Hepatitis C virus treatment as prevention in an extended network of people who inject drugs in the USA: a modelling study

Alexei Zelenev, Jianghong Li, Alyona Mazhnaya, Sanjay Basu, Frederick L Altice

Summary

Background Chronic infections with hepatitis C virus (HCV) and HIV are highly prevalent in the USA and concentrated in people who inject drugs. Treatment as prevention with highly effective new direct-acting antivirals is a prospective HCV elimination strategy. We used network-based modelling to analyse the effect of this strategy in HCV-infected people who inject drugs in a US city.

Methods Five graph models were fit using data from 1574 people who inject drugs in Hartford, CT, USA. We used a degree-corrected stochastic block model, based on goodness-of-fit, to model networks of injection drug users. We simulated transmission of HCV and HIV through this network with varying levels of HCV treatment coverage (0%, 3%, 6%, 12%, or 24%) and varying baseline HCV prevalence in people who inject drugs (30%, 60%, 75%, or 85%). We compared the effectiveness of seven treatment-as-prevention strategies on reducing HCV prevalence over 10 years and 20 years versus no treatment. The strategies consisted of treatment assigned to either a randomly chosen individual who injects drugs or to an individual with the highest number of injection partners. Additional strategies explored the effects of treating either none, half, or all of the injection partners of the selected individual, as well as a strategy based on respondent-driven recruitment into treatment.

Findings Our model estimates show that at the highest baseline HCV prevalence in people who inject drugs (85%), expansion of treatment coverage does not substantially reduce HCV prevalence for any treatment-as-prevention strategy. However, when baseline HCV prevalence is 60% or lower, treating more than 120 (12%) individuals per 1000 people who inject drugs per year would probably eliminate HCV within 10 years. On average, assigning treatment randomly to individuals who inject drugs is better than targeting individuals with the most injection partners. Treatment-as-prevention strategies that treat additional network members are among the best performing strategies and can enhance less effective strategies that target the degree (ie, the highest number of injection partners) within the network.

Interpretation Successful HCV treatment as prevention should incorporate the baseline HCV prevalence and will achieve the greatest benefit when coverage is sufficiently expanded.

Funding National Institute on Drug Abuse.

Lancet Infect Dis 2018; 18: 215–24

Published Online November 15, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30676-X

See Comment page 134

Department of Internal Medicine, Section of Infectious Diseases, AIDS Program, Yale School of Medicine, New Haven, CT, USA (A Zelenev PhD, Prof F L Altice MD); **Institute for Community Research, Hartford, CT, USA** (J Li MD); **ICF Alliance for Public Health, Kyiv, Ukraine** (A Mazhnaya MS); **Department of Health, Behavior & Society, Johns Hopkins Bloomberg School of Public Health, MD, USA** (A Mazhnaya); **Stanford University School of Medicine, Stanford, CA, USA** (S Basu PhD); **Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA** (Prof F L Altice); **and Centre of Excellence for Research in AIDS (CERiA), Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia** (Prof F L Altice)

Correspondence to: Dr Alexei Zelenev, Department of Internal Medicine, Section of Infectious Diseases, AIDS Program, Yale School of Medicine, New Haven, CT 06510-2283, USA **alexei.zelenev@yale.edu**

Introduction

Hepatitis C virus (HCV) and HIV, two common chronic viral infections, affect 71–80 million and 37 million people worldwide, respectively.[1,2] In the USA, more than 2·9 million people are infected with HCV and more than 25% of the 1·2 million people with HIV are also infected with HCV.[3,4] The number of HCV-related deaths now exceeds those from HIV, with 30 500 new infections every year.[5] As HCV-related deaths in the USA continue to increase, with death occurring about 20 years earlier than the US average life expectancy, the estimated costs associated with HCV are projected to increase from US$6·5 billion to $9·1 billion annually by 2024 if HCV is left untreated.[6,7] People who inject drugs account for more than 69% of new HCV infections and 78% of total HCV infections in the USA.[8] HCV incidence in people who inject drugs could be as high as 41·8 cases per 100 person-years,[9] while chronic HCV infection measured by detectable HCV RNA in people who inject drugs ranges from 60% to 90%.[10]

With the availability of more tolerable and effective direct-acting antivirals,[11] HCV treatment-as-prevention strategies could substantially curtail HCV transmission and reduce the burden of HCV.[12] Completely eliminating HCV (ie, reducing new cases of HCV to zero) will require a strategic combination of prevention (eg, harm reduction) and treatment-as-prevention strategies, including the expansion of HCV treatment into different clinical care settings. Because direct-acting antivirals are expensive, treatment-as-prevention strategies require resources to be allocated strategically, targeting those at greatest risk for transmitting HCV, especially in people who inject drugs. Provision of HCV treatment improves public and individual health outcomes by increasing life expectancy and reducing disability-adjusted life-years, as well as reducing incident HCV infections.

In the USA, HIV-infected people who inject drugs are disproportionately affected by HCV. An estimated 80% of HIV-infected people who inject drugs in the USA also

Research in context

Evidence before this study

We searched PubMed and Science Direct on Oct 2, 2016, without date restrictions with the terms "hepatitis C or HCV", "modeling", "treatment", and "direct-acting antivirals". We found several compartmental modelling studies, including two from the USA, and also identified five reports from one dataset in Australia that are based on empirically grounded injection networks of people who inject drugs that can be compared with the US context. The compartmental models are based on untested assumptions about mixing and thus might not apply to the USA directly. The two studies from the USA analysed the effect of HCV treatment scale-up on the reduction of HCV infections, but did not consider additional treatment as prevention policies. The only study that incorporates social networks and explores treatment as prevention strategies in people who inject drugs is based on Australian injection networks, which have different structural properties compared with the USA. Moreover, HIV infection is uncommon in people who inject drugs in Australia.

Added value of this study

To our knowledge, this is the first study to develop a dynamic stochastic network model from injection networks in the USA, which is used to simulate the course of the HCV and HIV epidemic over the next 20 years. To our knowledge, the network data represent the largest network of people who inject drugs for which HCV treatment-as-prevention modelling has been done. Our calibration procedure improves upon previous modelling studies by fitting several models and verifying that the resulting synthetic graphs are similar to the observed networks with respect to key network parameters. We found that when baseline HCV prevalence is 60% or lower, treating more than 120 (12%) individuals per 1000 people who inject drugs per year would probably eliminate HCV within 10 years. On average, assigning treatment randomly to individuals who inject drugs is better than targeting individuals with the most injection partners.

Implications of all the available evidence

How large-scale interventions should be designed to eliminate HCV in people who inject drugs will depend on the injection network structures of patients and the epidemiology of HCV. Our study offers some treatment as prevention strategies for reducing or eliminating HCV in injection drug users and improving the allocation of resources for the most effective and cost-effective intervention strategies.

have HCV, which more than triples the risk for long-term disability and liver-related mortality.[13] The immunosuppressive effects of HIV accelerate HCV-related fibrosis, complicate clinical care, and result in increased morbidity and mortality, including a 6·7-times increased risk of liver-related death in patients with HCV/HIV co-infection compared with HIV-infected patients without HCV.[14] In addition to accelerated HCV progression in patients with HIV, liver-related disease has become a leading cause of non-HIV-related deaths in HIV-infected people who inject drugs.[13]

See Online for appendix

Treatment of people who inject drugs is complex and understanding injecting networks and risk behaviours of people who inject drugs can help guide treatment strategies.[15] Several studies based on compartmental models suggest that if HCV treatment can be delivered efficiently to high-risk transmitters (people who inject drugs who continue injecting), HCV prevalence and incidence could decline substantially.[16] One such model in the USA showed that with universal HCV screening combined with HCV treatment, at least 30% of people who inject drugs need to be treated per year to eliminate HCV infection.[17] Another study using a compartmental model calibrated to young people (younger than 30 years) who inject drugs in Chicago estimated that treating 3·5% of all people who inject drugs could reduce HCV prevalence from 30% to 15% in 10 years.[18]

Compartmental models, however, are often based on unverified assumptions about population mixing and do not account for individual heterogeneity that could suggest a need for a broader class of treatment strategies that would extend beyond an increase in treatment coverage. Studies from Australia, where HIV infection is uncommon in people who inject drugs, showed that treating people within injecting drug networks could efficiently reduce HCV prevalence.[19] However, structures of injection networks in the USA are different because of the varying number of injection partners that individuals have in the USA, with some individuals injecting with up to 25 different partners within a 6-month period (eg, average number of injection partners is 2·5 in Australia[19] *vs* 4·2 in the USA; appendix p 7). Consequently, network-based treatment-as-prevention strategies could yield different results in the USA, especially in view of different prevalences of HCV and co-infection with HIV in the USA (appendix p 8). We assessed several new treatment-as-prevention strategies by use of a measurement-calibrated network model of injection partnerships in the USA to analyse the HCV and HIV transmissions in an injection-recruited network of people who inject drugs. Furthermore, dynamic elements of injection networks, which have been largely absent from previous network-based modelling studies, are incorporated into the model because injection networks often change over time.[20]

Methods

Study design and network data

We used a network-based modelling strategy to assess various treatment-as-prevention strategies for HCV, which focuses on reductions in HCV transmission.

The mathematical model used a stochastic discrete agent-based system consisting of two distinct parts: a network model that evolved from an empirically based risk network of people who inject drugs, and a transmission model that captures the process by which HCV and HIV spread among individuals who share injection equipment.

The injection network is defined in terms of partnerships (edges), in which people who inject drugs (nodes) inject drugs at the same time and location. To faithfully model the structure of networks, we analysed detailed partnership and risk behaviour data from a 2012–13 study in Hartford, CT, USA.[21] Hartford, a middle-sized city and one of the poorest cities in the USA, is highly representative of many trends shaping urban settings, including deindustrialisation and rises in income inequality, unemployment, and drug use. People who inject drugs were recruited by respondent-driven sampling (ie, a form of chain-referral sampling designed to efficiently recruit hidden populations) to examine the recruitment dynamics, network characteristics, and risk behaviours associated with drug injection. Study design and participant recruitment details have been described elsewhere.[21] People who inject drugs were eligible if they were aged 18 years or older, residents of Hartford, and had injected drugs within the past 30 days. Written informed consent was obtained from all participants before the interview. The research design and procedures were approved by the Institute for Community Research's Institutional Review Board. The data were collected through a survey questionnaire. The ego-alter network was constructed on the basis of respondents naming their peers, injection partners, and social contacts. Matching resulted in 2435 network members, including the 528 primary respondents. To narrow the social network to the injection network, we excluded from the analysis peers not recruited directly into the sample and who did not inject drugs at the same time and location as any of the respondents during the previous 6 months. The final sample consisted of 3308 injection partnerships (edges) among 1574 unique individuals (nodes; figure 1). See appendix (pp 1–6) for additional information about the network.

Network model

To develop a network simulation that has the same properties as the real network,[22,23] we used the following calibration procedure. Reconstructing the non-sampled edges, we estimated several key summary metrics that incorporated essential structural features of injection networks in our collected US data, including degree distribution, assortativity, clustering, and average path length.[22] We then simulated several network models including small-world, preferential attachment, exponential random graphs, and a degree-corrected stochastic block model[24] and calculated the same set of summary measures.[22] Finally, we compared the simulations to empirical data and chose the model that most closely matched the network properties. The degree-corrected stochastic block model performed well in terms of matching network parameters, and was chosen over the other models (appendix pp 1–6).

We added several dynamic elements to enable the networks to evolve over time through formation of new ties and dissolution of existing ties between injection partners. Using both the duration of partnerships as well as the longevity of drug injection on the basis of the Hartford data, we specified the probability with which the individual either leaves the partnership (dyad between injection partners), $1/\tau$, or the population of injecting drug users (eg, stops injecting or dies), $1/\pi$, based on a constant hazard rate assumption (table). Because the number of new ties that were formed was not directly assessed in the Hartford data, we assumed that the rate of new tie formation was equal to the rate of tie dissolution. This assumption conservatively ensures model stability.

Infection model

We adopted a two-compartment susceptible–infected framework to model the HCV and HIV epidemic and incorporated HCV treatment into the analytical

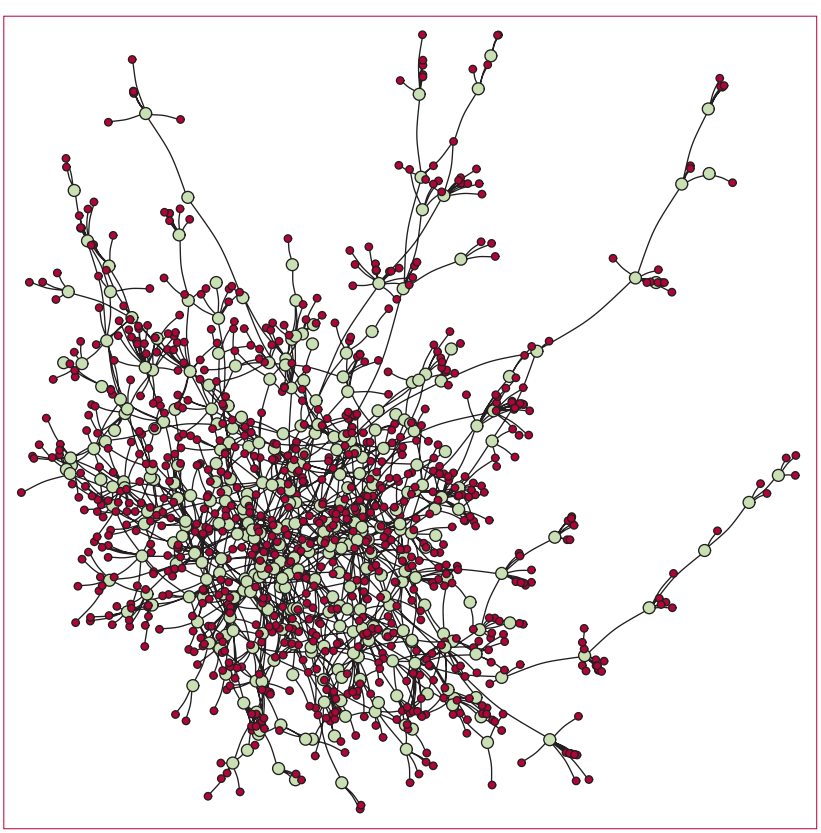

Figure 1: **Injection network of 1574 people who inject drugs in Hartford, CT, USA**
The depicted network is derived from respondent-driven sampling adapted to construct injection and social ties. Each node represents a person who injected drugs, and each edge represents an injection partnership. Green nodes are individuals sampled directly through recruitment, and red nodes are individuals who were not recruited into the sample through network referrals.

framework. The table shows the parameters. In our transmission model, susceptible individuals were those who had never been infected, had cleared their infection, or who had been successfully treated. The infectious compartment consisted of chronically HCV-infected individuals who were not treated, or whose treatment was not effective. Individuals were assigned randomly to treatment on the basis of a specified strategy in which we assumed that those being treated for HCV had ceased injecting drugs during the period of HCV treatment, and were therefore not infectious during periods of treatment. Although data suggest otherwise,[27] we conservatively assumed no adaptive immunity for individuals who were re-infected with HCV. Initially, we randomly selected 5–15% of the synthetic cohort, introduced HIV and HCV infection, and then simulated the transitions between different infectious states. The first equation provides the probability rule for the transition from susceptible to infected individual:

	Description	Value (range)	Source
ε	Efficacy of treatment (%)	90%	Dore et al (2016)[12]
δ	HCV spontaneous clearance probability	0·25 if HIV negative; 0 if HIV positive	Liu et al (2012)[25]
γ_{HCV}	Force of HCV infection	0·8, 0·07, 0·0235, 0·011	Calibrated
γ_{HIV}	Force of HIV infection	0·005	Calibrated
σ	Paraphernalia sharing (including needles and syringes, %)	27% (5–50%)*	Hartford data
θ	Treatment coverage (proportion of the network of people who inject drugs treated; %)	0%, 3%, 6%, 12%, 24%	Varied in the model
ϕ	Share of network members treated	0, 0·5, 1	Varied in the model
π	Average duration of injection drug use (years)	20·1 (10–30)*	Hartford data
τ	Average duration of network tie (years)	10·3 (5–25)*	Hartford data
ρ_{HCV}	Baseline HCV prevalence (%)	30%, 60%, 75%, 85%	Amon et al (2008)[11]†
ρ_{HIV}	Baseline HIV prevalence (%)	9% (3–20%)*	CDC (2015)[26]
$\rho_{HIV/HCV}$	Baseline HCV/HIV co-infection (%)	14% (0–30%)*	CDC (2011)[14]

CDC=Centers for Disease Control and Prevention. HCV=hepatitis C virus. *Point estimate used in the main simulation; sampling bounds used in the sensitivity analysis. †Additional sources are listed in the appendix (p 8).

***Table*: Model parameters**

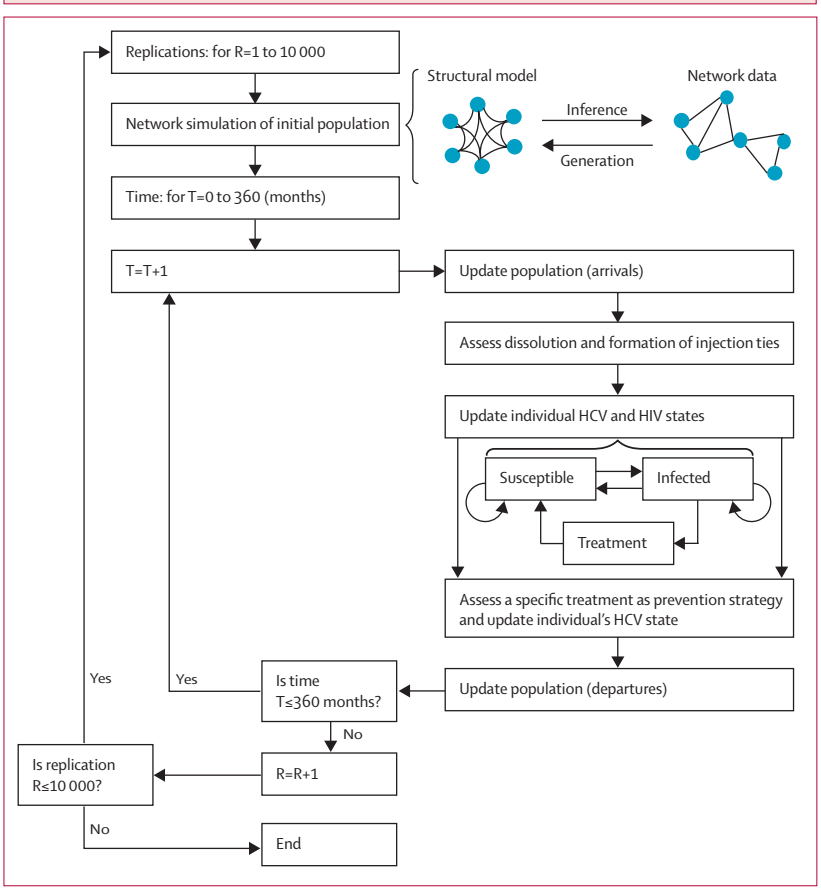

***Figure 2*: Network model simulation of HCV and HIV transmission and assessment of treatment as prevention strategies**
HCV=hepatitis C virus.

$$P\,(S_i\,(t) \rightarrow I_i\,(t+1)) = 1\text{–}\exp\,(-\gamma\Sigma\sigma_{ij}(t)I_j(t)A_{ij}(t))$$

where γ is the force of infection (calibrated separately for HIV and HCV), σ_{ij} is the probability that injection paraphernalia is shared between two partners; A_{ij} is the adjacency matrix of network links in the population; and I_j represents the infection status of an individual's injecting partner within the network. The HIV and HCV infections were modelled sequentially using two distinct equations for probability of transmission based on the formula above. At each discrete time step measured in months, a value for each individual's propensity to share paraphernalia was drawn from an estimated distribution of risky behaviours based on Hartford data, and two outcomes (susceptible or infected) were simulated for HCV and HIV. Additionally, when calibrating the model and selecting the force of infection, we verified that the probability of co-infection of HCV and HIV for the entire sample at the end of the burn-in period was between 12% and 15%, which represents the 95% CI based on the estimates reported by the CDC.[13] The individual's probability of transition from the infected state to the susceptible state is determined by the following equation:

$$P\,(I_i\,(t) \rightarrow S_i\,(t+1)) = \delta(I_{HIV})\zeta + P(T_i(t,\theta,\phi))\varepsilon)$$

where δ is the probability of spontaneous clearance within 6 months (which depends on HCV and HIV co-infection), ζ is the conditional probability of clearance at time t+1 (which we assume is derived from a uniform distribution), $P(T_i(t,\theta,\phi))$ is the probability that the individual is treated, and ε is the efficacy of treatment. Although HCV does not impact HIV progression, HIV decreases the rate at which HCV can undergo spontaneous clearance,[28,29] as reflected in the parameter δ, which will be dependent of the HIV status, I_{HIV}. Those not clearing HCV will progress to chronic infection, where they remain until their death, unless treated.

The probability of an individual being assigned treatment will depend on treatment coverage θ, and the treatment scenario, which includes the network coverage parameter ϕ. Figure 2 shows the model.

Simulation of various HCV treatment scenarios

We investigated the effect of seven network treatment strategies on HCV prevalence over 20 years. HCV treatment efficacy was assumed to be 90%. Population treatment coverage levels were set at 0, 30, 60, 120, and 240 people treated per 1000 people who inject drugs in the network per year. When population HCV prevalence is 60% and when treatment coverage is set at 30 people per 1000 people who inject drugs per year, for example, about 47 individuals would be treated annually in a network of 1574 people, or equivalently 5% of the 944 individuals with chronic HCV infection.

For each treatment coverage scenario, 10 000 simulations were performed. Infected HIV and HCV participants were scattered randomly, and the transmission model was run for the 10-year period without interferon-free treatment (burn-in period). After the baseline prevalence for HCV and HIV achieved a steady state, seven different treatment strategies were estimated and no interferon-free treatment was used as a control to which other strategies were compared. The outcome was the difference in HCV prevalence from the end of the 10-year and 20-year horizons observed in the baseline scenario, and scenarios based on seven different treatment strategies.

The control strategy was no HCV treatment and the seven HCV treatment-as-prevention strategies are listed in the panel. To simplify the different policy scenarios, we grouped them conceptually into two classes: random selection versus targeting highest node degree; and within the two classes the key difference among scenarios depended on the proportion of network peers that received treatment along with the selected individual.

Panel: **Treatment as prevention strategies for hepatitis C virus**

Random selection (no primary contacts)
Treatment assigned to a randomly chosen individual who injects drugs without any consideration given to the position within the injection network

Random selection (half primary contacts)
Treatment assigned to a randomly chosen individual who injects drugs, as well as half of the randomly chosen individual's injection partners

Random selection (all primary contacts)
Treatment assigned to a randomly chosen individual who injects drugs, as well as all of the individual's injection partners

Random chain treatment
Treatment begins with a randomly selected person who injects drugs within the network who serves as a seed for an expanding chain of treatment referrals, with a person injecting drugs referring one other person from the network of injection partners to enter treatment at each point in time

Targeting highest node degree (no primary contacts)
Treatment prioritised on the basis of the individual's number of injection partners

Targeting highest node degree (half primary contacts)
Treatment prioritised to the individual with the highest number of injection partners, with coverage extended to half of the selected individual's injection network

Targeting highest node degree (all primary contacts)
Treatment prioritised to the individual with the highest number of injection partners, with coverage extended to all of the selected individual's injection network

Model calibration and validation

We did several analyses to verify that the simulated prevalence from our models accurately reflected the average prevalence data reported from the USA. We ran the infection model for the first 10 years without introducing direct-acting antiviral treatment as a burn-in period. First, our model was calibrated against four different baseline HCV prevalence scenarios (30%, 60%, 75%, and 85%) that reflect the heterogeneity of HCV prevalence in people who inject drugs in different US metropolitan areas (see appendix p 8 for data sources). Second, we verified that the average degree at the end of the observation period was within 95% CI of the average degree observed in the Hartford data.

Additional sensitivity analyses

We did sensitivity analyses to determine how model projections change depending on the modelling assumptions and parameter distributions. The sensitivity analyses used US data[30] to first fit the lower and upper bound on HIV prevalence, which ranged from 3% to 20%. We then considered the effect of shorter duration of injection (10 years instead of 20 years); and also shorter durations of injection partnerships (5 years and 20 years, instead of 10 years). We also assessed the sensitivity to changes in the propensity to share injection equipment (5–50%). Finally, we considered the sensitivity to the selection of the algorithm for generating synthetic networks using exponential random graphs, which also fit the data well. We also explored the influence of network size scale-up by block-diagonalising the original network and subsequently running treatment simulations with 1000 replications on network with more than 15 000 nodes. The model was implemented in the mathematical programming language MATLAB 2016a.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full

access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our model estimates show that at the highest HCV prevalence in people who inject drugs (85%), expanding treatment coverage will not substantially reduce HCV prevalence over 10 years or 20 years for any treatment-as-prevention strategy (figures 3 and 4; appendix pp 9–12). When baseline HCV prevalence in people who inject drugs is 75%, increasing treatment coverage from 30 to 60 people (3% to 6%) per 1000 people who inject drugs per year would reduce HCV prevalence, on average, by 1–4% percentage points over 10 years, and expanding treatment coverage from 120 to 240 people (12% to 24%) per 1000 people who inject drugs per year would reduce HCV prevalence by as much as 50%, on average, depending on the strategy (figure 3; appendix pp 9–10). If baseline HCV prevalence in people who inject drugs was 60%, strategies that treat more than 120 (12%) individuals per 1000 people who inject drugs per year are likely to eliminate HCV within 10 years. If, however, HCV prevalence is 30%, HCV can be eliminated with relatively lower treatment coverage (60 [6%] individuals per 1000 people who inject drugs per year).

If the modelling horizon is extended to 20 years, the scenarios in which HCV prevalence in people who inject drugs is 30% at baseline attain HCV elimination within 20 years (figure 4; appendix pp 11–12). If the baseline prevalence is 60%, HCV elimination is attained within 20 years only if treatment coverage exceeds 60 (6%) per 1000 people who inject drugs per year. In the setting with HCV prevalence of 75%, HCV elimination can be attained within 20 years if treatment covers more than 240 (24%) per 1000 people who inject drugs and the optimal strategy, based on random selection of participants (either with no, half, or all of primary contacts), is chosen. If HCV prevalence is 85%, treatment coverage of 240 (24%) per 1000 people who inject drugs per year or lower is not likely to substantially reduce the proportion of HCV-infected individuals over 20 years.

At the two highest HCV prevalence strata (75% or 85%), if treatment coverage is relatively low (<60 people [<6%] per 1000 people who inject drugs per year), the difference among all seven strategies and the control is very small. In a pairwise comparison between the no treatment strategy and each of the seven strategies, the average differences were less than 1% and all seven corresponding p values were less than 0·0001 in the case of 85% prevalence; in the case of 75% prevalence, the differences between the no treatment strategy and each of the seven strategies were less than 4% and all p values were less than 0·0001 at either 10 years or 20 years. With expanded HCV treatment coverage, strategies in which treatment is assigned to a randomly chosen individual who injects drugs and their primary contacts perform better than strategies that target individuals with the highest number of injection partners for all baseline HCV prevalence levels (figures 3, 4;

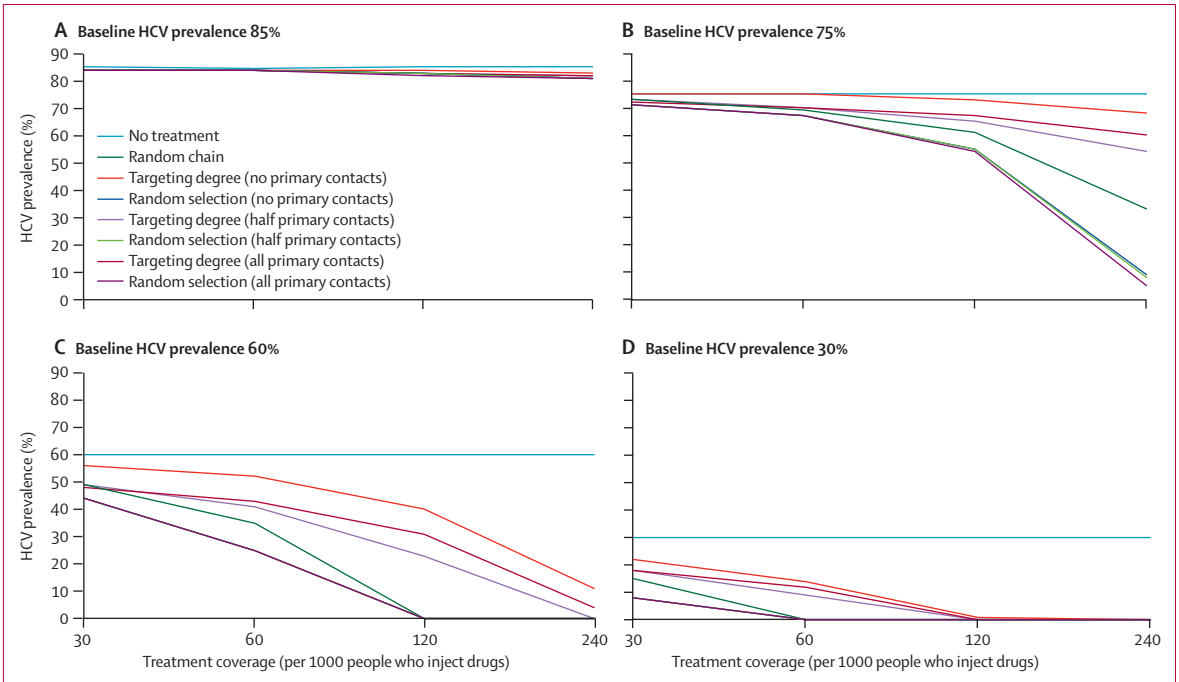

Figure 3: **Mean HCV prevalence at the end of the 10-year estimation simulation window (10 000 replications)**
The effect of expanding HCV treatment coverage on HCV prevalence over 10 years, stratified by baseline HCV prevalence. See panel for definitions of the seven treatment strategies. The confidence intervals for the means are reported in the appendix (pp 9–10). HCV=hepatitis C virus.

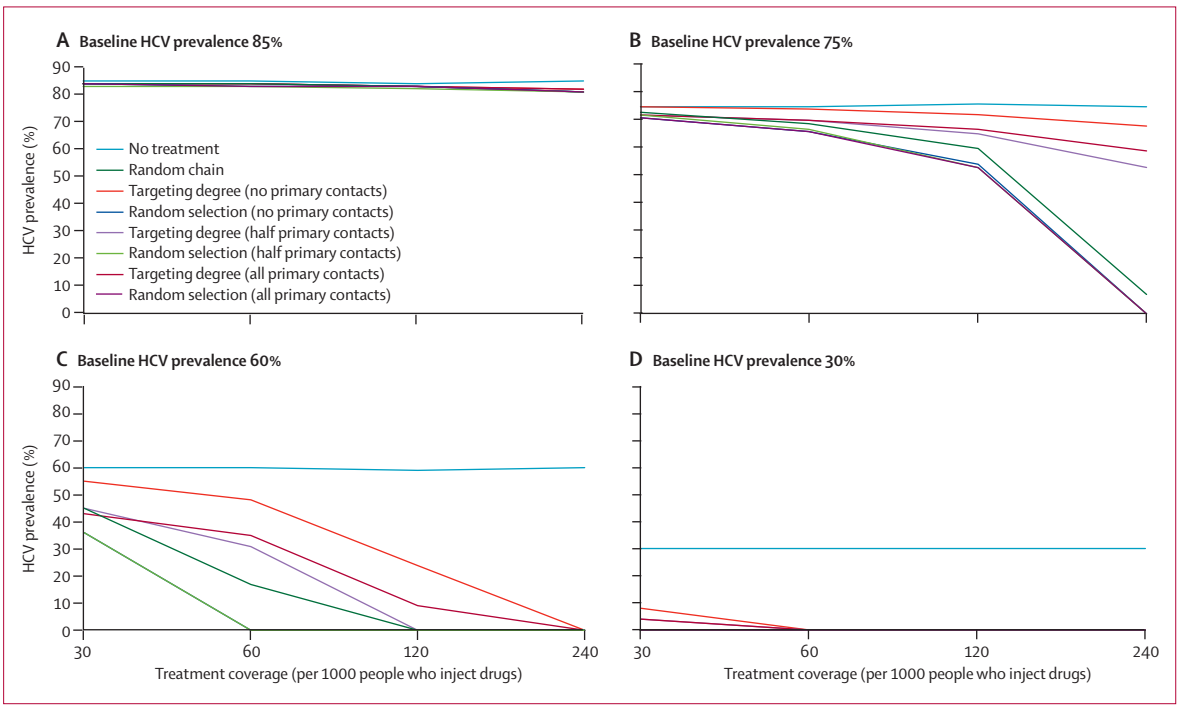

Figure 4: **Mean HCV prevalence at the end of the 20-year simulation window (10 000 replications)**
The effect of expanding HCV treatment coverage on HCV prevalence over 20 years, stratified by baseline HCV prevalence. See panel for definitions of the seven treatment strategies. The confidence intervals for the means are reported in the appendix (pp 11–12). HCV=hepatitis C virus.

appendix pp 9–12). The pattern is consistent for both the 10-year and 20-year horizons.

In settings where HCV prevalence is 75%, and treatment coverage is increased to 24% per year, treatment-as-prevention strategies that are based on random selection outperform strategies based on targeting of node degree (ie, the sum of all the connections that a given node [individual] has), and have the potential to reduce HCV prevalence to less than 10% within 10 years; for example, the most optimal strategy based on treating random people who inject drugs and all of their primary contacts can reduce HCV prevalence to approximately 5% on average within 10 years (figure 3; appendix p 9). For strategies with random treatment allocation, no significant differences in HCV prevalence reduction are evident between strategies that treat no primary contacts and half of primary contacts (p=0·35). By contrast, among strategies that target node degree, strategies that treat half of the primary contacts perform better than strategies that treat no primary contacts in terms of HCV reduction over the 10-year and 20-year horizons; on average, treating half of the primary contacts reduces prevalence to 54%, compared with 68% when no primary contacts are treated over 10-year and 20-year horizons (p<0·0001 for both 10 years and 20 years; appendix pp 9–13).

Our sensitivity analysis (appendix pp 13–22) showed that the findings from the main model were not sensitive to variability in the parameters and assumptions. When sharing of injection paraphernalia was both low (5%) and high (50%), the ranking of strategies by coverage was similar to the ranking with moderate sharing of injection paraphernalia (27%). Additionally, the ranking of strategies was not sensitive to the variations in the dissolution rate of networks. Similarly to the main model, random selection outperformed strategies that targeted the highest node degree in scenarios with baseline prevalence below 85%. Simulations based on exponential random graph models yielded similar ranking among policies, as well as a similar magnitude of the overall effect of treatment coverage. Higher prevalences of HIV were not found to affect the ranking among the various strategies. When we scaled up the network to 15 000 nodes, preserving the original network's properties, the results were similar to the smaller size network simulations.

Discussion

To our knowledge, our study is the largest injection network of people who inject drugs that models HCV treatment as prevention and the only network from the USA that uses empirical data from dynamic injection networks that have been carefully calibrated to a wide range of network measures, including long-tail degree distribution and clustering. Dynamic elements of injection networks, which have been largely absent from previous network-based modelling studies, were incorporated into the model because injection networks often change over time.

Our findings suggest that in dense urban settings where HCV prevalence in people who inject drugs is high (≥75%), any HCV treatment-as-prevention strategy would have little impact in lowering HCV prevalence over 10 years, unless treatment coverage is greatly expanded. This finding is similar to results from previous studies. For example, Durham and colleagues[17] calculated that treatment coverage has to exceed 30% of the diagnosed infections in people who inject drugs for HCV to be eliminated within 30 years when the baseline HCV prevalence is 75%. We found that within 10 years, the strategies based on random selection with either half or all primary contacts at this HCV prevalence can nearly eliminate HCV as long as annual coverage is higher than 24% (240 people per 1000 people who inject drugs), which implies that 32% of HCV-infected people who inject drugs would receive treatment per year. With other strategies, however, the decline in HCV prevalence would be minimal.

Unlike compartmental[16] and network[19] studies outside the USA, where networks of people who inject drugs differ, we find that modest treatment coverage (eg, 6% of people who inject drugs per year) is not likely to lead to substantial declines in HCV prevalence. In our analysis, when HCV prevalence was 60% (the prevalence estimated for people who inject drugs within the entire USA, but recognising geographical differences), selecting the optimal treatment as prevention that is based on random selection (either with no primary contacts, half of primary contacts, all of primary contacts, or as a random chain) could eliminate HCV within 10 years by expanding annual treatment coverage to 12%. HCV elimination could, however, be achieved by 20 years of treatment of 60 (6%) randomly selected people per 1000 people who inject drugs per year. If, however, an alternative and less effective strategy based on targeting people with the highest number of injection partners along with half of their primary contacts is chosen, HCV prevalence would decline from 60% to 31%. Lower levels of HCV prevalence reduction become even smaller at higher levels of HCV prevalence (eg, ≥75%). Comparing our estimates to those of Hellard and colleagues,[31] who also used network analysis, we find the effect of random treatment allocation to be higher in our study. In their model, treating 2·5% of people who inject drugs per year might lead to a 10% decline in HCV prevalence over 10 years, yet in a setting with a higher average number of injection network partners, we found that a random treatment strategy is likely to reduce HCV prevalence by at least 15%, when baseline HCV prevalence is similar. Our results are similar to those of Echevarria and colleagues,[18] who calibrated a compartmental model in young people who inject drugs from Chicago and found that coverage of 3·5% per year could reduce HCV prevalence from 30% to 15% over 10 years. We found similar reductions over 10 years when the random chain treatment-as-prevention strategy has coverage of 30 per 1000 people who inject drugs per year, but using our network-based model, the optimal strategy is random treatment selection, which reduces HCV prevalence by 22% on average.

High HCV prevalence in people who inject drugs (>85%) reduces the effectiveness of the HCV treatment-as-prevention paradigm, especially when the networks are dynamic and the rate of network turnover is high. If HCV treatment coverage is not expanded sufficiently, HCV prevalence is not likely to change substantially in the long term, because treatment does not seem to have a sustainable impact over 10 or 20 years. Additional harm reduction strategies such as expansion of medication-assisted treatment and increased access to needle and syringe programmes might enhance the effectiveness of HCV treatment coverage in such settings.

As with previous HCV modelling strategies, we found that treatment of a random selection of network members performs better than strategies that solely target the node degree.[19] Treating highest degree first (ie, those with whom an individual directly injects with) might appear useful, because it could reduce HCV prevalence; however, the high rates of HCV re-infection render this strategy ineffective, unless treatment coverage is near universal. Strategies that include random allocation across individuals and incorporate treatment of members of the injection network perform better than do strategies that focus solely on the individual. This finding is consistent with the results of the network modelling study in Australia.[19]

This study is not without limitations. First, the modelling assumes patients' acceptance of and adherence to treatment, whereas in reality, many people who inject drugs might decline testing, reject treatment, or cannot afford it. Our model does not fully account for differences in the risk behaviours between individuals who are spontaneously cleared and those who are never infected. Reductions in treatment uptake could potentially translate into higher probability that the HCV prevalence might not be completely eliminated within the projected horizons. In the model, one of the assumptions is that the probability of infection is constant throughout the duration of the infection, and also that those undergoing treatment do not alter their risky behaviour. If the probability of infection increases through a rise in risky sharing behaviour, greater treatment coverage might be needed to offset the rise in infections. Although sample size might limit interpretation of the data, our analyses are derived from the largest available network of people who inject drugs, and our sensitivity analysis suggests that the main results should hold if the sample size scale-up preserves structural properties of the network.

Additionally, the data from Hartford could have measurement error and errors due to recall bias. However, all recall was limited to the previous 6 months and we used a degree-corrected block model, which can

infer the structure of a network in the presence of misreported and missing ties.[24] Finally, the model does not consider the effect of concurrent addiction treatment scenarios (eg, with opioid agonist therapies such as methadone or buprenorphine), which might reduce re-infection further, making treatment more effective than in our models. An international study of opioid agonist therapies in people who inject drugs showed cure rates that exceeded 90%, even in patients with continuing drug use.

Several factors restrict access to direct-acting antivirals and HCV elimination in people who inject drugs, including high costs. The cost of direct-acting antivirals is decreasing as more medications reach the market, from more than US$130 000 to $26 000, with evidence of further declines. High costs have led to restrictions by private and governmental insurance, such as requiring prolonged abstinence from drugs, restricting treatment to patients with advanced fibrosis, and allowing only specialists to prescribe treatment.[32] Furthermore, changes in federal laws that expand states' authority to negotiate prices can also help to accelerate affordability of direct-acting antivirals to treat HCV. Medicaid expansion and enrolment under the Affordable Care Act should improve access and affordability of direct-acting antivirals, yet these programmes have expanded unevenly throughout the USA. Analogous programmes to the AIDS Drug Assistance Program, which provides HIV medications to low-income individuals and reaches approximately a third of people with HIV nationally, would be an important next step to improve access to direct-acting antivirals in the USA. As HCV treatment becomes more affordable, cost will become less of an impediment to treatment-as-prevention strategies. In the absence of sufficent coverage turning the tide on the HCV epidemic will be challenging.

Contributors

All authors contributed to the design of the study and the writing of the report. All authors critically revised the report and approved the final version. AZ analysed network data, developed and programmed network models, and ran simulations. JL participated in data collection and network analysis.

Declaration of interests

FLA has received honoraria for speaking from Gilead Sciences, Bristol-Myers Squibb, and Clinical Care Options. FLA has also received research grant support from Merck Pharmaceuticals and Gilead Sciences. All other authors declare no competing interests.

Acknowledgments

We acknowledge the following sources of funding: National Institutes of Health for career development (K01 DA037826 for AZ, K08 HL121056 for SB, K24 DA017072 for FLA); National Institute on Drug Abuse (R21 DA041953 for FLA, R01 DA0315940 for JL); and Merck Pharmaceuticals provided research support. Funding for AM was also provided by New York State International Training and Research Program through an in-country training grant funded by the Fogarty International Center (D43TW000233). The simulations were run at the Yale University Biomedical High Performance Computing Center, which is supported by National Institutes of Health grants RR19895 and RR029676-01.

References

1 Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; **5:** 558–67.
2 Wendt A, Adhoute X, Castellani P, et al. Chronic hepatitis C: future treatment. *Clin Pharmacol* 2014; **6:** 1–17.
3 Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol* 2017; **2:** 161–76.
4 Strader DB. Coinfection with HIV and hepatitis C virus in injection drug users and minority populations. *Clin Infect Dis* 2005; **41** (suppl 1)**:** S7–13.
5 Ly KN, Hughes EM, Jiles RB, Holmberg SD. Rising mortality associated with hepatitis C virus in the United States, 2003–2013. *Clin Infect Dis* 2016; **62:** 1287–88.
6 Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med* 2012; **156:** 271–78.
7 Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology* 2013; **57:** 2164–70.
8 Yehia BR, Schranz AJ, Umscheid CA, Lo Re V III. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. *PLoS One* 2014; **9:** e101554.
9 Judd A, Hickman M, Jones S, et al. Incidence of hepatitis C virus and HIV among new injecting drug users in London: prospective cohort study. *BMJ* 2005; **330:** 24–25.
10 Amon J, Garfein, RS, Ahdieh-Grant, L, et al. Prevalence of hepatitis C virus infection among injection drug users in the United States, 1994–2004. *Clin Infect Dis* 2008; **46:** 1852–58.
11 Dore G, Altice F, Litwin AH, et al. Elbasvir-grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. *Ann Intern Med* 2016; **165:** 625–34.
12 Grebely J, Matthews GV, Lloyd AR, Dore GJ. Elimination of hepatitis C virus infection among people who inject drugs through treatment as prevention: feasibility and future requirements. *Clin Infect Dis* 2013; **57:** 1014–20.
13 CDC. HIV and viral hepatitis factsheet. Washington, DC: Centers for Disease Control and Prevention, 2011.
14 Weber R, Sabin C, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med* 2006; **166:** 1632–41.
15 Rolls D, Daraganova G, Sacks-Davis R, et al. Modelling hepatitis C transmission over a social network of injecting drug users. *J Theor Biol* 2012; **297:** 73–87.
16 Martin NK, Vickerman P, Grebely J, et al. Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology* 2013; **58:** 1598–609.
17 Durham DP, Skrip LA, Bruce RD, et al. The impact of enhanced screening and treatment on hepatitis C in the United States. *Clin Infect Dis* 2016; **62:** 298–304.
18 Echevarria D, Gutfraind A, Boodram B, et al. Mathematical modeling of hepatitis C prevalence reduction with antiviral treatment scale-up in persons who inject drugs in metropolitan Chicago. *PLoS One* 2015; **10:** e0135901.
19 Rolls D, Sacks-Davis R, Jenkinson R, et al. Hepatitis C transmission and treatment in contact networks of people who inject drugs. *PLoS One* 2013; **8:** e78286.
20 Costenbader E, Astone NM, Latkin CA. The dynamics of injection drug users' personal networks and HIV risk behaviors. *Addiction* 2006; **101:** 1003–13.
21 Li J, Valente TW, Shin H, et al. Overlooked threats to respondent driven sampling estimators: peer recruitment reality, degree measures, and non-random selection. *Aids Behav* 2017; published online June 28. DOI:10.1007/s10461-017-1827-1.
22 Newman M. Networks: an introduction. New York: Oxford University Press, 2011.
23 Sala A, Cao L, Wilson C, Zablit R, Zheng H, Zhao BY. Measurement-calibrated graph models for social network experiments. 19th International World Wide Web Conference; Raleigh, NC, USA; April 26–30, 2010; pp 861–70.

24 Guimerà R, Sales-Pardo, M. Missing and spurious interactions and the reconstruction of complex networks. *Proc Natl Acad Sci USA* 2009; **106:** 22073–78.

25 Liu L, Fisher BE, Thomas DL, Cox AL, Ray SC. Spontaneous clearance of primary acute hepatitis C virus infection correlated with high initial viral RNA level and rapid HVR1 evolution. *Hepatology* 2012; **55:** 1684–91.

26 CDC. HIV infection, risk, prevention, and testing behaviors among persons who inject drugs—National HIV behavioral surveillance: injection drug use, 20 U.S. cities, 2012. HIV Surveillance Special Report 11, 2015. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-HSSR_NHBS_PWID_2012.pdf (accessed Oct 2, 2017).

27 Terilli RR, Cox AL. Immunity and hepatitis C: a review. *Current HIV/AIDS Rep* 2013; **10:** 51–58.

28 Rehermann B. Hepatitis C virus versus innate and adaptive immune responses: a tale of coevolution and coexistence. *J Clin Invest* 2009; **119:** 1745–54.

29 Kim AY, Schulze zur Wiesch J, Kuntzen T, et al. Impaired hepatitis C virus-specific T cell responses and recurrent hepatitis C virus in HIV coinfection. *PLoS Med* 2006; **3:** e492.

30 CDC. HIV infection, risk, prevention, and testing behaviors among persons who inject drugs. National HIV behavioral surveillance: injection drug use. 20 U.S. cities, 2012. HIV Surveillance Special Report 11; August, 2015. https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-HSSR_NHBS_PWID_2012.pdf (accessed Nov 11, 2017).

31 Hellard M, Rolls DA, Sacks-Davis R, et al. The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. *Hepatology* 2014; **60:** 1861–70.

32 Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE. Restrictions for Medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States. *Ann Intern Med* 2015; **163:** 215–23.