High connectivity is associated with HIV co-infection in the transmission network of people with recent hepatitis C virus infection in Australia

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Introduction

- Infectious diseases like human immunodeficiency virus (HIV) and hepatitis C virus (HCV) spread through contacts within social-injecting and sexual networks. The dynamic structure of these networks, such as number of injecting partners or sexual partners, governs spread of infection.
- Network features commonly defined through interview and partner tracing. However, this is of limited value when the infectious disease has a long incubation period between transmission and disease state and low transmission rate per contact, like HIV and HCV.
- It has been shown that HCV phylogenetic clustering is associated with the social-injecting network in a cohort of people who inject drugs [1] and that HIV nucleotide sequence data can be used to construct partial Molecular Transmission Networks [2, 3], which reflect transmission pathways.
- Molecular Transmission Networks represent a powerful scientific and clinical tool which could be used to study networks through which diseases are transmitted & help monitor epidemics.
- It is hypothesised that Molecular Transmission Network methodology could be applied to HCV epidemics to gain insight in to the network through which HCV is transmitted.
- Insight gained on this network could help guide the implementation of interferon-free HCV treatment and public health interventions, such as Treatment as Prevention.

Aims

1. To construct and characterize the molecular transmission network of recently acquired HCV infection in Australia
2. To evaluate the degree distribution of the molecular transmission network of recently acquired HCV infection in Australia and investigate factors associated with being highly connected in the network

Method

- Participants selected from three cohorts studying HCV; The Australian Trial in Acute Hepatitis C (ATAHC) [4], the Hepatitis C Incidence and Transmission Study in prison (HITS-p) [5] and the Hepatitis C Incidence and Transmission Study in the community (HITS-c) [6].
- Selected participants had recently acquired HCV infection defined by an initial positive anti-HCV test and either
  1) a negative anti-HCV test within two years prior to the initial positive anti-HCV test, or
  2) acute clinical hepatitis (either jaundice or ALT >400 IU/mL) within 12 months of the initial positive anti-HCV result
- Viral RNA extracted from EDTA plasma samples collected at time of HCV detection, partial Core–E2 (1300bp) region of HCV amplified with nested PCR and sanger sequenced [7].
- Multiple sequence alignment constructed using ClustalX2.1 and pairwise genetic distance calculated using TN93 nucleotide substitution algorithm in Mega 5.2.
- Partial Molecular Transmission Network constructed in CytoScape 2.3.1 by creating an edge between any sequences whose pairwise nucleotide divergence was ≤4%.
- Connectivity (degree) defined as the number of links (edges) an individual (node) had to other individuals in the network.
- Edges were directed based on year of estimated date of infection (outbound arrow points to later year, only indicating that direction of transmission could not have travelled in opposite direction).
- Hubs were considered to be any node with >2 outbound or undirected edges.
- Four degree distributions (Negative Binomial, Pareto, Waring and Yule) were compared using the Bayesian Information Criterion.
- Multivariate logistic regression in Stata 11 was used to identify factors associated with being highly connected (≥2 links) in the network.

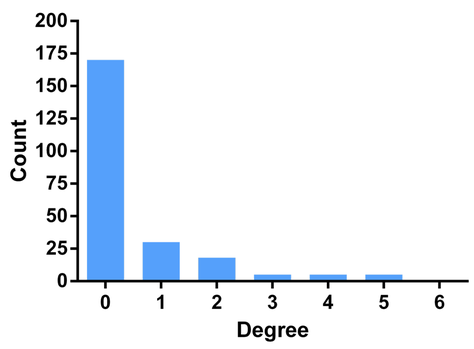

Figure 2. Distribution of edges in the partial Molecular Transmission Network of recently acquired HCV infection in Australia between 2004 and 2014. The degree defined as the number of edges a node had, represented on the X-axis. The degree of all nodes was tallied (including unconnected nodes, represented as degree 0) and is represented on the Y-axis.

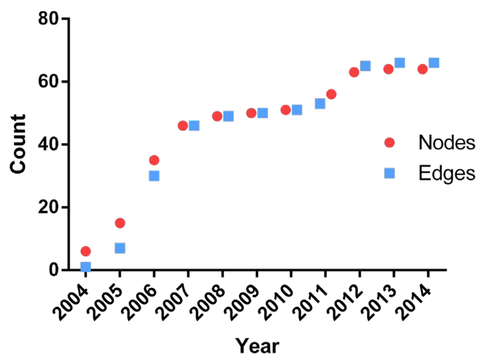

Figure 3. Accumulation of edges and nodes over time in the partial Molecular Transmission Network of recently acquired HCV infection in Australia between 2004 and 2014. Nodes are dated based on year of estimated date of infection of individual. Number of nodes in the network at a given year is indicated by red circle and number of edges by a blue square.

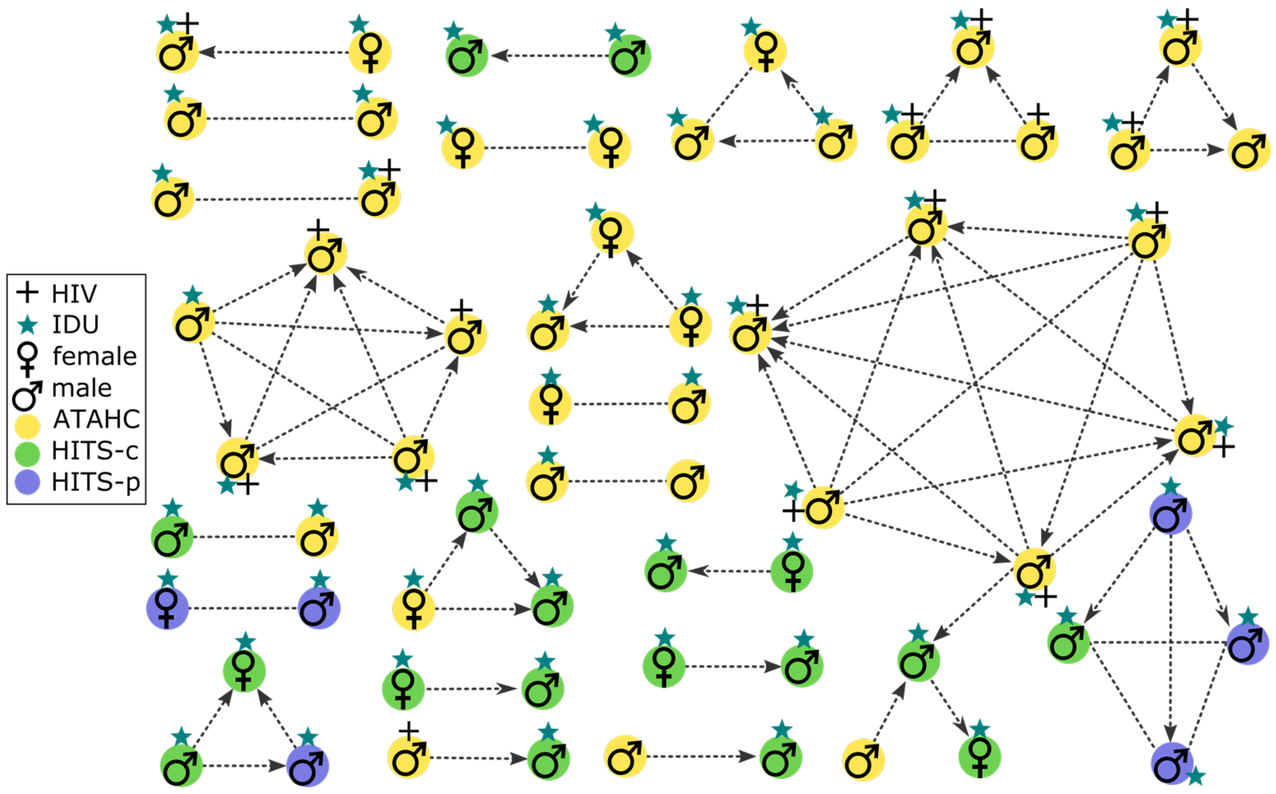

Figure 1. Partial Molecular Transmission Network of recently acquired HCV infection in Australia between 2004 and 2014. Each coloured circle (node) represents an individual, with study of origin indicated by yellow for ATAHC, green for HITS-c and blue for HITS-p. Sex is indicated by male and female symbols. HIV positive individuals are indicated by a plus sign. Individuals with history of injecting drug use are indicated with a star symbol. Nodes without any connections are not shown.

Results

- 234 participants (ATAHC, n=123; HITS-p, n=91; HITS-c, n=20) were eligible for inclusion, with 60% having recently injected drugs and 17% HCV/HIV co-infection.
- Overall, 73% (n=170) of individuals were un-linked in the network, 21% (n=48) were linked to 1 or 2 individuals and 7% (n=16) were linked to 3 or more individuals. Highly connected nodes were observed in the network in **Figure 1**, with some hubs seen.
- The negative binomial distribution provided best fit for the degree distribution, and a long tail was not exhibited, as seen in **Figure 2**. Two plateaus were seen in the accumulation of nodes and edges over time, as seen in **Figure 3**.
- Being connected in the network (≥1 or more connections) was independently associated with HCV/HIV co-infection [odds ratio (OR) 3.05; 95% confidence interval (CI) 1.42, 6.56] and HCV G1a infection [OR 2.85; 95% CI 1.52, 5.34].
- Overall, 42% (15/36) of HCV/HIV co-infected participants were highly connected in the network, compared to 11% (20/189) with HCV alone. Being highly connected in the network (≥2 or more connections) was associated with HCV/HIV co-infection [OR 3.90; 95% CI 1.82, 7.93] and being in prison [OR 3.99; 95%CI 0.10, 0.63] in unadjusted analysis. In adjusted analysis, HCV/HIV co-infection was the only factor independently associated with being highly connected in the network [OR 6.05, 95% CI 2.69, 13.55].

Discussion

- These results demonstrate that sequence data from people with recent HCV infection can be used to characterize highly connected Molecular Transmission Networks.
- Although the negative binomial distribution was the best fitting model and no long tail was seen, hubs were evident in the network, suggesting preferential attachment may still play a role in network formation.
- Mathematical modelling of the impact in reduction of transmission from targeting Treatment as Prevention to highly-connected nodes, or hubs, will be explored in the future.
- Highly connected components of the network containing HCV/HIV co-infected men was evident, and HCV/HIV co-infection was independently associated with being highly connected.
- Further studies are warranted to investigate the feasibility and effectiveness of enhanced prevention programs including hepatitis C Treatment as Prevention in the setting of HCV/HIV co-infection.

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