HHS Public Access

Author manuscript

Int J Drug Policy. Author manuscript; available in PMC 2025 August 01.

Published in final edited form as:

Int J Drug Policy. 2024 August ; 130: 104539. doi:10.1016/j.drugpo.2024.104539.

Potential impact of curative and preventive interventions toward hepatitis C elimination in people who inject drugs – a network modeling study

Lin Zhu[1,2,*], **William W. Thompson**[3], **Liesl Hagan**[3], **Liisa M. Randall**[4], **Abby E. Rudolph**[5], **April M. Young**[6,7], **Jennifer R. Havens**[6], **Joshua A. Salomon**[2], **Benjamin P. Linas**[8,9]

[1]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[2]Department of Health Policy, School of Medicine, Stanford University, Stanford, CA, USA

[3]Prevention Branch, Division of Viral Hepatitis, Centers for Disease Control and Prevention, GA, USA

[4]Bureau of Infectious Disease and Laboratory Sciences, Massachusetts Department of Public Health, Boston, MA, USA

[5]Department of Epidemiology and Biostatistics, Temple University College of Public Health, Philadelphia, PA, USA

[6]Center on Drug and Alcohol Research, University of Kentucky, Lexington, KY, USA

[7]Department of Epidemiology, College of Public Health, University of Kentucky, Lexington, KY, USA

[8]Section of Infectious Disease, Department of Medicine, Boston Medical Center, Boston, MA, USA

[9]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

Abstract

Background—Injection-equipment-sharing networks play an important role in hepatitis C virus (HCV) transmission among people who inject drugs (PWID). Direct-acting antiviral (DAA)

[*]Corresponding author: Lin Zhu, MBBS, PhD, Department of Health Policy, School of Medicine, Center for Health Policy, Freeman Spogli Institute for International Studies, Stanford University, 615 Crothers Way, Encina Commons, Office 113, Stanford, CA 94305-6006, linzhu1@stanford.edu.

Author Contributions:

LZ, WT, LH, LR, JS, and BP have contributed to the conceptualization of the study; LZ, JS, BP have contributed to methodology and funding acquisition; AR, AY, and JH have contributed to data curation; LZ developed the model, performed formal analysis and visualization; LZ wrote the original draft of the manuscript; All authors have contributed to review and editing.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention, or the authors' affiliated institutions.

Declarations of interest: We declare no conflict of interest.

treatments for HCV infection and interventions to prevent HCV transmission are critical components of an overall hepatitis C elimination strategy, but how they contribute to the elimination outcomes in different PWID network settings are unclear.

Methods—We developed an agent-based network model of HCV transmission through the sharing of injection equipment among PWID and parameterized and calibrated the model with rural PWID data in the United States. We modeled curative and preventive interventions at annual coverage levels of 12.5%, 25%, or 37.5% (cumulative % of eligible engaged), and two allocation approaches: random vs targeting PWID with more injection partners (hereafter 'degree-based'). We compared the impact of these intervention strategies on prevalence and incidence of HCV infections. We conducted sensitivity analysis on key parameters governing the effects of curative and preventive interventions and PWID network characteristics.

Results—Combining curative and preventive interventions at 37.5% annual coverage with degree-based allocation decreased prevalence and incidence of HCV infection by 67% and 70% over two years, respectively. Curative interventions decreased prevalence by six to 12 times more than preventive interventions, while curative and preventive interventions had comparable effectiveness on reducing incidence. Intervention impact increased with coverage almost linearly across all intervention strategies, and degree-based allocation was always more effective than random allocation, especially for preventive interventions. Results were sensitive to parameter values defining intervention effects and network mean degree.

Conclusion—DAA treatments are effective in reducing both prevalence and incidence of HCV infection in PWID, but preventive interventions play a significant role in reducing incidence when intervention coverage is low. Increasing coverage, including efforts in reaching individuals with the most injection partners, preventing reinfection, and improving compliance and retention in preventive services can substantially improve the outcomes. PWID network characteristics should be considered when designing hepatitis C elimination programs.

Keywords

people who inject drugs; hepatitis C; social network; simulation model; direct-acting antiviral treatment; harm reduction

Background

The advent of highly effective and well tolerated direct-acting antiviral (DAA) treatments for hepatitis C virus (HCV) infection (Gane, et al., 2013; Poordad, et al., 2013) has raised prospects for the elimination of hepatitis C. In 2015, it is estimated that 71 million people globally lived with chronic HCV infection (WHO, 2017). In 2016, the World Health Organization has set goals to reduce new HCV infections by 90% and reduce HCV-related deaths by 65% by 2030 (WHO, 2016). In the United States, it is estimated that more than 2.4 million people had hepatitis C over 2017 to 2020 (Hall, et al., 2024), and people who inject drugs (PWID) face high risks of HCV infection, accounting for 67% of new HCV infections (Trickey, et al., 2019). The ongoing opioid crisis in the United States has led to increased incidence of HCV infection in recent years, and rural regions have been disproportionally affected (CDC, 2021a, 2021b; Zibbell, et al., 2018), contributing to an urgent need for effective control strategies for HCV infection especially in rural PWID populations.

There are two essential dimensions to hepatitis C elimination strategies among PWID (WHO, 2016). The first dimension is to treat and cure HCV infections to reduce mortality and morbidity and interrupt transmission through the use of DAA treatments (Metzig, et al., 2017; Zelenev, Li, Mazhnaya, Basu, & Altice, 2017). The second dimension is to reduce the risk of HCV transmission among PWID through preventive interventions that decrease exposure via shared injection equipment. Prevention includes harm reduction interventions such as syringe services programs (SSPs) and medications for opioid use disorder (MOUD) (Wilson, Donald, Shattock, Wilson, & Fraser-Hurt, 2015). Studies have shown that engagement in MOUD reduced incidence of HCV infection (Jordan, et al., 2020; Minoyan, et al., 2020; Palmateer, et al., 2022; Platt, et al., 2018), and that combining MOUD and SSPs can substantially reduce HCV transmission (Platt, et al., 2018), with somewhat weaker evidence on the effectiveness of SSPs alone in reducing HCV transmission among PWID (Palmateer, et al., 2022; Platt, et al., 2018). Ultimately, the most effective hepatitis C elimination strategy may involve both curative and preventive interventions; however, evidence on the impact of different interventions as well as how this impact may vary by PWID populations is currently limited.

Mathematical modeling studies have previously examined the impact of hepatitis C control interventions among PWID. In general, these studies have found that the most effective hepatitis C elimination strategies include some type of combined approach (Fraser, et al., 2018; Heffernan, Cooke, Nayagam, Thursz, & Hallett, 2019; Martin, Hickman, Hutchinson, Goldberg, & Vickerman, 2013; Pitcher, Borquez, Skaathun, & Martin, 2019). Most of these studies used compartmental models, which are well suited for high-level evaluation such as projecting population-level outcomes for a country. However, compartmental models typically adopt relatively strong structural assumptions, for example that the risk of transmission is the same for all PWID or varies between a limited number of risk groups, which may affect the modeled outcomes. HCV is transmitted through the injection-equipment-sharing network among PWID, and therefore, incorporating details of the network can also enable evaluation of network-based interventions (Bansal, Grenfell, & Meyers, 2007; Hellard, et al., 2014; Johnson & Geffen, 2016; Metzig, et al., 2017; Sacks-Davis, et al., 2012).

Agent-based network models have incorporated heterogeneous injection-equipment-sharing behaviors and transmission risks among individuals to evaluate local elimination strategies among PWID networks. Many such models have evaluated “treatment as prevention (TasP)” strategies but have not included preventive interventions (Bellerose, et al., 2019; Hellard, et al., 2015; Metzig, et al., 2017; Rolls, et al., 2013; Zelenev, et al., 2017). One recent network modeling study of an urban PWID network concluded that scale-up of TasP was the most effective strategy for micro-elimination, while scale-up of opioid agonist therapies was important when TasP coverage was low (Zelenev, Li, Shea, Hecht, & Altice, 2020).

Injection network characteristics can vary greatly between locations. Generally, PWID have fewer injection partners and lower access to interventions including DAA treatments and SSPs in rural areas compared to urban areas (Barranco, et al., 2022; Dombrowski, 2020; Du, Wang, Kong, Riley III, & Jung, 2021; Welch-Lazoritz, et al., 2017). In this study, we focus on comparative evaluation of the impact of curative and preventive interventions on hepatitis

C elimination in a rural PWID network setting. This evaluation examines the impact of different intervention coverage levels and allocation approaches, along with possible variations in intervention effects and PWID network characteristics, to illuminate the potential contributions of different interventions as components of hepatitis C elimination strategies for rural PWID.

Methods

Data

We analyzed data from the Social Networks among Appalachian People (SNAP) study (Havens, et al., 2013; Young, Rudolph, & Havens, 2018), to characterize the demographics and injection-equipment-sharing network characteristics in a rural PWID network. SNAP is a cohort study of people who use drugs in rural Eastern Kentucky, which has a high burden of opioid-related overdose and HCV infection (Havens, et al., 2013; Havens, et al., 2011). This rich dataset provides unique details on the social relationships between the participants. Participants in the SNAP study were recruited through respondent-driven sampling between 2008 and 2010 and followed up at six-months intervals. Participants reported up to 24 people with whom they used drugs, had sex, or received social support in the past six months. Fuzzy look-up was used to cross-reference the names of reported alters with those of participants to produce possible matches based on name similarity (Young, et al., 2018). We analyzed data from a subsample of 287 SNAP participants who reported recent (past 6 months) injection drug use, and we used the baseline data (most complete and accurate on partnerships based on personal communication with the investigators) to describe the injection network. We defined the partnership as an injection equipment sharing partnership if at least one member of the pair reported sharing needles or cookers with the other. We used two years' follow-up data to estimate prevalence and incidence of HCV infection for model calibration. The mean age of the PWID sample was 32 years, 59% were male, 94% were non-Hispanic white, and all reported ever using opioids. The injection network characteristics and HCV measures are summarized in Table 1.

Network Model

We used exponential random graph models (ERGMs) (Hunter, Handcock, Butts, Goodreau, & Morris, 2008), which predict the probability that any two individuals in the population share injection equipment based on individual-, dyad-, and network-level attributes, to simulate the injection-equipment-sharing network. The target network statistics used to estimate ERGM coefficients were derived from the SNAP data and literature review (Table 1). Figure 1 shows one simulated baseline network in our main analysis (we generated multiple networks that incorporated stochasticity with ERGM for the analysis).

Natural history of HCV infection

At each monthly time step, the model evaluates each partnership in a random order. If the HCV infection status (i.e., RNA positivity) of the two individuals is discordant, HCV transmission can occur based on a transmission probability. We calibrated the monthly transmission probability per HCV-discordant partnership to match the seroconversion incidence rate estimated from the SNAP data (Table 1): we first ran simulations with a series

of transmission probabilities between 0 and 1 and compared the simulated seroconversion incidences to the estimated incidence in SNAP. To generate a distribution of incidence rates that include the SNAP estimate, the range of transmission probabilities for sero-discordant pairs was determined to be between 0.03 and 0.06 per month. We then used a Bayesian approach for model calibration, in which we ran 10,000 simulations with transmission probabilities sampled from a uniform distribution across that range and calculated the likelihood for each run with a Poisson distribution. We finally calculated the mean of the 10,000 transmission probabilities weighted by their likelihood, which equals 0.031 per discordant tie per month. During the first six months after acute infection, individuals have a cumulative spontaneous clearance rate of 25% before transitioning to chronic infection (Smith, Jordan, Frank, & Hagan, 2016).

Curative and preventive interventions

We used DAA treatments to represent curative interventions. We assumed that HCV viral suppression starts in the first month of treatment (Gane, et al., 2013) and therefore individuals are not infectious after the start of DAA treatment. We also assumed that PWID may reduce drug use and equipment-sharing during and after DAA treatment, and assigned a relative risk of 0.34 of the primary infection risk during and after DAA treatment in the main analysis according to results from systematic reviews (Esmaeili, et al., 2017; Hajarizadeh, et al., 2020; Valencia, et al., 2019) (altered in sensitivity analysis).

From the perspective of HCV transmission, preventive interventions reduce exposure to HCV via reduced injection drug use and/or reduced sharing of injection equipment. We modeled the effect of preventive interventions by reducing monthly HCV transmission probabilities between the individuals engaging in preventive interventions and their sero-discordant partners. Further, we modeled a limited duration for participation in preventive interventions to account for attrition (Rudolph, Upton, McDonald, Young, & Havens, 2019; Rudolph, Upton, Young, & Havens, 2020). In sensitivity analyses, we relaxed these assumptions to explore their impact on hepatitis C elimination outcomes. All parameters relating to curative and preventive interventions are summarized in Table 1.

Intervention strategies, allocation approaches, and coverages

We simulated three intervention strategies: 1) curative intervention without preventive intervention (“curative alone”), 2) preventive intervention without curative intervention (“preventive alone”), 3) curative and preventive interventions (“curative + preventive”), as well as a no-intervention “status quo”. Since individuals eligible for curative and preventive interventions are different -- only those with current HCV infection are eligible for curative intervention but all PWID are eligible for preventive intervention -- to meet the coverage for both in the “curative + preventive” strategy, we assigned curative and preventive interventions to individuals independently. We did not explicitly model any curative or preventive interventions in the status quo scenario, which were uncommon during the period over which the baseline SNAP data were collected (Fraser, et al., 2019). However, any baseline interventions were already reflected in the modeled network; for example, PWID who engage in SSPs would report fewer partnerships, which would be reflected as lower mean degree in the modeled network.

For each intervention strategy, we compared two allocation approaches: 1) randomly assigning the interventions to PWID, noted as “random”, and 2) preferentially assigning the interventions to those with higher degree (i.e., more equipment-sharing partners), noted as “degree-based”. Degree-based allocation was implemented in the model by inducing correlation between each individual’s probability of being selected for intervention and that individual’s degree (i.e., using degree as the sampling weight).

Lastly, for each intervention strategy and allocation approach, we simulated three annual coverage levels of 12.5%, 25%, and 37.5%, which represent the cumulative percentage of eligible individuals receiving the interventions. Only individuals with current HCV infection are eligible for curative interventions, and all PWID are eligible for preventive interventions. Individuals who have completed curative or preventive interventions could be selected again when becoming eligible. PWID were selected for the interventions gradually over time: for example, in our main analysis, a network of 1000 PWID with an HCV-antibody positivity of 59% at baseline (59%×75% with current HCV infection), 25% annual coverage of curative interventions equals to approximately nine (1000×59%×75%×25%/12) individuals receiving DAA per month. Similarly, approximately 21 (1000×25%/12) individuals would begin to engage in preventive interventions per month, and the total number of PWID currently engaged in preventive interventions would increase from zero to 250 over the first 12 months, and equilibrate (due to initiations and drop outs) at 250 afterwards since the engagement duration was 12 months. Of note, PWID who do not have any injection-equipment-sharing partners (37%) are also eligible for preventive interventions, but because the modeled effect of preventive interventions is reduced transmission probability, preventive interventions assigned to these individuals would have no effect on HCV transmission.

Time horizon and simulation

The average duration of injection equipment sharing partnerships in the SNAP sample is unknown, but the average duration of knowing each other among the equipment sharing partners was 10 years, which is the same as reported in another study in Hartford, Connecticut (Zelenev, et al., 2017). Based on these relatively stable average partnership durations, we used a static network model which does not capture partnership turnover or other population dynamics, and we focused on short-term outcomes over a two-year time horizon. We performed 1000 simulation iterations for each intervention scenario, with parameter values fixed across iterations within a given intervention scenario, but allowing for stochasticity across multiple iterations that use the same parameter values. In each iteration, we pre-drew a random order of the partnerships that would be evaluated for HCV transmission for each time step, and used this same partnership order matrix across different intervention strategies in the iteration to reduce stochastic error. We also pre-drew the potential transmission event for each partnership at each time step randomly for each iteration. If HCV infection status were discordant in a partnership at a given time step, the model would refer to this transmission matrix to determine whether transmission would occur. In each of the 1000 iterations, we used the fitted ERGM to initiate a new network, and conducted one simulation for each intervention scenario.

Outcome measures and analyses

At each time step we recorded numbers of HCV-positive individuals, numbers of incident infections (including new infections and re-infections), and numbers of susceptible individuals. We converted these numbers to prevalence at the end of year two, cumulative person-years of infection and incidence rates (per 100 person-year-at-risk) over two years. We then calculated the relative reduction (i.e., percentage reduction) in person-years of infection and incidence rates for each intervention strategy compared to the status-quo and plotted means and 95% confidence intervals of the relative reductions over 1000 iterations.

Sensitivity analyses

We did not model any specific preventive intervention because in this study we focus on comparing the potential impact of curative vs preventive interventions and how intervention effect parameters and other factors affect the outcomes. In real world practice, different interventions have different mechanisms of preventive effect; for example, SSPs and supervised injection sites reduce the sharing of injection equipment, MOUD reduce overall drug use, people who are serviced by SSP may receive linkage to MOUD, etc. These nuances and potential variation between programs may lead to different effects on reducing HCV transmission. To quantify the sensitivity of results to uncertainty around effects of curative and preventive interventions, we altered the relative risk of infection during and after DAA treatment, the percentage reduction in transmission probability while engaging in preventive interventions, and the duration of preventive intervention engagement, in each case using values that are 50% higher or 50% lower than the values used in the main analysis.

To evaluate the impact of variation in rural PWID networks on hepatitis C elimination outcomes, we first conducted a literature review on rural PWID networks in the United States. Based on this review, we selected a range of alternative values for parameters governing population size, HCV infection prevalence, mean degree (average number of injection partners per person), ratio of mean degree between HCV antibody positive and negative PWID, percentage of sero-discordant partnerships, and transitivity (i.e., “a friend’s friend is more likely to be a friend” phenomenon on injection partnerships, represented by density of partnership triangles), and simulated 12 alternative networks that varied each of these parameters one at a time (Table 1). For parsimony given that results were qualitatively similar across different coverage levels and allocation approaches, we present the impact on the intervention strategy of curative + preventive interventions with 25% annual coverage and degree-based allocation in the main text for the sensitivity analyses and included results of all coverage levels and allocation approaches in the Supplement.

Results

Main analysis

In the status-quo scenario, the prevalence of HCV infection increased from 45% at baseline to 57% by the end of the two-year simulation, and there were a cumulative 1074 person-years of infection and 120 incident infections representing an incidence rate of 12.4 per 100 person-years at-risk in the simulated network of 1000 PWID over two years. The most

intensive strategy examined (curative + preventive at 37.5% annual coverage with degree-based allocation) led to the greatest reductions in all the HCV-related outcomes, reducing prevalence to 19% (relative reduction of 67%) by the end of year two, reducing person-years of infection to 681 (37%), and reducing incidence rate to 3.8 per 100 person-years-at-risk (relative reduction of 70%) over two years.

Figure 2 shows the relative reductions in person-years of HCV infection and incidence rates compared to the status quo for all scenarios, which varied interventions, coverage levels, and allocation approaches. The intervention impact (relative reductions) increased with coverage levels almost linearly across different interventions and allocation approaches. Degree-based allocation was more effective than random allocation in all intervention scenarios, and the differences were more substantial for preventive interventions than curative interventions. For person-years of infection, curative alone led to six to 12 times greater reductions compared to preventive alone across different coverage levels and allocation strategies. For incidence, the difference between curative and preventive interventions was relatively modest, and the order of comparison changed depending on coverage: preventive interventions were more effective than curative interventions when coverage was lower, and curative interventions were more effective at higher coverage levels.

Sensitivity analyses

Figure 3a shows the impact of parameters defining effect of curative and preventive interventions on the relative reductions in person-years of infection and incidence rate compared to status quo. Varying the parameter values by 50% resulted in absolute value changes in relative reductions of less than 2% for person-years of infection, and 6% to 15% for incidence rate. The variations in curative and preventive intervention effects could change the comparative results on incidence reductions between curative and preventive interventions in the main analysis. For example, if relative risk of infection after DAA treatment decreased by 50% (less reinfection), curative interventions would become more effective than preventive interventions in reducing incidence. Similarly, if relative risk of infection while engaging in preventive interventions increased by 50% or if engagement duration of preventive interventions decreased by 50%, preventive interventions would be less effective than curative interventions in reducing incidence.

As shown in Figures 3b and 3c, varying characteristics of the PWID network could alter person-years and incidence of HCV infection both without (Figure 3b) and with curative + preventive interventions (Figure 3c) compared to the base-case scenario in the main analysis. For example, increases in mean degree, initial prevalence of HCV infection, or percentage of sero-discordant partnership would lead to increased person-years of infection and incidence in the population without any intervention. In addition, mean degree had a substantial impact on the relative reductions in person-years of infection and incidence: the relative reductions were smaller in networks with higher mean degree and greater in networks with lower mean degree. The impact of other parameters was relatively modest; population size and transitivity had minimal impact both without and with intervention.

Discussion

In this study we evaluated the potential impact of both curative and preventive interventions on hepatitis C elimination among PWID using a network simulation model. We compared a range of strategies that included combinations of interventions for treating HCV infections and for reducing exposures to infection risk, and with varying levels of intervention coverage and allocation strategies that were either random or targeted toward those with greater numbers of injection partners. We performed sensitivity analysis on key parameters governing intervention effects as well as PWID network characteristics.

Among the evaluated strategies, curative + preventive interventions with degree-based allocation and 37.5% annual coverage achieved the greatest reduction in both prevalence and incidence of HCV infection, decreasing prevalence by 67% by the end of year two, and decreasing person-years of infection by 37% and incidence rate by 70% over two years. Our finding that both curative and preventive interventions are required to maximize impact is consistent with previous studies (Fraser, et al., 2019; Fraser, et al., 2018; Martin, et al., 2013), but we reach that conclusion through a network modeling approach, in which the transmission risk for an individual is dependent on their equipment-sharing partners and hence heterogeneous across the population. Fraser, et al. used a compartmental model to project prevalence and incidence of HCV infection among PWID from 2017 to 2030 with three intervention strategies in Perry County, Kentucky. Although our modeled interventions and time horizon are different, the relative reductions per year with similar intervention components and coverage levels are comparable (Fraser, et al., 2019).

Our study provides insight into the roles that curative and preventive interventions could play in seeking to achieve hepatitis C elimination. We show that although preventive interventions also reduce person-years of infection by reducing incident infection, curative interventions are substantially more effective, which reflects the fact that HCV treatment quickly addresses prevalent HCV infection, preventing multiple years of infected person-time and reducing the infection risk for their partners while they are HCV-negative. However, our results also show that although reinfection risk after treatment is lower than the risk of primary infection, HCV treatment has less impact on reducing incidence than preventive interventions when coverage is low. It is therefore very important that hepatitis C elimination plans combine preventive interventions with HCV treatment to control HCV transmission.

Our study also provides potential insight into the role of leveraging network effects by allocating interventions to PWID with more equipment-sharing partners. Previous modeling work has reported inconsistent results. For example, one study found that targeting HCV peer education services to PWID with the highest degree led to three times more HCV infections averted over a 10-year period than allocating the intervention randomly (Fu, Gutfraind, & Brandeau, 2016). However, another study by Zelenev et al. demonstrated that assigning DAA treatment randomly to PWID is on average more effective than targeting individuals with the most equipment-sharing partners (Zelenev, et al., 2017). Our study found that degree-based allocation was more effective for both curative and preventive interventions, but the difference was greater for preventive interventions. An important

difference between our model assumptions and the second study mentioned (Zelenev, et al., 2017) is that we assumed reduced risk of reinfection after DAA treatment (relative to primary infection) based on meta-analyses of primary infection and reinfection after treatment among PWID (Esmaeili, et al., 2017; Hajarizadeh, et al., 2020). In a sensitivity analysis where we increased the risk of reinfection by 50%, random allocation of curative interventions at coverage of 12.5% became more effective than degree-based allocation (Table S1), consistent with the study by Zelenev and colleagues. In an additional simulation where we assumed reinfection risk was equal to the risk of primary infection, random allocation of curative interventions was also more effective with the higher coverage levels. These findings explain why the previous studies came to different conclusions: the effect of the allocation approach may be different depending on the type of intervention. PWID with higher degrees are more likely to transmit and acquire HCV, thus are at higher priority for any intervention that reduces transmission risks, including harm reduction services and DAA treatment with a protection benefit for reinfection. At the same time, however, since PWID with a higher degree are also more likely to be reinfected after they are treated and cured, prioritizing high degree individuals for DAA treatment without preventing reinfection is less efficient. In the current study we did not consider the possible peer influence on partner's behaviors (e.g., secondary syringe exchange) and uptake of interventions, which may play a role in the effectiveness of prioritizing higher degree individuals (Rudolph, et al., 2019). And there are more aspects to consider such as ethics and equity when making real-world decisions on this choice.

Eligibility and health plan coverage for DAA treatment varies, with some plans requiring abstinence from substance use prior to treatment whereas others do not, which may affect people's injecting behavior during and after DAA treatment. The impact on injecting and equipment-sharing behaviors (compliance) and engagement duration (retention) of preventive interventions may also vary. Our findings show that variations in parameters governing effect of the interventions could substantially affect their impact on reducing incidence, emphasizing the importance of preventing reinfection after DAA treatment, and improving compliance and retention of preventive interventions. In our model, we assigned curative and preventive interventions independently to individuals in the curative + preventive strategy. In real-world practice, programs such as SSPs could be used to refer people to HCV treatment, so the overlap between curative and preventive interventions could be higher than by random. Given the same coverage level, we don't expect the extent of overlap to substantially alter the impact on prevalence and incidence of HCV infection, however, preventing reinfection among the cured individuals especially for those with more advanced fibrosis may increase the overall quality-adjusted life years and decrease the overall mortality.

Our sensitivity analyses on PWID network characteristics show that mean degree of a PWID network had the highest impact on the reduction of both person-years and incidence of HCV infection. PWID studies often collect information on number of injection partners. Our findings suggest that when this information is available for a PWID population, it should be considered in the design of hepatitis C elimination programs. For example, for a denser PWID network like those typical in large cities, more coverage of interventions is needed to achieve the same reduction in prevalence and incidence compared to sparser networks.

There are several limitations in our study. First, we modeled a static network and a closed population. In reality, entries and exits of PWID might change the population composition, and injection partnerships can change, although the average duration of injection partnerships reported in the SNAP PWID sample and another urban PWID sample were both 10 years (Rudolph, Upton, McDonald, Young, & Havens, 2020; Zelenev, et al., 2017). Therefore, we limited our simulations to a two-year time horizon instead of providing a long-term prediction toward hepatitis C elimination. With longer-term interventions, the prevalence and incidence of HCV infection can further decrease. Second, we model a single transmission probability across all HCV-discordant partnerships, ignoring differences in behaviors, like sharing frequency and type of equipment shared. A number of network simulation models take the same approach (Metzig, et al., 2017; Zelenev, et al., 2017), while others model equipment-sharing probability as a fraction of injection probability, which may vary between individuals (Rolls, et al., 2013). We chose to simplify transmission dynamics in this manner to avoid additional assumptions on the different transmission probabilities of different types of sharing (e.g., sharing needle vs. sharing cotton used to prepare drugs). We calibrated the transmission probability to the prevalence and incidence over only two years, which could be biased due to the small number of calibration targets. A cohort study estimated the transmission probability per sharing event to be 0.57%, with a weighted mean of 51 sharing events per year, the monthly transmission probability would be 0.024, compared to 0.031 in our study (Boelen, et al., 2014). Third, we included a selected number of network statistics that are considered important for disease transmission and available from the SNAP data, not incorporating other network characteristics could potentially affect the distribution of transmission. Fourth, our model and the sensitivity analyses on network characteristics are mostly based on data from rural PWID population. In future work it will be useful to expand the model to include urban PWID to see if findings are comparable. However, as PWID networks consist of distinct populations and their interconnections, caution should always be taken to generalize results between different PWID populations.

Conclusion

Hepatitis C elimination strategies for rural PWID require expanded access to HCV treatment, and also infrastructure to complement HCV treatment with preventive interventions such as harm reduction services especially when treatment coverage is low. DAA treatments are effective in reducing both HCV infection prevalence and incidence, but efforts to prevent ongoing transmission risk are required to maximize its impact. Increasing intervention coverage, taking efforts to deliver preventive interventions to those with more injection-equipment-sharing partners, and improving compliance and retention to preventive interventions can substantially improve the outcomes of hepatitis C elimination interventions. PWID network characteristics including average number of injection partners could substantially affect the intervention outcomes and should be considered when designing hepatitis C elimination programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement:

We would like to thank Jianing Wang, Shayla Nolen, Golnaz Eftekhari Yazdi, Christian Testa, Minttu Ronn, Rebecca Earnest, Meghan Bellerose, Yelena Malyuta, Marissa Reitsma, and Teresa Puente for their help and discussion during the study. We would also like to thank the SNAP Study participants and staff for their contributions to this research.

Funding sources:

This work was supported by the U.S. Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Epidemiologic and Economic Modeling Agreement [U38PS004644, NU38PS004651 to LZ, JS, BL], National Institute on Drug Abuse [R01DA033862, R01DA024598 to AR, AY, JH, R37DA015612 to LZ, JS, K99DA056297 to LZ], and institutional funding for staff at the Massachusetts Department of Public Health [to LR].

References

Abadie R, Welch-Lazoritz M, Gelpi-Acosta C, Reyes JC, & Dombrowski K (2016). Understanding differences in HIV/HCV prevalence according to differentiated risk behaviors in a sample of PWID in rural Puerto Rico. Harm reduction journal, 13, 10. [PubMed: 26956029]

Abdul-Quader AS, Feelemyer J, Modi S, Stein ES, Briceno A, Semaan S, Horvath T, Kennedy GE, & Des Jarlais DC (2013). Effectiveness of structural-level needle/syringe programs to reduce HCV and HIV infection among people who inject drugs: a systematic review. AIDS and Behavior, 17, 2878–2892. [PubMed: 23975473]

Bansal S, Grenfell BT, & Meyers LA (2007). When individual behaviour matters: homogeneous and network models in epidemiology. Journal of the Royal Society Interface, 4, 879–891. [PubMed: 17640863]

Barranco MA, Rosenberg ES, Flanigan C, Shufelt S, Bruce EM, Wilberschied LA, Parker MM, Duncan E, & Udo T (2022). A cross-sectional study of hepatitis C prevalence and correlates among persons who inject drugs in rural and non-rural communities. Journal of viral hepatitis, 29, 994–1003. [PubMed: 35925950]

Bellerose M, Zhu L, Hagan LM, Thompson WW, Randall LM, Malyuta Y, Salomon JA, & Linas BP (2019). A review of network simulation models of hepatitis C virus and HIV among people who inject drugs. International Journal of Drug Policy, 102580. [PubMed: 31740175]

Boelen L, Teutsch S, Wilson DP, Dolan K, Dore GJ, Lloyd AR, Luciani F, & investigators H (2014). Per-event probability of hepatitis C infection during sharing of injecting equipment. PloS one, 9, e100749. [PubMed: 25000496]

Campbell EM, Jia H, Shankar A, Hanson D, Luo W, Masciotra S, Owen SM, Oster AM, Galang RR, & Spiller MW (2017). Detailed transmission network analysis of a large opiate-driven outbreak of HIV infection in the United States. The Journal of infectious diseases, 216, 1053–1062. [PubMed: 29029156]

CDC. (2021a). Number and rate* of newly reported cases† of chronic Hepatitis C virus infection, by demographic characteristics — United States, 2021.

CDC. (2021b). Numbers and rates* of reported cases† of acute Hepatitis C virus infection, by demographic characteristics — United States, 2017–2021. In.

Dombrowski K (2020). Disease Risk Network Topologies Among People who Inject Drugs in Rural Puerto Rico. In Vermont Center for Behavioral Health Fall 2020 Conference.

Du P, Wang X, Kong L, Riley III T, & Jung J (2021). Changing urban–rural disparities in the utilization of direct-acting antiviral agents for hepatitis C in US Medicare patients, 2014–2017. American Journal of Preventive Medicine, 60, 285–293. [PubMed: 33221144]

Duncan I, Habecker P, Abadie R, Curtis R, Khan B, & Dombrowski K (2017). Needle acquisition patterns, network risk and social capital among rural PWID in Puerto Rico. Harm reduction journal, 14, 69. [PubMed: 29047371]

Esmaeili A, Mirzazadeh A, Carter GM, Esmaeili A, Hajarizadeh B, Sacks HS, & Page KA (2017). Higher incidence of HCV in females compared to males who inject drugs: a systematic review and meta-analysis. Journal of viral hepatitis, 24, 117–127. [PubMed: 27790803]

Fraser H, Vellozzi C, Hoerger TJ, Evans JL, Kral AH, Havens J, Young AM, Stone J, Handanagic S, & Hariri S (2019). Scaling up hepatitis C prevention and treatment interventions for achieving elimination in the United States: a rural and urban comparison. American journal of epidemiology, 188, 1539–1551. [PubMed: 31150044]

Fraser H, Zibbell J, Hoerger T, Hariri S, Vellozzi C, Martin NK, Kral AH, Hickman M, Ward JW, & Vickerman P (2018). Scaling-up HCV prevention and treatment interventions in rural United States—model projections for tackling an increasing epidemic. Addiction, 113, 173–182. [PubMed: 28734093]

Fu R, Gutfraind A, & Brandeau ML (2016). Modeling a dynamic bi-layer contact network of injection drug users and the spread of blood-borne infections. Mathematical biosciences, 273, 102–113. [PubMed: 26775738]

Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, & Berrey MM (2013). Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. New England Journal of Medicine, 368, 34–44. [PubMed: 23281974]

Gindi RM, Rucker MG, Serio-Chapman CE, & Sherman SG (2009). Utilization patterns and correlates of retention among clients of the needle exchange program in Baltimore, Maryland. Drug and Alcohol Dependence, 103, 93–98. [PubMed: 19464827]

Grande KM, Stanley M, Redo C, Wergin A, Guilfoyle S, & Gasiorowicz M (2015). Social network diagramming as an applied tool for public health: Lessons learned from an HCV cluster. American journal of public health, 105, 1611–1616. [PubMed: 25689190]

Grau LE, Zhan W, & Heimer R (2016). Prevention knowledge, risk behaviours and seroprevalence among nonurban injectors of southwest Connecticut. Drug and alcohol review, 35, 628–636. [PubMed: 27073014]

Grebely J, Raffa JD, Lai C, Krajden M, Conway B, & Tyndall MW (2007). Factors associated with spontaneous clearance of hepatitis C virus among illicit drug users. Canadian Journal of Gastroenterology and Hepatology, 21, 447–451.

Habecker P, Abadie R, Welch-Lazoritz M, Reyes JC, Khan B, & Dombrowski K (2018). Injection partners, HCV, and HIV status among rural persons who inject drugs in Puerto Rico. Substance use & misuse, 53, 1128–1138. [PubMed: 29166134]

Hajarizadeh B, Cunningham EB, Valerio H, Martinello M, Law M, Janjua NZ, Midgard H, Dalgard O, Dillon J, & Hickman M (2020). Hepatitis C reinfection after successful antiviral treatment among people who inject drugs: A meta-analysis. Journal of hepatology, 72, 643–657. [PubMed: 31785345]

Hall EW, Bradley H, Barker LK, Lewis K, Shealey J, Valverde E, Sullivan P, Gupta N, & Hofmeister MG (2024). Estimating hepatitis C prevalence in the United States, 2017–2020. Hepatology, 10.1097.

Havens JR, Lofwall MR, Frost SD, Oser CB, Leukefeld CG, & Crosby RA (2013). Individual and network factors associated with prevalent hepatitis C infection among rural Appalachian injection drug users. American journal of public health, 103, e44–e52.

Havens JR, Oser CB, Knudsen HK, Lofwall M, Stoops WW, Walsh SL, Leukefeld CG, & Kral AH (2011). Individual and network factors associated with non-fatal overdose among rural Appalachian drug users. Drug and Alcohol Dependence, 115, 107–112. [PubMed: 21126831]

Heffernan A, Cooke GS, Nayagam S, Thursz M, & Hallett TB (2019). Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. The Lancet, 393, 1319–1329.

Hellard M, McBryde E, Davis RS, Rolls DA, Higgs P, Aitken C, Thompson A, Doyle J, Pattison P, & Robins G (2015). Hepatitis C transmission and treatment as prevention–The role of the injecting network. International Journal of Drug Policy, 26, 958–962. [PubMed: 26072105]

Hellard M, Rolls DA, Sacks-Davis R, Robins G, Pattison P, Higgs P, Aitken C, & McBryde E (2014). The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. Hepatology, 60, 1861–1870. [PubMed: 25163856]

Hofer H, Watkins-Riedel T, Janata O, Penner E, Holzmann H, Steindl-Munda P, Gangl A, & Ferenci P (2003). Spontaneous viral clearance in patients with acute hepatitis C can be predicted by repeated measurements of serum viral load. Hepatology, 37, 60–64. [PubMed: 12500189]

Hunter DR, Handcock MS, Butts CT, Goodreau SM, & Morris M (2008). ergm: A package to fit, simulate and diagnose exponential-family models for networks. Journal of statistical software, 24, nihpa54860.

Johnson LF, & Geffen N (2016). A comparison of two mathematical modeling frameworks for evaluating sexually transmitted infection epidemiology. Sexually transmitted diseases, 43, 139–146. [PubMed: 26859800]

Jordan AE, Cleland CM, Wyka K, Schackman BR, Perlman DC, & Nash D (2020). Hepatitis C virus incidence in a cohort in medication-assisted treatment for opioid use disorder in New York City. The Journal of infectious diseases, 222, S322–S334. [PubMed: 32877567]

Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, & Vickerman P (2013). Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clinical Infectious Diseases, 57, S39–S45. [PubMed: 23884064]

Metzig C, Surey J, Francis M, Conneely J, Abubakar I, & White PJ (2017). Impact of Hepatitis C Treatment as Prevention for People Who Inject Drugs is sensitive to contact network structure. Scientific Reports, 7, 1833. [PubMed: 28500290]

Micallef J, Kaldor J, & Dore G (2006). Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. Journal of viral hepatitis, 13, 34–41. [PubMed: 16364080]

Minoyan N, Artenie AA, Zang G, Jutras-Aswad D, Turcotte M-È, & Bruneau J (2020). Harm reduction coverage and hepatitis C incidence: findings from a cohort of people who inject drugs. American Journal of Preventive Medicine, 58, 845–853. [PubMed: 32444003]

Palmateer N, Hamill V, Bergenstrom A, Bloomfield H, Gordon L, Stone J, Fraser H, Seyler T, Duan Y, & Tran R (2022). Interventions to prevent HIV and Hepatitis C among people who inject drugs: latest evidence of effectiveness from a systematic review (2011 to 2020). International Journal of Drug Policy, 109, 103872. [PubMed: 36202039]

Patel MR, Foote C, Duwve J, Chapman E, Combs B, Fry A, Hall P, Roseberry J, Brooks JT, & Broz D (2018). Reduction of injection-related risk behaviors after emergency implementation of a syringe services program during an HIV outbreak. JAIDS Journal of Acquired Immune Deficiency Syndromes, 77, 373–382. [PubMed: 29271829]

Pitcher AB, Borquez A, Skaathun B, & Martin NK (2019). Mathematical modeling of hepatitis c virus (HCV) prevention among people who inject drugs: A review of the literature and insights for elimination strategies. Journal of theoretical biology, 481, 194–201. [PubMed: 30452959]

Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, Jordan A, Degenhardt L, Hope V, & Hutchinson S (2018). Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. Addiction, 113, 545–563. [PubMed: 28891267]

Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, Heckaman M, Larsen L, Menon R, & Koev G (2013). Exploratory study of oral combination antiviral therapy for hepatitis C. New England Journal of Medicine, 368, 45–53. [PubMed: 23281975]

Rolls DA, Sacks-Davis R, Jenkinson R, McBryde E, Pattison P, Robins G, & Hellard M (2013). Hepatitis C transmission and treatment in contact networks of people who inject drugs. PloS one, 8, e78286. [PubMed: 24223787]

Rudolph AE, Upton E, McDonald MJ, Young AM, & Havens JR (2019). Peer influence of injection drug use cessation among dyads in rural eastern Kentucky. International Journal of Drug Policy, 102604. [PubMed: 31740176]

Rudolph AE, Upton E, McDonald MJ, Young AM, & Havens JR (2020). Peer influence of injection drug use cessation among dyads in rural eastern Kentucky. International Journal of Drug Policy, 85, 102604. [PubMed: 31740176]

Rudolph AE, Upton E, Young AM, & Havens JR (2020). Social network predictors of recent and sustained injection drug use cessation: findings from a longitudinal cohort study. Addiction.

Sacks-Davis R, Daraganova G, Aitken C, Higgs P, Tracy L, Bowden S, Jenkinson R, Rolls D, Pattison P, & Robins G (2012). Hepatitis C virus phylogenetic clustering is associated with the

social-injecting network in a cohort of people who inject drugs. PloS one, 7, e47335. [PubMed: 23110068]

Smith DJ, Jordan AE, Frank M, & Hagan H (2016). Spontaneous viral clearance of hepatitis C virus (HCV) infection among people who inject drugs (PWID) and HIVpositive men who have sex with men (HIV+ MSM): a systematic review and meta-analysis. BMC infectious diseases, 16, 1–13. [PubMed: 26729246]

Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'hUigin C, Kidd J, Kidd K, Khakoo SI, & Alexander G (2009). Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature, 461, 798–801. [PubMed: 19759533]

Thrash C, Welch-Lazoritz M, Gauthier G, Khan B, Abadie R, Dombrowski K, De Leon SM, & Rolon Colon Y (2018). Rural and urban injection drug use in Puerto Rico: Network implications for human immunodeficiency virus and hepatitis C virus infection. Journal of ethnicity in substance abuse, 17, 199–222. [PubMed: 28665196]

Trickey A, Fraser H, Lim AG, Peacock A, Colledge S, Walker JG, Leung J, Grebely J, Larney S, & Martin NK (2019). The contribution of injection drug use to hepatitis C virus transmission globally, regionally, and at country level: a modelling study. The Lancet Gastroenterology & Hepatology, 4, 435–444. [PubMed: 30981685]

Valencia J, Alvaro-Meca A, Troya J, Cuevas G, Gutiérrez J, Morro A, Alvarez J, Pulido L, Cañamares I, & Escobar I (2019). High rates of early HCV reinfection after DAA treatment in people with recent drug use attended at mobile harm reduction units. International Journal of Drug Policy, 72, 181–188. [PubMed: 31253391]

Welch-Lazoritz M, Habecker P, Dombrowski K, Villegas AR, Davila CA, Colón YR, & De León SM (2017). Differential access to syringe exchange and other prevention activities among people who inject drugs in rural and urban areas of Puerto Rico. International Journal of Drug Policy, 43, 16–22. [PubMed: 28160735]

WHO. (2016). Global health sector strategy on viral hepatitis 2016–2021. Geneva: World Health Organization.

WHO. (2017). Global hepatitis report 2017: World Health Organization.

Wilson DP, Donald B, Shattock AJ, Wilson D, & Fraser-Hurt N (2015). The cost-effectiveness of harm reduction. International Journal of Drug Policy, 26, S5–S11. [PubMed: 25727260]

Young AM, Crosby RA, Oser CB, Leukefeld CG, Stephens DB, & Havens JR (2012). Hepatitis C viremia and genotype distribution among a sample of nonmedical prescription drug users exposed to HCV in rural Appalachia. Journal of medical virology, 84, 1376–1387. [PubMed: 22825816]

Young AM, Rudolph AE, & Havens JR (2018). Network-based research on rural opioid use: an overview of methods and lessons learned. Current HIV/AIDS Reports, 15, 113–119. [PubMed: 29457200]

Zelenev A, Li J, Mazhnaya A, Basu S, & Altice FL (2017). Hepatitis C virus treatment as prevention in an extended network of people who inject drugs in the USA: a modelling study. The Lancet Infectious Diseases.

Zelenev A, Li J, Shea P, Hecht R, & Altice FL (2020). Modeling Combination HCV Treatment and Prevention Strategies in a Network of People Who Inject Drugs in the USA. Clinical Infectious Diseases.

Zibbell JE, Asher AK, Patel RC, Kupronis B, Iqbal K, Ward JW, & Holtzman D (2018). Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. American journal of public health, e1–e7.

Zibbell JE, Hart-Malloy R, Barry J, Fan L, & Flanigan C (2014). Risk factors for HCV infection among young adults in rural New York who inject prescription opioid analgesics. American journal of public health, 104, 2226–2232. [PubMed: 25211717]

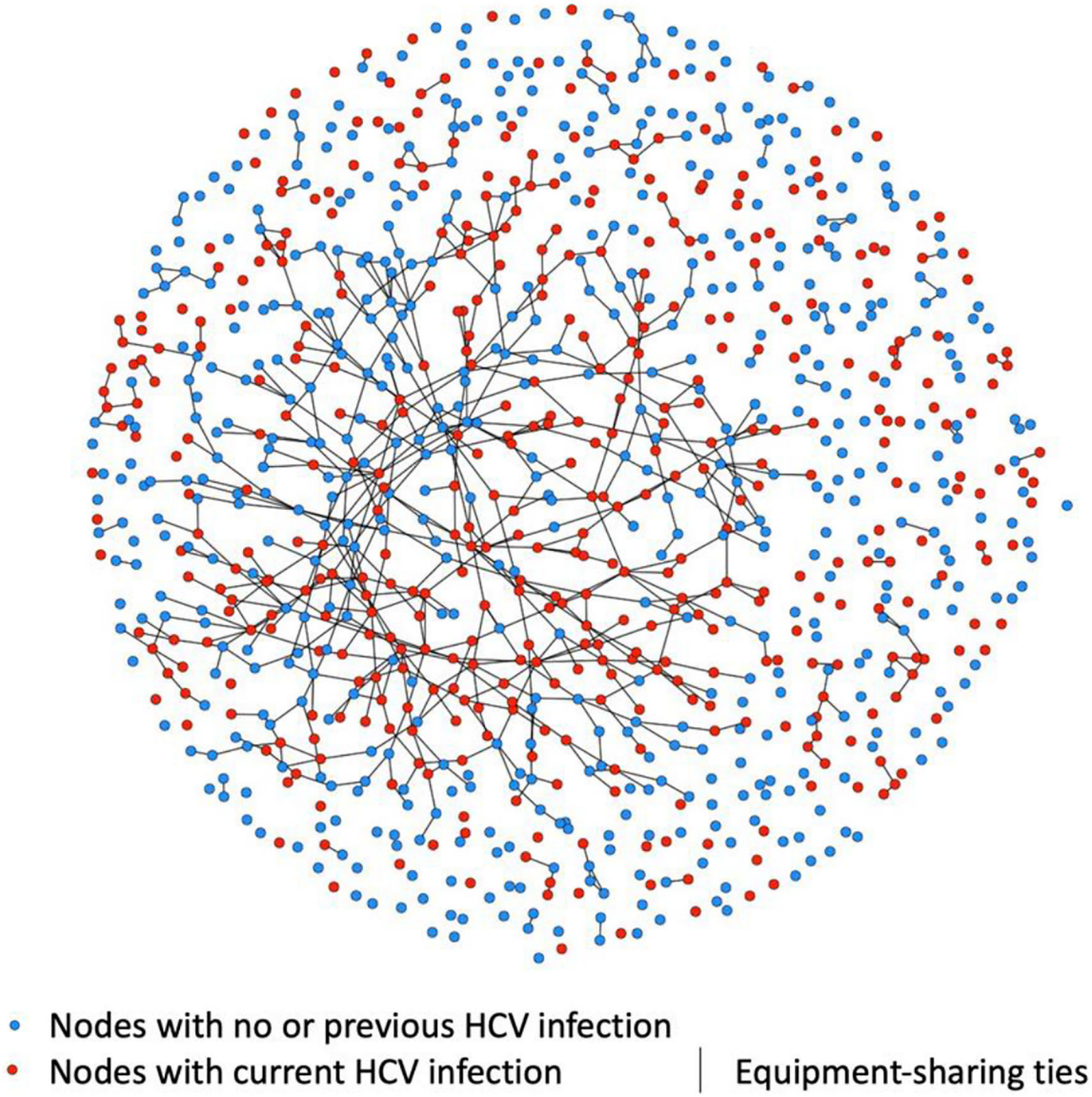

Figure 1. PWID network graph for the main analysis

The graph shows an example of the injection network in our main analysis. PWID (the nodes) either with current HCV infection (red) or non or previous HCV infection (blue) are connected with injection-equipment-sharing partnerships (ties).

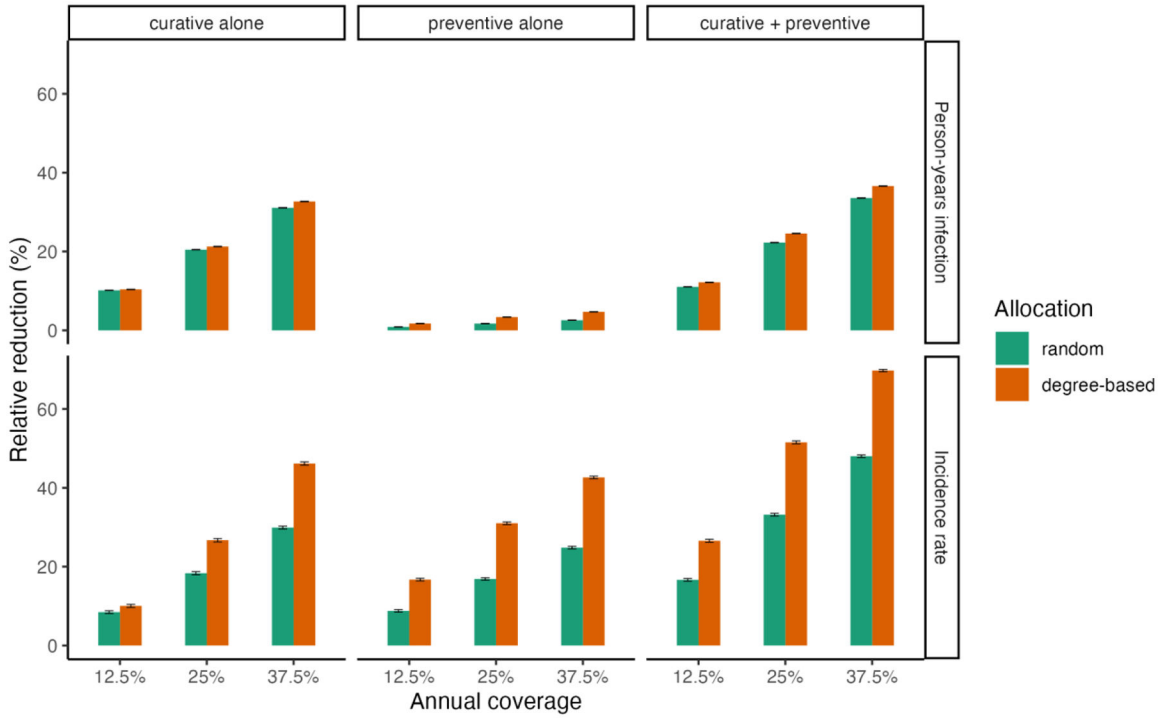

Figure 2. Relative (percentage) reductions in person-years of HCV infection and incidence rate over two years among the simulated PWID network with different intervention strategies, coverage levels, and allocation approaches

The results of relative reductions (y-axis) are presented by outcome measures (row titles), intervention strategies (column titles), coverage levels (x-axis), and allocation approaches (colors). In each panel, the bars and error bars show the means and 95% CI over 1000 iterations of model simulation.

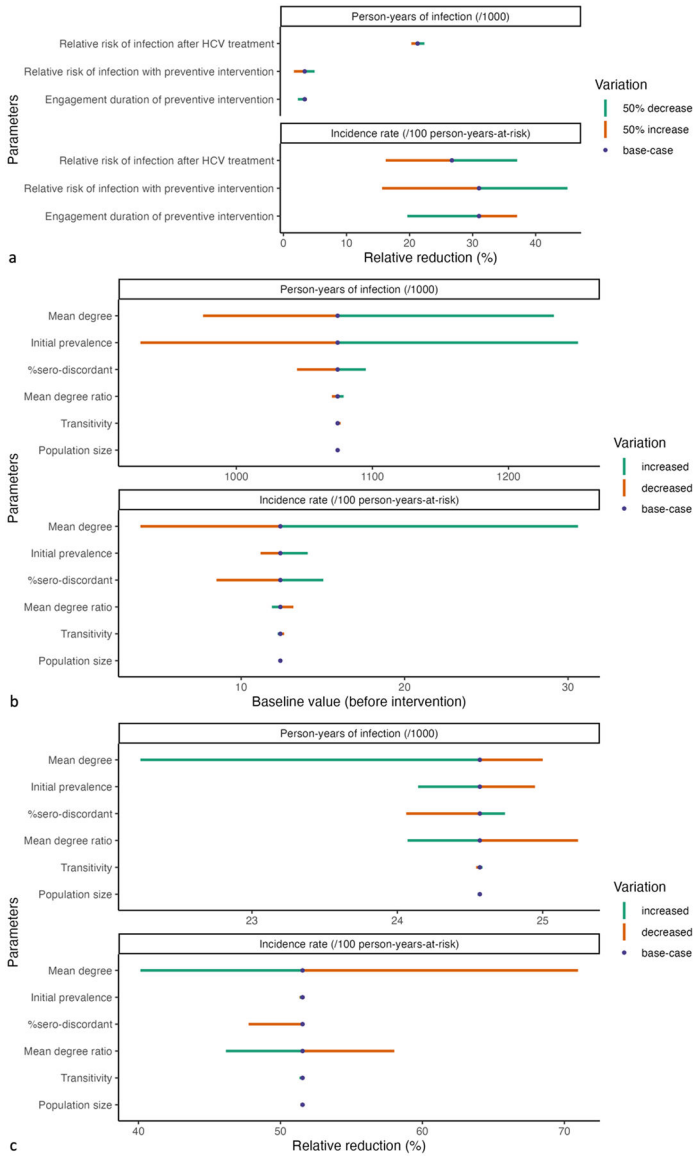

Figure 3. Impact of curative and preventive intervention effect parameters and network parameters on person-years and incidence of HCV infection

Figure 3a presents results for person-years of infection in the upper panel and incidence rate in the bottom panel. In each panel, the parameters varied in the sensitivity analysis are shown as row labels, and the value axis shows relative reductions in the outcomes in relation to differences in the parameter values. For each parameter, the point in the middle represents the relative reduction for a corresponding intervention ("curative alone" for curative intervention parameters, "preventive alone" for preventive intervention parameters) in the main analysis (base-case), and the endpoints of lines represent relative reductions when the parameter value was varied from the base-case level (variation noted by line colors). The results are from interventions at an annual coverage of 25% and degree-based allocation, results of other coverage levels and allocation approaches are qualitatively similar (summarized in the Supplement Figure S1).

Figure 3b presents results for person-years of infection in the upper panel and incidence rate in the bottom panel. In each panel, the parameters varied in the sensitivity analysis are shown as row labels, and the value axis shows baseline values (before intervention) of the outcome under variation in parameter values. For each parameter, the point in the middle represents the baseline value of the corresponding outcome in the main analysis (base-case), and the endpoints of lines represent the baseline values of the corresponding outcomes when the parameter value was varied from the base-case level (variation noted by line colors). Figure 3c presents results for person-years of infection in the upper panel and incidence rate in the bottom panel. In each panel, the parameters varied in the sensitivity analysis are shown as row labels, and the value axis shows relative reductions in the outcomes in relation to differences in the parameter values. For each parameter, the point in the middle represents the relative reduction after intervention in the main analysis (base-case), and the endpoints of lines represent relative reductions when the parameter value was varied from the base-case level (variation noted by line colors). The results are from curative + preventive at an annual coverage of 25% and degree-based allocation, results of other coverage levels and allocation approaches are qualitatively similar (summarized in the Supplement Figure S1).

Table 1

Model parameter values

Parameters	Main analysis	Sensitivity analyses	References
Network simulation			
Population size	1000	500, 2000	Expert opinion
Baseline HCV antibody positivity, %	59	50, 70	SNAP, (Grande, et al., 2015; Grau, Zhan, & Heimer, 2016; Habecker, et al., 2018; Zibbell, Hart-Malloy, Barry, Fan, & Flanigan, 2014)
Mean degree (i.e., average number of partners * per person)	1.43	0.5, 3	SNAP, (Abadie, Welch-Lazoritz, Gelpi-Acosta, Reyes, & Dombrowski, 2016; Campbell, et al., 2017; Duncan, et al., 2017; Grande, et al., 2015; Grau, et al., 2016; Habecker, et al., 2018; Thrash, et al., 2018; Zibbell, et al., 2014)
Isolates, % (i.e., individuals with no partners *)	37	NA	SNAP
Ratio of mean degree * between HCV antibody (+) and (−) PWID	1.73	1, 3	SNAP, (Abadie, et al., 2016; Zibbell, et al., 2014)
HCV sero-discordant partnerships *, %	29	15, random ‡	SNAP, expert opinion
Transitivity (triangle density †)	0.28	random ‡, 0.4	SNAP, expert opinion
HCV transmission and natural history			
HCV seroconversion incidence rate, per 100 person-year-at-risk §	24.8	-	SNAP
Monthly transmission probability per HCV-discordant partnership	0.031	-	Calibrated
HCV spontaneous clearance, %	25	-	(Grebely, et al., 2007; Hofer, et al., 2003; Micallef, Kaldor, & Dore, 2006; Smith, et al., 2016; Thomas, et al., 2009; Young, et al., 2012)
Interventions			
DAA efficacy (cure rate), %	95	-	(Gane, et al., 2013; Poordad, et al., 2013)
DAA treatment duration, months	3	-	(Gane, et al., 2013; Poordad, et al., 2013)
Relative risk of HCV infection and transmission during and after DAA treatment ¶	0.34	0.17, 0.51	(Esmaeili, et al., 2017; Hajarizadeh, et al., 2020; Valencia, et al., 2019), expert opinion
Relative reduction in transmission probability while engaged in preventive interventions	0.5	0.25, 0.75	(Abdul-Quader, et al., 2013; Patel, et al., 2018), expert opinion
Duration of engagement in preventive interventions, months	12	6, 18	(Gindi, Rucker, Serio-Chapman, & Sherman, 2009), expert opinion

Abbreviation: HCV, hepatitis C virus; PWID, people who inject drugs; SNAP, Social Networks among Appalachian People.

* Partnerships defined as injection-equipment-sharing partnerships

† There were 7% of partnership triangles (three PWID sharing injection equipment with each other) that are closed, i.e., number of triangles divided by number of 2-stars (two PWID sharing with another common PWID). We transformed the measure as proportion of partnerships that belongs to at least one triangle, corresponding to normalized geographically weighted edge-wise shared partner (GWESP(0)) in ERGM.

‡ For these network variations, we did not find information from literature to specify the ranges for sensitivity analyses. In nature, when there is more serosorting, percentage of discordant partnership would be lower and we hence used half of the main analysis value as the lower bound; since no heterophily (individuals prefer to partner with individuals with different infection status) has been observed, we used random (i.e., excluding this term in ERGM, letting discordant partnerships to emerge at random) as the upper bound, and the average percentage of discordant partnership in simulated networks with this setting was 0.41. Similarly, we used random as the lower bound for transitivity, and the mean in the simulated networks was 0.006.

[§]The SNAP study collected HCV antibody testing results. To calculate seroconversion incidence, only those who were HCV antibody negative were counted as susceptible (denominator), and those who were newly infected but spontaneously cleared would still be counted in the numerator because they would still develop antibody. These make the value greater than the true HCV infection incidence as shown in our simulation results.

[¶]The relative risk is applied to the transmission probability. We used incidences of reinfection and primary infection in the two systematic reviews to calculate the relative risk.