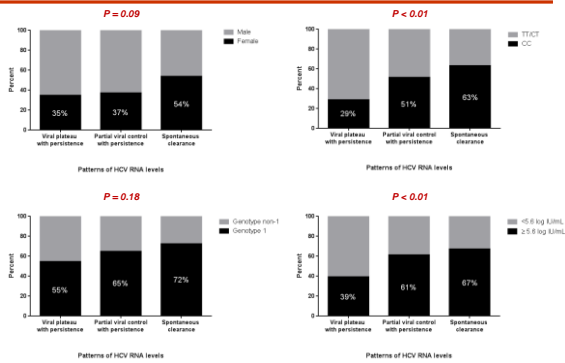
Patterns of HCV RNA levels



Patterns of HCV RNA levels



Factors associated with HCV RNA patterns



Factors associated with HCV RNA patterns

Adjusted multinomial logistic regression model (n=128)

Partial viral control vs. Viral plateau

Adjusted OR (95% CI)

Sex	Adjusted OR (95% CI)	p
Male	1.00	
Female	1.08 (0.42, 2.82)	0.87

IFNL3 genotype

IFNL3 genotype	Adjusted OR (95% CI)	p
TT/CT	1.00	
CC	2.75 (1.08, 7.02)	0.03

HCV genotype

HCV genotype	Adjusted OR (95% CI)	p
Genotype non-1	1.00	
Genotype 1	1.65 (0.65, 4.20)	0.29

Peak HCV RNA levels

Peak HCV RNA levels	Adjusted OR (95% CI)	p
<5.6 log IU/mL	1.00	
≥5.6 log IU/mL	2.15 (0.85, 5.41)	0.10

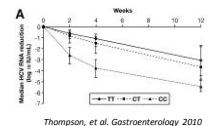
Conclusion

- ▶ This is the first large study describing HCV RNA profiles from acute through to early chronic infection.
- ▶ Initial enhanced HCV virological control was seen in both individuals with clearance and persistence, with divergence of HCV RNA levels between two groups occurring at approximately three months following infection.
- ▶ *IFNL3* CC genotype appears to be the most predictive factor of initial viral control.
- ▶ Female sex is particularly important for determining whether someone will ultimately spontaneously clear the infection.

Discussion

The mechanisms and role of *IFNL3* genotype in viral control in acute HCV infection

- ▶ *IFNL3* CC genotype mainly influence early viral decline in treatment-induced HCV clearance in chronic infection.
- ▶ *IFNL3* CC genotype is associated with innate immune function of natural killer cells to interferon-based therapy in chronic infection.
- ▶ *IFNL3* regulates the interferon stimulated genes (ISGs) in chronic HCV infection.
- ▶ The association of *IFNL3* genotype and initial viral control suggests a role for *IFNL3* genotype in innate immune response against HCV but further research is needed to support this hypothesis



Naggie, et al. Hepatology 2012

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

Discussion

The mechanisms and role of female gender in viral control in acute HCV infection

- ▶ Female sex is a well-established factor associated with HCV spontaneous clearance
Grebely, et al. Hepatology 2014
- ▶ Lower rate of treatment-induced HCV clearance in chronic infection in postmenopausal women compared to premenopausal women.
Villa, et al. Gastroenterology 2011
Floresani, et al. Eur J Gastro Hepato 2011
- ▶ Estrogen receptor alpha promotes HCV replication by interaction with the NS5B protein.
Hillung, et al. J Gen Virol 2012
- ▶ Higher interferon- α induction after Toll-like receptor 7 (TLR7) stimulation among healthy females compared to males
Berghofec, et al. J Immunol 2006
- ▶ More data is needed to explain the sex-based differences in immunological profiles in individuals with acute HCV infection

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