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

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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

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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.

Introduction

Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV), two highly prevalent chronic viral infections affecting 71–80 and 36.9 million people globally.^{1,2} In the U.S., over 2.9 million are infected with HCV and over 25% of the 1.2 million people living with HIV (PLH) are HCV/HIV co-infected.^{3,4} HCV-related deaths now exceed those from HIV, with 30,500 new infections annually.⁵ As HCV-related deaths in the U.S. continue to increase, with death occurring ~20 years below U.S. average life expectancy, the estimated HCV costs are projected to increase from \$6.5 billion to \$9.1 billion annually by 2024 if HCV is left untreated.^{6,7} PWID now account for over 69% of new HCV infections and 78% of total infections in the U.S. HCV incidence among PWID has been reported as high as 41.8 cases per 100 person years,⁹ while chronic HCV infection measured by detectable HCV RNA among PWID ranges from 60–90%.¹⁰

With the availability of more tolerable and efficacious direct-acting antivirals (DAAs), HCV Treatment as Prevention (TasP) strategies may markedly curtail HCV transmission and reduce the burden of HCV.⁸ Completely eliminating HCV (i.e. reducing new cases of HCV to zero) will require a strategic combination of prevention (e.g., harm reduction) and TasP strategies, including HCV treatment expansion into diverse clinical care settings. While the current HCV treatment costs are staggering, TasP strategies require allocation of resources for a more strategic approach that targets those at greatest risk for transmitting HCV to others, especially in people who inject drugs (PWID) who comprise most people with HCV in the U.S. 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. The Centers for Disease Control and Prevention (CDC) estimate that 80% of PWID with HIV in the US also have HCV, which more than triples the risk for long-term disability and liver-related mortality.¹³ The immunosuppressant effects of HIV accelerates HCV-related

fibrosis, complicates clinical care and results in increased morbidity and mortality, including a 6.7-fold increased risk of liver-related death than in HIV 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 among PWID with HIV.¹³

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. Several recent mathematical studies based on compartmental models suggest that if HCV treatment can be delivered efficiently to high-risk transmitters, specifically PWID who continue injecting, the resulting declines in HCV prevalence and incidence could be substantial.¹⁵ One such HCV TasP compartmental model in the U.S. found that with universal HCV screening combined with HCV treatment, that annual coverage must increase to 30% to eliminate HCV infection.¹⁶ 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.

Compartmental models, however, are often based on unverified assumptions about population mixing and do not account for individual heterogeneity that could suggest a broader class of treatment strategies that would extend beyond an increase in treatment coverage. Recent studies from Australia where HIV infection is uncommon in PWID found that treating members within PWID networks could efficiently reduce HCV prevalence.¹⁷ 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 Australia¹⁹ vs 4.2 in the USA; see on-line appendix). Consequently, network-based TasP strategies elsewhere may yield different results in the US, especially given different HCV prevalence levels and co-infection with HIV (see online supplement). Here, we evaluate several new TasP modeling strategies by using a measurement-calibrated network model of injection partnerships in the U.S. to analyze the HCV and HIV transmissions among an injection-recruited network of PWID. Further, dynamic elements of injection networks, which have been largely absent from previous network-based modeling studies, are now incorporated into the modeling since injection networks often change over time.¹⁸

Methods

We used a network-based modeling strategy to assess various TasP strategies for HCV, which focuses on reductions in HCV transmission. This strategy differs from the various understandings of TasP for HIV because HCV can be ‘cured’ in 8–12 weeks using medications that are highly tolerable, improve both individual and public health and potentially eliminate HCV in the local context. The mathematical model deployed a stochastic discrete agent-based system consisting of two distinct parts: a network model that evolved from an empirically-based PWID risk network, and a transmission model that captures the process by which HCV/HIV spreads among individuals who share injection equipment.

Network Data and Model

The injection network is defined in terms of partnerships (edges), in which PWID (nodes) inject drugs in the same time and location. In order to faithfully model the structure of networks, we analyzed detailed partnership and risk behavior data from a 2012–2013 study in Hartford, Connecticut that was designed to assess extensive network information. Hartford, a middle sized city and one of the poorest cities in the USA, is highly representative of many trends shaping urban settings, including deindustrialization, and rise in income inequality, unemployment and drug use. PWID (N=528) were recruited using respondent-driven sampling (RDS) to examine the recruitment dynamics, network characteristics and risk behaviors associated with drug injection. Study design and participant recruitment details have been previously described.¹⁹ Inclusion criteria were : 1) age 18 years or older; 2) Hartford residence; and 3) drug injection 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 2,435 PWID 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 in the same time and location with any of the respondents during the previous 6 months. The final sample consisted of 3308 observed injection partnerships (edges) among 1574 unique individuals (nodes). Figure 1 displays the injection network as nodes (sampled and non-sampled PWID) and edges (observed injection partnerships). See online supplement for additional information about the PWID network.

Because the sampling procedure was based on a partially observed network derived from RDS, we used a degree corrected stochastic block model to reconstruct the observed network.²⁰ To develop the network simulation, 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 *observed* US data. Key summary measures on which the comparison is based included degree distribution, assortativity, clustering and average path length.²¹ We then simulated several well-known network models including small-world, preferential attachment and exponential random graphs (ERGM) and calculated the same set of summary measures²¹. Finally, we compared the simulations to real empirical data and chose the model that most closely matched the observed network properties. This calibration procedure allowed us to choose an algorithm that can generate new artificial PWID risk networks that have the same properties as the observed networks.^{21,22} The degree-corrected stochastic block model performed well in terms of matching network parameters, and was chosen over the other models. A more detailed illustration of network reconstruction process, as well as a comparison of key measures between the theoretical models and empirical data is provided in the online supplement.

In addition, we added several dynamic elements to the network model, as we allowed the networks to evolve over time through formation of new ties as well as dissolution of existing

ties between injection partners. Using both the duration of partnerships as well as the longevity of drug injection based on the observed Hartford data, we specified the probability with which the individual either leaves the partnership (dyad between injection partners), $1/\tau$, or the PWID population (e.g., stops injecting or dies), $1/\pi$ based on a constant-hazard rate assumption (Table 1). Because the number of new ties that were formed was not directly assessed in the Hartford data, we further assumed that the rate of new tie formation 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/HIV disease epidemic and incorporated HCV treatment into the analytical framework. Parameters used from the PWID network data and from the literature are presented in Table 1. In our transmission model, the susceptible individuals included those who had never been infected, had cleared their infection or those that who had been successfully treated. The infectious compartment included chronically HCV-infected individuals who were not treated, or whose treatment was not effective. Individuals are assigned to treatment randomly based on a specified strategy where we assumed that those being treated for HCV had ceased injecting drugs during the period of HCV treatment, and are therefore not infectious during periods of treatment. Though data suggest otherwise,³⁰ we conservatively assumed no adaptive immunity for individuals who were re-infected with HCV. Initially, we randomly selected 5% to 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 i :

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

where γ is the force of infection (calibrated separately for HIV & HCV), σ_{ij} is the probability that partners of sharing injection paraphernalia between two partners; A_{ij} is the adjacency matrix of network links in the population; and I_j represents infection status of individual's injecting partner within the network. The HIV and HCV infections were modelled sequentially using two distinct probability of transmission equations based on the formula in (1). 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 behaviors based on Hartford data, and two outcomes for HCV and HIV were simulated. In addition, 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 12–15%, which represents the 95% confidence interval 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:

$$P(I_i(t) \rightarrow S_i(t+1)) = \delta(I_{HIV})\zeta + P(T_i(t, \theta, \varphi))\epsilon \quad (2)$$

where δ is the probability of spontaneous clearance within 6 months (which depends on HCV and HIV coinfection), ζ is the conditional probability of clearance at time $t + 1$ (which we assume is derived from a uniform distribution), $P(T_i(t, \theta, \varphi))$ is the probability that the individual is treated, and ε is the efficacy of treatment. While HCV does not impact HIV progression, HIV decreases the rate at which HCV can undergo spontaneous clearance,^{23,24} as reflected in the parameter δ , which will depend 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 rate θ the treatment scenario, which includes the network coverage parameter φ . Figure 2 contains a visual representation of the model.

Simulation of Various HCV Treatment Scenarios

The effect of seven network treatment strategies on HCV prevalence over 20 years was investigated. HCV treatment efficacy was assumed to be 90%. Population treatment coverage levels of PWID were set to 0, 30, 60, 120 and 240 per 1000 PWID in the network per year, which translates to a fixed number treated per year based on baseline HCV prevalence. For example, when population HCV prevalence is 60% and when treatment coverage is set to 30 per 1000 PWID, this would result in ~47 individuals being treated annually in a network of 1574, or equivalently 5% of the ~944 individuals with chronic HCV infection.

In each treatment efficacy coverage scenario, 10,000 simulations were performed. Infected HIV and HCV participants were scattered randomly, and the transmission model was run for a 10-year and 20-year observation period without interferon-free treatment (status quo). After the baseline prevalence for HCV and HIV achieved saturation, five different treatment strategies were estimated and “no interferon-free treatment” was used as a control to which other strategies were compared. The measured outcome was the difference in the HCV prevalence from the end of the burn-in period to the end of the 10-year and 20-year horizons.

The one control and seven HCV TasP strategies were as follows:

- 0) *Control*: No HCV treatment;
- 1) *Random Treatment Strategy (No Primary Contacts)*: treatment was assigned to a randomly-chosen PWID without any consideration given to the position within their injection network;
- 2) *Random Treatment with 1/2 of Primary Contacts*: treatment was assigned to a randomly-chosen PWID, as well as half of the randomly-chosen individual's injection partners;
- 3) *Random Treatment with All of Primary Contacts*: treatment was assigned to a randomly-chosen PWID, as well as all of the individual's injection partners;
- 4) *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.;

5) *Targeting highest node degree (No Primary Contacts)*: Treatment prioritised on the basis of the individual's number of injection partners

6) *Targeting highest node degree (with 1/2 of 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

7) *Targeting highest node degree (with All of 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.

To simplify the different policy scenarios, we grouped them conceptually into two classes: Random vs Targeting Highest Node Degree; and within the two classes the key difference among scenarios depends on the proportion of network peer's that receive treatment along with the selected individual.

Model Calibration and Validation

Several analyses were performed to verify that the simulated prevalence from our models accurately reflect the average prevalence data reported from the U.S. We ran the HCV/HIV model for the first 10 years without introducing DAA 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 among PWID in different US Metropolitan areas (please refer to Table S3 in the online supplement 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

Sensitivity analyses were performed to determine how model projections change depending on the modeling assumptions and parameter distributions. The sensitivity analyses used US data to first fit the lower and upper bound on HIV prevalence, which ranged from 3% and 20%, in accordance with the US data. 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.

Results

Figures 3 & 4 depicts the impact of expanding HCV treatment coverage on HCV prevalence over the 10-year and 20 years horizons, respectively, stratified by baseline HCV prevalence. The confidence intervals for the means are reported in the on-line supplement for the 10 and 20 year periods (Table S4 & S5). At the highest HCV prevalence (85%), expanding treatment coverage will not appreciably reduce HCV prevalence for any TasP strategy. When

HCV prevalence is 75%, however, increasing treatment coverage from 30 to 60 individuals per 1000 (3% to 6%) per year should reduce HCV prevalence, on average, by 1% to 4% reduction, but expanding treatment coverage from 120 to 240 per 1000 PWID (12%–24%), HCV prevalence should decrease by as much as 50%, on average, depending on the selected TasP strategy (Figure 3). If HCV prevalence is reduced to 60%, strategies that favor treatment coverage expansion for over 120 individuals per 1000 (12%) PWID per year are likely to yield HCV elimination over the 10-year horizon. If, however, HCV prevalence is set at 30%, HCV elimination can be achieved with relatively lower (6%) coverage (60 individuals per 1000 per year).

If the modelling horizon is extended to 20 years (Figure 4), the scenarios in which HCV prevalence is 30% at the 10-year window attain HCV elimination within 20 years. If the baseline prevalence is 60%, HCV elimination is attained within 20 years only if treatment coverage exceeds 60 per 1000 (6%) PWID. In the setting with 75% HCV prevalence, HCV elimination can be attained within 20 years if the treatment coverage is set above 240 per 1000 PWID (24%) and the most optimal strategy is chosen. In the settings with HCV prevalence of 85%, HCV treatment coverage of 240 per 1000 PWID (24%) per year or lower is not likely to yield substantial reduction in 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); The pattern is consistent for both the 10-year and 20-year horizons.

In settings where the HCV prevalence is 75%, and treatment coverage is increased to 24% per year, strategies that are based on random selection outperform strategies based on targeting of network degree, and have the potential to reduce the HCV prevalence to the levels below 10% within 10 years. In the case of random treatment strategies, there were no statistical differences in HCV prevalence reductions between strategies that treat no primary contacts and those that treat either half or all of the primary contacts. 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; on-line appendix).

Sensitivity Analysis

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

This mathematical modeling study contributes to a growing body of literature using various analytical techniques to determine how HCV TasP might contribute to HCV prevalence reduction and even elimination now that cure can be achieved in 90–100% of PWID using DAAs. Impediments to treatment expansion, including costs, restrictions by third-party payers, and clinicians' unwillingness to treat active PWID require strategic planning to improve both individual and public health. We comprehensively assessed 7 HCV TasP strategies from an extensive injection network of PWID using a measurement-calibrated network model of injection partnerships in the U.S. to analyze the HCV and HIV transmissions among an injection-recruited network of PWID. Network-based TasP strategies elsewhere, however, likely yield different results when the network structures differ. This is especially important with differing levels of mean number of injection partners, HCV prevalence levels and presence of HIV infection (please see online supplement).¹⁷ For example, U.S. network data differs from that in Australia where the mean number of sharing-partners (4.2 vs 2.5) and HIV prevalence (9.6% vs 0%) is substantially higher and consequently contributes differentially to HCV transmission. To our knowledge, this is the largest injection network of PWID that models HCV TasP and the only from the U.S. that uses empiric data from dynamic injection networks that has been carefully calibrated to a wide range of network measures, including long-tail degree distribution, as well as clustering. Here, the extensive detail of the injection networks includes not only the frequency of sharing paraphernalia, but also the longevity of injection ties and the duration of drug injection, which has been carefully calibrated based on the empirical data. Further, dynamic elements of injection networks, which have been largely absent from previous network-based modeling studies, are now incorporated into the modeling since injection networks often change over time.

From our model estimates, we can conclude that in dense urban settings where HCV prevalence is high (75% or higher), that any HCV TasP would have little impact in lowering HCV prevalence over a 10-year horizon, unless coverage is greatly expanded. This finding is comparable to previous studies. Durham (2015)¹⁶ for example, finds that treatment coverage

has to exceed 30% of the diagnosed infections among PIWD for HCV to be eliminated within 30 years when the baseline HCV prevalence in PWID is 75%. We find that within 10 years, the most optimal strategy at this HCV prevalence can nearly eliminate HCV as long as coverage is above 24% (240 per 1000 PWID), which implies 32% of HCV-infected would receive treatment per year. If the most optimal strategy is not chosen, however, the decline in HCV prevalence would be minimal. Unlike compartmental (Martin 2013)¹⁵ and network (Rolls 2013)¹⁷ studies outside the U.S., where PWID injection networks differ, we find that modest treatment coverage (e.g., 6% of PWID per year) is not likely to lead to substantial declines in HCV prevalence. In our analysis, where HCV prevalence was set to 60% (the prevalence estimated for PWID within the entire U.S., but recognizes geographical differences), selecting the optimal TasP strategy could eliminate HCV within 10 years by expanding annual treatment coverage to 12%. HCV elimination could, however, be achieved for random treatment selection and coverage of 60 per 1000 PWID (6%) if the treatment horizon was extended to 20 years. If, however, an alternative and less effective strategy were chosen, HCV prevalence would decline, but only by a third, from 60% baseline to approximately 39%. Lower levels of HCV prevalence reduction become even smaller at higher levels of HCV prevalence (e.g., >75%). Comparing our estimates to Hellard (2014),²⁵ who also used network analysis, we also find the impact of random treatment allocation to be higher. In their model, treating 2.5% of PWID may lead to a 10% decline in HCV prevalence over 10 years, yet in a setting with higher average number of injection network partners, we find that the impact of 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 the Echevaria (2015) who calibrated a compartmental in young PWID from Chicago and found 3.5% coverage per year can reduce HCV prevalence from 30% to 15% over 10 years.²⁶ We find similar reductions over 10 years when the random chain TasP strategy uses treatment coverage of 30 per 1000 PWID, but using our network-based model, the most optimal strategy is random treatment selection that reduces HCV prevalence on average by 22%, which is higher than in the Chicago study.

High HCV prevalence (above 85%) levels reduce the effectiveness of the HCV TasP 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 dramatically over the long run, as treatment does not appear to have a sustainable impact over 10-year and 20 year periods. Additional harm reduction such as expansion of Medication Assisted Treatment (MAT) and increased access to Needles and Syringe Programs (NSP) may be necessary to enhance the effectiveness of HCV treatment coverage in setting of high HCV prevalence.

As with previous HCV modeling strategies, we find that random selection of network members performs relatively better than strategies that solely target the node degree.¹⁷ The strategy of treating highest degree first (i.e., those with whom an individual directly injects with) might appear useful, as it has the potential to reduce HCV prevalence; however, the high rates of HCV reinfection render this strategy ineffective, unless near universal treatment coverage is provided. Strategies that favor random allocation across individuals and incorporate treatment of members of the injection network perform more favorably than

strategies that focus solely on the individual. This finding is consistent with the network modeling study in Australia.¹⁷

Despite the many important findings, this study is not without limitations. First, the modeling assumes client acceptance of and adherence to treatment, whereas in reality, many PWID may decline testing, reject treatment or can't afford it. If there are differences in the risk behaviors between those who are spontaneously cleared and those who are never infected, our model does not fully account for individual heterogeneity due to limitations in the available data. Reductions in treatment uptake could potentially translate into lower treatment coverage levels among patients, and potentially higher probability that the HCV prevalence might not be completely eliminated within the projected horizons. The study also assumes that the probability of infection is constant throughout the duration of the infection, and also that those undergoing treatment do not alter their risky behavior. If the probability of infection increases through a rise in risky sharing behavior, a more extensive expansion of treatment coverage might be needed to offset the rise in infections depending the change in the HCV prevalence levels. 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. In addition, the data derived from RDS could have measurement error and errors due to recall bias, yet all recall was limited to the previous 6 months. A degree-corrected block model was designed to overcome this limitation due to its ability to infer structure of the network in the presence of misreported and missing ties.²⁰ Consequently, recall bias was likely minimal, as the sampling frame for most questions did not exceed a 6 months window prior to the interview date. Last, the model does not consider the impact of concurrent addiction treatment scenarios (e.g., with opioid agonist therapies like methadone or buprenorphine), which might reduce the rates of re-infection further than estimated here, making treatment more effective than in the current modeling. For example, recent data from an international study of PWID on opioid agonist therapies showed cure rates that exceeded 90%, even in the setting of ongoing drug use. Nonetheless, findings here suggest contemporary direct-acting antivirals HCV treatment among members of a large injection network is likely to have large preventive benefits, provided that coverage is adequately extended to the members of the at-risk PWID population. Such expanded coverage, however, will require that treatment is affordable and implemented in the context of high HCV prevalence.

Several factors restrict access to DAAs and HCV elimination in PWID, including costs. The high cost of DAAs, however, continues to decrease as more medications reach the market. In the DAA era, costs have markedly reduced from over \$130,000 for treatment to \$26,000, with evidence of further declines. These costs have remained a major impediment to HCV elimination strategies, including restrictions by private and governmental insurance, like requiring prolonged abstinence from drugs, restricting treatment to advanced fibrosis and allowing only specialists to prescribe treatment.²⁷ Furthermore, changes in federal laws that impose the restrictions on state's authority to negotiate prices can also help to accelerate the affordability of DAAs to treat HCV. Continued Medicaid expansion and enrollment under the Affordable Care Act is ideally positioned to allow individuals with low income improved access and affordability of DAAs to many people with HCV, yet these expansion programs

have been uneven throughout the U.S. Analogous programs to the AIDS Drug Assistance Program, which provides HIV medications to low income individuals and reaches approximately one third of people with HIV nationally, would be an important next step to improve access to the DAA's in the U.S. As HCV treatment becomes more affordable, which is evolving as more treatment options become available, cost of treatment will become less of an impediment to TasP strategies. In the absence of such coverage, and especially in the newly described volatile HIV and HCV transmission epidemics that have recently emerged in the U.S., turning the tide on the HCV epidemic will be challenging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context

Evidence before this study

A comprehensive review was conducted in PubMed as well as in Science Direct in October 2016 without date restrictions using the terms “Hepatitis C or HCV”, “Modeling”, “treatment”, and “direct-acting antivirals”. Although several compartmental modeling studies were found, including two for the US, there were five manuscripts from one dataset in Australia that are based on empirically grounded injection networks among people who inject drugs that can be compared to the US context. Most of the modeling studies on HCV treatment are based on compartmental models calibrated to a range of international settings that do not consider an injection network directly, but are based on a series of mixing assumptions that are left untested. As a result, these analyses may not apply to the United States directly. The two compartmental modeling studies published from US settings analyze the impact of HCV treatment scale-up on the reduction of HCV infections, but do not consider additional control (i.e., TasP) policies. In sum, there are practically no modeling studies of HCV transmission that evaluate and compare Treatment as Prevention Strategies. The only study that incorporates social networks and explores treatment as prevention strategies among people who inject drugs is based on Australian injection networks, which have different structural properties relative to networks in other settings, like in the US, including a shorter tailed degree distribution and smaller numbers of injection partners. Moreover, the HCV epidemic in PWID differs markedly in Australia and the U.S. because HIV infection is uncommon in the Australian PWID context.

Value added

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.

Implication of all 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.

Figure 1. The Injection Network among People Who Inject Drugs in Hartford, CT (N=1574)
Legend: 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 – an injection partnership. Green Nodes were sampled directly through recruitment, and red nodes were not recruited into the sample through network referrals.

Figure 2.
Network Model Simulation of HCV and HIV Transmission and Evaluation of Various
Treatment as Prevention Strategies

Figure 3.
Mean HCV Prevalence at the End of the 10-year estimation simulation window (10,000 replications)

Figure 4.
Mean HCV Prevalence at the End of the 20-year simulation window (10,000 replications)

Table 1

Model Parameters Notation, Definitions, Point Estimates & Sampling Bounds, Sources

Parameter	Description	Value	Source
ε	Efficacy of Treatment	90%	11
δ	HCV Spontaneous Clearance Rate	¼ if HIV negative; 0 if HIV positive	28
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: % of the Network of PWID treated	(0%,3%,6%,12%,24%)	Varied
φ	Share of Network Members Treated	(0,1/2, 1)	Varied
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%)	10 ^{††}
ρ_{hiv}	Baseline HIV Prevalence	9% [3–20%] [†]	29
$\rho_{\text{hiv/hcv}}$	Baseline HCV/HIV Coinfection	14% [0–30%] [†]	13

[†]Point Estimate Used in the Main Simulation; Sampling bounds used in the Sensitivity Analysis^{††}Additional sources are contained in the on-line supplement Table S3