Modelling the effects of targeted DAA hepatitis C virus treatment strategies using a Molecular Transmission Network of people with recent infection

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Introduction

- Combining phylogenetic and network methodologies has the potential to better inform targeted interventions to prevent and treat infectious diseases, such as Hepatitis C virus (HCV).
- This study reconstructed a molecular transmission network for people with recent hepatitis C virus (HCV) infection. Participants were from three studies of people with recently acquired HCV infection in Australia recruited between 2004–2014
- Factors associated with higher network connectivity were assessed and the network was used to model the impact of targeting directly acting antiviral (DAA) treatment for HCV.

Aims

- To construct and characterise the molecular transmission network of recently acquired HCV in Australia
- Investigate factors associated with being highly connected in the network
- To model the impact of targeting HCV DAA therapy to those with an elevated transmission risk

Method

- Samples obtained from participants at the time of HCV detection
- Core-E2 region amplified and sanger sequenced (1300bp)
- Sequences aligned in ClustalX 2.1 and pairwise genetic distance calculated by TN93 nucleotide substitution algorithm in HIV-TRACE (www.hivtrace.org) adapted to HCV
- Transmission network constructed by creating an edge between two subjects when TN93 distance ≤3% (≤0.03 substitutions/site)
- Directionality of network based on estimated date of infection of participants.
- Factors associated with having more than 2 connections analysed by multivariate logistic regression in Stata 11.
- The impact of targeting HCV direct acting antivirals (DAAs), assuming 90% treatment efficacy, at both HIV co-infected and random nodes was simulated (1 million replicates).

Results

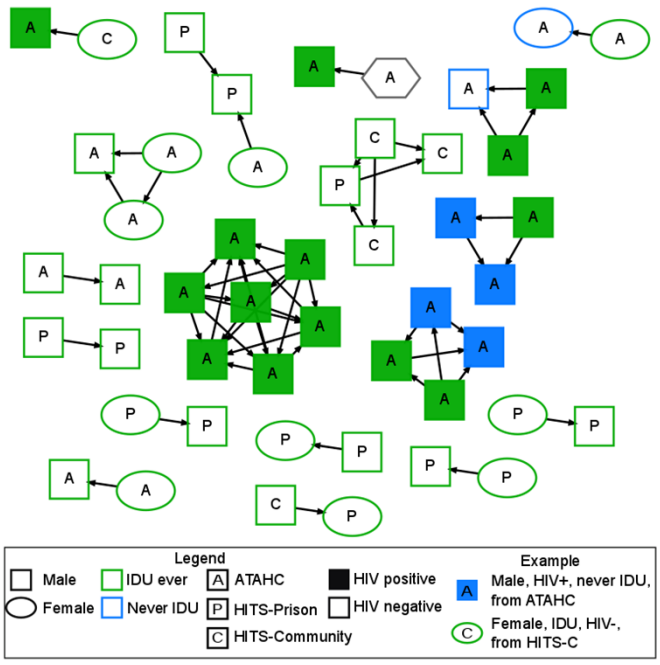

Figure 1. Molecular transmission network of recently acquired HCV infection in Australia. Network reconstructed based on divergence of ≤0.03 substitutions/site in HCV nucleotide sequences from a 1104 bp region encompassing the Core to E2 (minus HVR1) region. Only clustered individuals (nodes) within the network are shown (28%).

Table 1. Characteristics of participants overall, according to being in the network and logistic regression of factors associated with being in the network at ≤0.03 substitutions/site cut off for participants with recently acquired HCV infection in Australia between 2004 and 2014.

Characteristic	Overall	Not in network	In network	Connected in network		
Total n (%)	(n=236)	(n=187)	(n=49)	Odds ratio	95% CI	P
Age ≥25 (vs. <25)	67 (28%)	52 (30%)	15 (30%)	1.07	0.54, 2.12	0.838
≤30 (vs. >30)	101 (45%)	79 (45%)	22 (44%)	1.00	0.53, 1.90	0.999
≤35 (vs. >35)	77 (32%)	57 (32%)	20 (40%)	1.46	0.77, 2.78	0.248
Female sex (vs. male sex)	70 (31%)	57 (32%)	13 (26%)	0.74	0.36, 1.51	0.408
HIV infection (vs. none)	36 (16%)	19 (11%)	17 (34%)	**4.40**	**2.06, 9.36**	**<0.001**
Injection drug use						
Ever (vs. never)	204 (90%)	160 (91%)	44 (88%)	0.825	0.28, 2.39	0.723
Recent [a b] (vs. none)	130 (59%)	106 (60%)	24 (48%)	0.60	0.32, 1.15	0.125
High school or higher						
(vs. < high school)	138 (61%)	103 (59%)	35 (70%)	1.86	0.92, 3.75	0.085
Unstable housing [c]						
(vs. stable)	101 (45%)	82 (47%)	19 (38%)	0.67	0.35, 1.29	0.232
Incarceration						
Ever (vs. never)	114 (50%)	94 (53%)	20 (40%)	0.57	0.30, 1.09	0.089
Currently [b] (vs. not)	92 (41%)	77 (44%)	15 (30%)	0.57	0.29, 1.12	0.100
Study						
ATAHC (vs. other)	121 (51%)	92 (49%)	29 (59%)	1.38	0.73, 2.60	0.323
HITS-P (vs. other)	92 (39%)	78 (42%)	14 (29%)	0.57	0.28, 1.15	0.118
HITS-C (vs. other)	23 (10%)	17 (9%)	6 (12%)	1.52	0.40, 5.41	0.828
HCV Gt 1a (vs. other)	90 (38%)	65 (35%)	25 (51%)	1.96	1.04, 3.69	0.039

Table 2. Effect of DAA therapy targeted at HIV-coinfected individuals versus random individuals at 90% treatment efficacy.

HIV coinfected-targeted[1]	Randomly targeted[1]	Prevention yield improvement[2]
0.346	0.137	**2.530**

[1]Median number of prevented infections per targeted individual
[2]Ratio of median number of prevented infections between HIV-coinfection targeted and randomly delivered DAA therapy

Conclusion

- These findings demonstrate that sequence data from people with recent HCV infection can be used to characterise highly connected transmission networks.
- Targeted interventions of DAA HCV therapy to networks of people with HCV/HIV co-infection may be useful to prevent onward transmission in treatment as prevention strategies.

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