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Scaling-up Hepatitis C Prevention and Treatment Interventions for Achieving Elimination in the United States – a Rural and Urban Comparison

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Conflict of Interest:

NKM and PV have received unrestricted research grants from Gilead unrelated to this work, and NKM has received honoraria from Merck, AbbVie, and Janssen. MH has received honoraria unrelated to this work from Merck, Abbvie and Gilead. HF has received an honorarium from MSD. JS has received a conference attendance sponsorship from Gilead. KP has received research grant funding from Gilead unrelated to this work. JW, SH, AY, CV, AK, JZ and TH declare no conflict of interest.

Running head: Interventions for achieving HCV Elimination in the US

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Abbreviations

DAA - direct-acting antivirals
HCV – Hepatitis C virus
HR – harm reduction
MAT - medication-assisted treatment
NHBS - National HIV Behavioural Surveillance
PWID – people who inject drugs
SNAP - Social Networks Among Appalachian People
SSP - syringe service programs
UHS – Urban Health Study
WHO – World Health Organisation

Abstract: (200 words)

In the U.S. Hepatitis C virus (HCV) transmission is increasing among people who inject drugs (PWID). Many regions have insufficient prevention intervention coverage. Using modelling, we investigate the impact of scaling-up prevention and treatment interventions on HCV transmission among PWID in Perry County, Kentucky (PC), and San Francisco, California (SF), where HCV sero-prevalence among PWID is >50%. A greater proportion of PWID access medication-assisted treatment (MAT) or syringe service programs (SSP) in urban SF (established community) than rural PC (young, expanding community). We model the proportion of HCV-infected PWID needing HCV-treatment annually to reduce HCV-incidence by 90% by 2030, with and without MAT scale-up (50% coverage, both settings) and SSP scale-up (PC only) from 2017. With current MAT&SSP coverage during 2017-2030, HCV-incidence will increase in PC (21.3 to 22.6 per 100 person-years (/100pyrs)) and decrease in SF (12.9 to 11.9/100pyrs). With concurrent MAT&SSP scale-up, 5%/year of HCV-infected PWID need HCV-treatment in PC to achieve incidence targets; 13%/year without MAT&SSP scale-up. In SF, a similar proportion need HCV-treatment (10%/year) irrespective of MAT scale-up. Reaching the same impact by 2025 requires increases in treatment rates of 45-82%. Achievable provision of HCV-treatment, alongside MAT&SSP scale-up (PC) and MAT scale-up (SF), could reduce HCV-incidence.

Keywords: direct-acting-antiviral HCV-treatment; Hepatitis C virus; medication-assisted treatment; modelling; persons who inject drugs; syringe service programs;

An estimated 3.5 million individuals are infected with hepatitis C virus (HCV) in the United States (U.S)[1], with annual mortality rates greater than for HIV[2]. In the U.S., over 80% of HCV transmission occurs among people who inject drugs (PWID)[3].

Harm reduction (HR) services for PWID such as medication-assisted treatment (MAT) and syringe service programs (SSPs) can reduce the risk of HCV acquisition[4,5]. All-oral direct-acting antivirals (DAA) cure HCV in 8-12 weeks[6,7]. Modelling from non-U.S. settings[8-13] has shown scaling-up HR alongside DAAs could substantially reduce the HCV-burden. This is crucial for achieving the World Health Organization (WHO) and U.S. National Academies of Sciences, Engineering and Medicine (NASEM)[14] HCV elimination targets of reducing HCV incidence by 90% by 2030[14-16].

The availability of HR services[17-19] varies across the U.S., with some cities having established SSPs[20,21] whilst other settings having none[17,18,22]. PWID demographics and their associated HCV transmission patterns[23,24] also vary geographically. Most large cities have established PWID populations[25] and stable HCV infection rates, while rural settings have an expanding younger demographic of PWID[22] with increasing HCV transmission[24]. This expansion is particularly acute in Appalachia, where the prevalence of injecting and rate of new HCV infections have increased 3-fold between 2006-2012[24,26].

In this study, we model the epidemic situation among PWID in San Francisco (California) and Perry County (Kentucky), capturing differences in HR availability, HCV epidemiology, and injecting drug use dynamics. In line with WHO and the U.S. National Academies of Sciences, Engineering and Medicine HCV-elimination strategies[14,15], we project the required

scale-up of HR interventions and HCV-treatment to decrease HCV incidence in these settings by 90% by 2030 and 2025.

METHODS

Model description

We developed two deterministic HCV transmission models among PWID (see Web Figures 1-4); one for each setting. The models differed in several ways due to differences in data availability.

The modelled PWID population in both sites was stratified by risk status (high-risk defined as sharing works (syringes/cottons/cookers) in past 6 months), intervention status (on MAT and/or SSP or neither) and HCV infection status. PWID demographics differed between the sites; with the Perry County model stratifying by injecting duration (<3 and ≥3 years) and the San Francisco model stratifying by age (15-24, 25-29, 30-49 and 50+ years). Both models incorporated time-varying rates of initiating injecting, with PWID leaving due to injecting cessation (unaffected by MAT status) or mortality (drug or non-drug related). Injecting cessation is via temporary cessation in the San Francisco model (if relapse does not occur), but not in the Perry County model due to insufficient data. Due to the long timeframe associated with HCV disease progression and mortality[27] we assumed no additional mortality due to HCV complications or the impact of HIV co-infection on this, with the former confirmed by PWID mortality studies in North America[28,29].

In both settings, individuals initiate injecting as low- or high-risk, HCV susceptible without HR. PWID transition between risk and intervention states over time. HCV transmission occurs at a per-capita rate, dependent on chronic HCV-infection prevalence (RNA-positive), with transmission risk reduced if PWID are on HR interventions[5], but increased if they are high-risk or young/new. Mixing between PWID to form transmission contacts ranges from random to fully like-with-like, either by age or duration of injecting and risk status.

Once infected, some individuals spontaneously clear infection[30,31], moving to the previously infected group, while the remainder develop chronic HCV-infection. Chronic HCV-infection is lifelong unless treated, which typically results in cure (sustained viral response, SVR). We assume all PWID have equal access to treatment irrespective of disease stage because we are modelling to maximise prevention benefits. Cured individuals are susceptible to re-infection at the same level as for primary infection, independent on age, injecting risk and intervention status. Those not cured remain chronically HCV-infected but can be retreated.

Web Appendices 1 and 2 give further model details.

Model parameterisation and calibration

Most model parameters for Perry County and San Francisco are context-specific. Exceptions were the efficacy of MAT and SSP, assumed to individually reduce transmission risk by 50% and 56%, respectively[5], with efficacies multiplied if PWID access both. Both models assumed no HCV-treatment at baseline because local experts suggest treatment for active PWID was negligible before DAAs become available. Model parameters are given in Tables 1-3, with most parameters having uncertainty distributions assigned to them (usually 95% confidence intervals). These distributions were **randomly sampled to give 5,000 parameter**

sets for each setting, with this variability being propagated to the model projections. For each sampled parameter set, unknown model parameters (see below) were estimated through model calibration to data using a non-linear least squares algorithm in MATLAB, giving a large number of **baseline model fits** for each setting. This model calibration was checked to ensure it accurately fit the data.

Perry County, Kentucky

The Perry County model was parameterised primarily using data from the Social Networks Among Appalachian People (SNAP) study, analysed for this project (Table 2)[22]. This on-going longitudinal study of PWID from Perry County started in 2008, initially recruiting through respondent driven sampling. See Web Appendix 1 for details.

[Table 2 here]

The time-varying number of individuals initiating injecting annually and their cessation rate were calibrated to give the estimated PWID population size for Perry County in 2009 (700+/-20%, analysis for this project), while assuming an 8-fold increase in the number of individuals initiating injecting over 1990-2000 (Web Figure 5); consistent with other data[26].

Based on SNAP data, we assumed 14.5% of PWID were high-risk (reported sharing works in last 6 months), with an increased HCV acquisition risk (3.2-fold). Movement of PWID from low- to high-risk was estimated through model calibration while assuming the rate that PWID transition from high to low-risk is 0.47 per year. SNAP data suggested MAT coverage was 4.7% in 2009, but there was no SSP. The recruitment rate onto MAT was derived through calibration to this MAT coverage, while assuming stable coverage and a mean duration on

MAT of 6 months based on SNAP data. We assumed PWID injecting <3 years had greater HCV acquisition risk (2.2-fold) compared to those injecting ≥3years. Because SNAP data[22] suggests 87.3% of PWID injecting ≥3 years have an injection partner that has injected ≥3 years, we assumed this same like-with-like mixing in the model. We assume PWID inject for 5-25 years.

The baseline HCV transmission rate (among low-risk PWID not accessing HR and injecting ≥3years) was estimated through model calibration to the HCV sero-prevalence among those injecting <3 years in 2009 (36.0%). SNAP data on HCV sero-prevalence in those injecting ≥3 years in 2009 and HCV incidence over 2008-2015 (PWID injecting < 3 years or ≥3 years) were used for model validation.

San Francisco, California

The San Francisco model was parameterised with data from the UFO Study [32,33] (young adult PWID <30 years enrolled in prospective follow-up since 2000), the National HIV Behavioural Surveillance (NHBS) System for PWID [17,18,21,34], and the Urban Health Study (UHS)[35] (Table 3). See Web Appendix 2 for details.

[Table 3 here]

The age individuals start injecting came from UHS and NHBS data[17,34], while the temporary cessation rate (cessation incidence 16%/100 pyrs) for PWID <30 years and injecting relapse rates (incidence of relapse 56/100 pyrs for those aged 15-29 and 30/100pyrs for those aged ≥ 30) came from UFO data[36]. The temporary cessation rate of PWID aged ≥30, permanent cessation rate, and time-varying number of individuals initiating injecting annually were

estimated through calibrating the model to the estimated number of PWID aged <30 years (~6,000) and ≥30 years (~20,000) in San Francisco for 2007[25], and the proportion aged ≥30[34].

Time-varying recruitment rates on to MAT and SSP were estimated through calibrating a sub-model to the changing coverage of MAT and SSP, while assuming a duration on MAT/SSP of 1.0 year[37]. Based on UFO data we assumed MAT started in 2000, increased to 2.6% coverage by 2004 and 12.2% by 2015. SSP started in 1989[20], and was assumed to scale-up to high coverage (83.7% obtained needles from a SSP in last month) by 1997[20], and then remain stable[17,18].

Based on UFO data, we assumed 61.1% of PWID were high-risk (reported sharing works in last 6 months) pre-2002 and 48.3% post-2002, with an increased HCV acquisition risk (1.6-fold – UFO data analysis). Movement of PWID from low- to high-risk pre-2002 and post-2002 was estimated through model calibration whilst assuming the rate PWID transition from high- to low-risk is 1.6 annually (UFO data), i.e. over 100% generally transition from high- to low-risk in a year.

We estimated baseline model transmission rates (among low-risk PWID not accessing HR) for PWID aged <30 and ≥30 years by calibrating the model to HCV incidence in PWID <30 years for 2000-2001 (25.1 per 100pyrs)[32,38] and HCV sero-prevalence among PWID aged ≥50 years (96.3%) in 1999[35]. Estimates of HCV sero-prevalence in other age-groups were used for model validation. Lastly, because UFO data suggests 58.0% of PWID aged <30 years have an injection partner aged <30 years, we assumed this same like-with-like mixing in the model.

Further information on the model parameterisation and calibration is in Web Appendices 1 and 2.

Model analyses

The baseline model fits for each setting were used to estimate the impact on chronic HCV prevalence and incidence of scaling-up MAT to 50% coverage and SSP coverage in Perry County to the same as San Francisco (84%) (denoted full harm reduction, full HR), with or without treating 20 or 50 per 1000 (/1000) PWID at any stage of disease progression with DAAs annually, all from 2017 onwards. For each baseline model fit, we then determined the annual HCV-treatment rate required among PWID to decrease HCV incidence by 90% by 2025 or 2030, with or without full HR.

Uncertainty analysis

To ascertain which parameters are important for determining variability in the projections across the baseline model fits, a linear regression analysis of covariance (ANCOVA)[39] was performed on the projected initial percentage of chronically HCV-infected PWID needing HCV-treatment each year to reduce incidence by 90% by 2030 with full HR. The proportion of the sum of squares contributed by each parameter was calculated to determine each parameters' importance to the variability in our projections.

RESULTS

Baseline epidemic projections and illustrative examples

For Perry County, 5,000 baseline model fits were obtained (see Figure 1, Web Appendix 3 and Web Figures 6 and 7), with 90% of these fits lying within the 95% confidence intervals (95%CI) of one of the validation data points (see methods) and 33.6% lying within two or more.

For Perry County, the model projected that chronic HCV prevalence and incidence fell from 1990 due to increasing susceptible PWID entering the population. Chronic HCV prevalence then increased post-2000 as the PWID population began to stabilise (Figure 1). HCV chronic prevalence is estimated to be 59.5% in 2017, and without intervention scale-up, is projected to increase to 65.0% by 2030. Similarly, from 2017-2030, HCV incidence will increase from 21.3 to 22.6 per 100pyrs (/100pyrs). Conversely, with full HR scale-up from 2017, HCV chronic prevalence and incidence will decrease by 35.3% (95% credibility interval (95%CrI) 12.7-71.5%) and 77.0% (95%CrI 47.6-92.2%) by 2030, respectively. Additionally, treating 20/1,000 or 50/1,000 PWID annually with DAAs (equivalent to 3.4% or 8.3% of chronic HCV-infections being treated in the first-year, Web Table 1) would decrease incidence to low-levels, by 86.0% (95%CrI 60.1-99.4%) or 99.2% (95%CrI 79.7-100.0%) over 2017-2030, respectively.

[Figure 1 here]

For San Francisco, 997 baseline model fits were obtained (see Figure 2, Web Appendix 3 and Web Figures 8 and 9), with 89.4% of these model fits lying within the 95%CI of one of the validation data points (see methods) and 37.1% lying within two.

For San Francisco, the model projects that HCV incidence decreased considerably after 1989 due to the scale-up in SSP, with chronic HCV prevalence decreasing more slowly. By 2017,

HCV incidence has stabilised at 12.9/100pyrs and chronic HCV prevalence is projected to be 75.5% (Figure 2). Without intervention scale-up, both are projected to remain stable until 2030. Conversely, scaling-up to full HR will decrease chronic HCV prevalence by 10.7% (95%CrI 7.0-15.8%) and incidence by 30.4% (95%CrI 22.7-37.4%) by 2030. Additionally, treating 20/1,000 or 50/1,000 PWID (equivalent to 2.7% or 6.6% of chronic HCV-infections being treated in the first-year, Web Table 2) would decrease incidence by 56.3% (95%CrI 44.9-63.6%) or 86.9% (95%CrI 75.3-95.7%) by 2030, respectively.

[Figure 2 here]

Treatment scale-up for reaching HCV-elimination targets

With or without full HR scale-up, a 90% reduction in incidence is possible in Perry County and San Francisco by 2030 if sufficient HCV-treatment occurs (Figure 3). In San Francisco, scaling-up to full HR has little impact due to existing moderate to high levels of coverage; with 8-9% of chronically HCV-infected PWID initially needing treatment each year (1,418-1,574 treatments in first year, 56-63/1,000 PWID annually) to reduce incidence by 90% by 2030. Conversely, in Perry County, scaling-up to full HR has more impact, with the resulting HCV-treatment rate being less than San Francisco (4.7% of chronically HCV-infected PWID initially needing treatment each year - 22 treatments in first year or 26.6/1000 PWID per year). However, the treatment is over two-fold greater than this (12.6% - 58 treatments or 73.1/1000 PWID per year) without full HR scale-up. To achieve the same impact by 2025, the initial required treatment rates in both sites need to be increased by 45-60% without full HR or 60-82% with full HR (Figure 3), but the overall cumulative number of PWID needing treatment is similar (Web tables 3 and 4). Table 4 presents all these results with 95% credible intervals, emphasising there is generally more uncertainty in the projected number of PWID

needing treatment to reach the elimination targets than the yearly percentage needing treatment. Similar treatment numbers are needed to achieve a 90% reduction in prevalence (Web Figure 10).

[Figure 3 here]

Uncertainty analysis

For Perry County, uncertainty in the permanent cessation rate contributes to three-quarters of the variation (74%) in the projected yearly percentage of chronically HCV-infected PWID needing HCV-treatment to reach the incidence target (Web Figure 11a). Uncertainty in HCV sero-prevalence in 2009 and heightened transmission risk among recently initiated PWID also account for 15% and 6% of the variation, respectively. Conversely, for San Francisco, uncertainty in the HCV prevalence among PWID aged $\geq$ 50 in 1999 contributes a third (32%) to the variability in the yearly treatment percentage (Web Figure 11b). The level of like-with-like mixing by age, SVR rate, year when the rate of initiation of new injectors decreased, and HCV-incidence amongst PWID aged <30 in 2000-2001 contribute a further 18%, 18%, 14% and 8%, respectively. In both settings, other parameters contribute <5% to the variation.

DISCUSSION

Aligned with the WHO's HCV-elimination strategy, the U.S. National Academies of Sciences, Engineering and Medicine recently developed strategy for the U.S. sets targets to reduce HCV incidence by 90% by 2030. For two U.S. settings, urban San Francisco and rural Perry County, our model projections suggest modest HCV-treatment uptake (<20% of chronic HCV-infections treated annually) could achieve this target by 2030 or 2025. With

concurrent MAT (to 50% of PWID) and SSP (only needed in Perry County, to 84% of PWID) scale-up, only 5-9% of chronically HCV-infected PWID need treating annually to decrease HCV incidence by 90% in both settings by 2030. Conversely, without scaling-up these interventions, higher HCV-treatment rates (13% annually) are needed in Perry County, but not San Francisco. To achieve the same impact by 2025, HCV-treatment rates need to increase by over half in both settings. Encouragingly, recent Australian data suggests these treatment rates are achievable (21% of infected PWID treated in 2016[40]).

With HR scale-up, achieving the HCV incidence elimination target by 2030 will initially require 1,418 annual HCV-treatments among PWID in San Francisco, but only 22 in Perry County (19,019 and 288 overall between 2017-2030). Although these treatment numbers for San Francisco are comparable to the 1,400 planned for 2017, and 2,100 for 2018 and 2019, by the San Francisco Department of Public Health "*End Hep C SF"* initiative[41], these treatment targets are for all groups – illustrating additional treatment scale-up among PWID may be necessary. This will require expanding HCV case-finding and treatment interventions, likely involving MAT and SSP and prison interventions. The feasibility of such strategies is being evaluated in the U.S.[42-44], and are planned by the *End Hep C SF* initiative[41], and in Kentucky. However, their scale-up will be a challenge; HR interventions are limited in most U.S. settings, with about half of PWID not accessing SSP in the last year,[17] and the nearest SSP being on average 37 miles away[19]. Nationwide expansion of HR interventions is necessary to enable scale-up of community-based testing and treatment interventions, requiring substantial additional resources to HCV case-finding and treatment costs. This expansion will have other benefits though[45,46], and will reduce the number of treatments needed to achieve and maintain HCV elimination[47].

Strengths and Limitations

The strength of our modelling is undertaking detailed site-specific models. Unlike previous models evaluating the impact of HCV prevention and treatment interventions[9,10,48], our models incorporate the changing epidemiology of each setting. We use empirical estimates for MAT and SSP efficacy[5], and incorporate how HCV transmission risk differs by other factors, improving the validity of our projections.

Despite this, our modelling is subject to limitations. First, the empirical estimates for efficacy of SSP[5] are uncertain. We used synthesised estimates for SSP from Europe instead of North America as review level evidence from North America suggests little protective benefit of SSP compared to a halving in risk from European studies[5]. Explanations for this difference include differences in measurement of exposure to high coverage SSP, greater confounding by indication in studies from North America (where high-risk PWID are more likely to use SSP[49]), and reduced benefit in stimulant injectors. We assumed European efficacy estimates on the basis that U.S. SSPs should achieve the same impact as in Europe if they are designed in a similar way.

Second, empirical data availability and uncertainties contributed to uncertainty in our model projections. Specifically, although recent HCV incidence estimates were available for San Francisco[38], HCV prevalence estimates were unavailable post-2000[35]. While our model agrees with existing data, only further data collection will confirm whether our model fully captures the current HCV epidemic in San Francisco. Additionally, limited data on PWID population size estimates[25] meant it was difficult to determine changing PWID population dynamics over time. Improved size estimation studies are needed to better understand the changing burden of injecting, critical for assessing their intervention coverage and needs,

particularly during the current opioid crisis. Importantly, even with current levels of data uncertainty, the model still projected important insights on required levels of prevention and treatment needed to eliminate HCV.

Third, we did not model HIV co-infection. While HIV prevalence among PWID is negligible in Kentucky[22], 12% of PWID were HIV-positive in San Francisco in 2012[21]. This should not have affected our projections due to the low incidence of new infections (<1/100pyrs) in San Francisco[50] and low HIV-related mortality[51] because many HIV-infected PWID (66%) are on HIV treatment.[21] Additionally, we did not explicitly model the consequences of HCV on mortality. This was done because it is unlikely to substantially contribute to mortality amongst current PWID as found in previous mortality studies from North America[28,52].

Fourth, we did not model men who have sex with men (MSM) that have heightened HCV risk and may overlap with PWID. This was done because recent data from the NHBS survey suggest that MSM that inject drugs probably have different injecting networks to non-MSM PWID due to differences in the primary drug injected and transmission among MSM frequently being linked to high-risk sexual activities, unlike in PWID[53]. This is supported by phylogenetic analyses from Europe suggesting a separate epidemic of HCV among MSM to PWID[54].

Lastly, we did not model the process through which HCV-treatment scale-up will be undertaken or financed, which needs to be considered in future analyses.

Comparisons with other literature

Previous modelling for non-U.S. settings have estimated the impact of scaling-up HR services, with or without HCV-treatment scale-up[8-11,13]. Recent U.S. modelling studies have considered the impact of HCV-treatment among prisoners[55], and PWID in urban[48] and non-urban settings[47,56]. These have generally not accounted for local heterogeneity, and/or used relatively simple models[47,55]. One study used a more complex network-based model, suggesting comparable treatment rates were needed in their lower prevalence scenario (60% chronic HCV prevalence) as projected for Perry County, but higher treatment rates were needed in their high prevalence scenario (75%) than we projected for San Francisco. The reasons why our model suggested lower treatment rates being needed in San Francisco are uncertain, but could be due to the reductions in HCV incidence that resulted from high SSP availability. Our modelling complements this and other analyses, by undertaking detailed site-specific modelling in two contrasting settings, using longitudinal data to capture changes in their HCV epidemics. This allowed us to consider whether the impact of scaling-up prevention and treatment interventions could vary across urban and non-urban locations in the U.S., typifying the main epidemic types occurring. Importantly, one crucial difference between our model and many previous models[57,58] is that we assume a constant number being treated each year instead of a rate of treatment which decreases as chronic prevalence decreases. Previous modelling[59] has shown the limitation of this latter assumption because it results in much higher treatment rates being initially needed to compensate for large decreases in treatment as prevalence decreases.

Conclusions

Despite the existence of effective harm reduction (HR) interventions[5], the availability of highly effective HCV treatment provides opportunities to augment MAT/SSP programs with

HCV-treatment as prevention strategies[60]. Our modelling can guide these initiatives by projecting the HCV-treatment needed to eliminate HCV infection as a public health threat[8,9,47]. Our study reveals that modest scale-up of HCV-treatment, together with MAT and SSP where needed, can reverse the expanding HCV burden in the U.S, reaching elimination goals in 10-15 years. In urban areas (e.g. San Francisco) with existing moderate to high-coverage of HR services, HCV-treatment should be scaled up to reduce transmission. Conversely, in U.S. settings with low-coverage of HR services[19], scaling-up MAT and SSP is also necessary to reduce incidence of new and re-infections, enhancing the impact of HCV-treatment as prevention strategies. Scaling-up MAT and SSP also enables the expansion of case-finding, necessary to increase HCV-treatment uptake among PWID[61-64]. Field studies are required to demonstrate the feasibility and impact of these strategies, helping inform HR policy changes, so enabling the U.S. to reduce HCV as a public health threat.

Figures

Figure 1: The impact of different intervention scenarios on (a) chronic hepatitis C virus (HCV) prevalence among all people who inject drugs (PWID) and (b) incidence among susceptible PWID over time in Perry County, Kentucky. Median projections for each intervention scenario applied to the baseline model fits are shown with the 95% credibility intervals (95%CrI) only included for the no intervention scale-up scenario for the baseline model fits. Medication-assisted treatment (MAT) is assumed to start between 1990 and 1999 and is scaled-up from 2017 to 50% coverage. Both syringe service programs (SSP) and HCV-treatment are started in 2017, SSP scaling-up to 84% coverage and treatment to either 20/1000 PWID or 50/1000 PWID respectively. The grey points show chronic HCV prevalence and incidence data from the SNAP study, which was not fit to, but is shown for comparison. Note that the model was fit to data on antibody prevalence among those injecting < 3yrs in 2009 (36.0% (22.9-50.8%)). Incidence is estimated among susceptible PWID. In both figures the pale grey area shows the 95%CrI for the no intervention scale-up scenario; the solid black line shows the median of model runs for the no intervention scale-up scenario; the pale grey solid line shows the median of model for scale-up to 84% SSP and 50% MAT coverage (Full harm reduction (HR); the dashed mid-grey line shows the median of model runs for full HR and HCV-treating 20 per 1000 PWID annually; the dot-dashed dark-grey line shows the median of model runs for full HR and HCV-treating 50 per 1000 PWID annually; the solid dark grey dot and vertical line shows the data estimate and it's 95% confidence interval from the Social Networks Among Appalachian People study and the vertical dotted grey line shows the time from when MAT, SSP and HCV treatment are started.

Figure 2: The impact of different intervention scenarios on chronic hepatitis C virus (HCV) prevalence (a) and incidence (b) among people who inject drugs (PWID) over time in San Francisco, California. Median projections for each intervention scenario applied to the baseline model fits are shown with the 95% credibility intervals only included for the no intervention scale-up scenario for the baseline model fits (no intervention scale-up). Syringe service programs (SSP) is assumed to start in 1989 and is stable at a high coverage (84%) from 1997. Medication-assisted treatment (MAT) is assumed to scale-up to 50% coverage from 2017 and HCV-treatment also starts in 2017 with either 20/1000 PWID or 50/1000 PWID treated annually. The model was fit to data on HCV incidence in PWID <30 for 2000-2001 (25.1/100pyrs; 95% CI 18.7-32.9)[32,38] and HCV sero-prevalence among PWID aged ≥50 years (96.3%; 95% CI 94.3-98.7%) in 1999[35]. Incidence is estimated among susceptible PWID. No incidence data estimate shown for the whole PWID population because of a lack of data, whereas an estimated chronic HCV prevalence for the whole population is shown in Figure 2a, which was obtained from an available HCV sero-prevalence data estimate for 1999 by adjusting it for the modelled proportion of antibody positive PWID that have chronic HCV-infection. In both figures the pale grey area shows the 95%CrI for the no intervention scale-up scenario; the solid black line shows the median of model runs for the no intervention scale-up scenario; the pale grey solid line shows the median of model for scale-up to 50% MAT coverage (alongside 84% SSP coverage - full harm reduction (HR); the dashed mid-grey line shows the median of model runs for full HR and HCV-treating 20 per 1000 PWID annually; the dot-dashed dark grey line shows the median of model runs for full HR and HCV-treating 50 per 1000 PWID annually; the vertical dotted grey line in 1989 shows when SSP was scaled-up in San Francisco and the vertical dotted grey line in 2017 shows when we model scale-up of MAT and HCV-treatment from; the solid dark grey dot and vertical line in figure (a) shows the data estimate and 95% confidence interval from the Urban Health Study (UHS).

Figure 3: (a) Annual number needing treatment per 1000 people who inject drugs (PWID) and (b) initial percentage of chronic infections requiring treatment per year to decrease HCV incidence by 90% by 2025 or 2030 in Perry County and San Francisco. Figures show the projected number per 1000 PWID and initial percentage of chronic infections that need to be treated each year to decrease incidence by 90% by 2030 or 2025 in Perry County (Kentucky – solid bars) and San Francisco (California – striped bars), without and with full harm reduction (50% medication-assisted treatment (MAT) and 84% syringe service programs (SSP) coverage). In all figures, bars show the median projections across all baseline model fits for Perry County and San Francisco, and the whiskers show the 95% credibility intervals. The solid bars are for Perry County and striped bars are for San Francisco, with the dark grey showing the number/percentage needed without MAT/SSP scale-up and the light grey showing the number/percentage needed with MAT/SSP scale-up.

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Conflict of Interest:

NKM and PV have received unrestricted research grants from Gilead unrelated to this work, and NKM has received honoraria from Merck, AbbVie, and Janssen. MH has received honoraria unrelated to this work from Merck, Abbvie and Gilead. HF has received an honorarium from MSD. JS has received a conference attendance sponsorship from Gilead. KP has received research grant funding from Gilead unrelated to this work. JW, SH, AY, CV, AK, JZ and TH declare no conflict of interest.

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Tables

Table 1: Shared natural history and intervention related parameters and uncertainty bounds for Perry County, Kentucky and San Francisco, California.

Parameter	Mean	95%CI	Point estimate	Range	Distribution	References
Prevention intervention effectiveness parameters						
Relative risk of acquiring HCV while on MAT[a]	0.5	0.4, 0.63			Log-normal	[5]
Relative risk of acquiring HCV while on SSP[a]	0.44	0.24, 0.80			Log-normal	[5]
HCV-Treatment and clearance parameters						
SVR rate (%)				85–95	Uniform	[7]
Duration of treatment (weeks)			12		N/A	[7]
Treatment start year[b]			2017		N/A	
Average proportion of infections that clear spontaneously				0.22–0.29	Uniform	[30]

Abbreviations: HCV: hepatitis C virus; MAT: medication-assisted treatment; SSP: syringe service programs; SVR: sustained viral response; 95%CI: 95% confidence interval. [a]The relative risk of acquiring HCV while on MAT+SSP is the product of relative risk for MAT and SSP. [b]The treatment number per year is varied depending on scenario.

Table 2: Model parameters and calibration data with uncertainty bounds (usually 95% confidence intervals) for Perry County, Kentucky.

Parameter	Mean	95%CI	Point estimate	Range	Distribution	Source/	Notes
PWID and HCV-related parameters							
HCV seroprevalence among PWID injecting < 3yrs (%)	36.0	22.9, 50.8			Normal	Analysis of SNAP data.	Used to calibrate HCV transmission risk per year (among low-risk PWID not on MAT/SSP and injecting < 3yrs) (0.23; 95%CrI: 0.14-0.39)
HCV seroprevalence among PWID injecting ≥ 3yrs (%)	55.8	50.4, 61.3			Normal	Analysis of SNAP data	
HCV seroprevalence among all PWID (%)	53.3	48.2, 58.3			Normal	Analysis of SNAP data	
HCV incidence per 100 pyrs	18.3	14.9, 22.4			Normal	Analysis of SNAP data	
Population size of PWID[a]				560–840	Uniform	Analysis of SNAP data	Estimated 700 PWID from analysis of SNAP data. Used to calibrate the rate that individuals initiate injecting per year to fit the sampled population size in 2009 and scale-up in injecting post-1990.
Fold increase in number of individuals initiating injecting between 1990 and 2000.			8			Analysis of SNAP data.	Used to calibrate the increase in initiation rate of injecting between 1990 and 2000
Overall duration of injecting (yrs)				5–25	Uniform		Young expanding population of injectors so uncertainty in duration of injecting - wide range assumed.
Overall drug and non-drug mortality rate per year (%)	1.0				Poisson	Analysis of SNAP data	
Rate ratio for acquiring HCV if injecting < 3yrs compared to injecting ≥3yrs	2.2	1.4, 3.6			Log-normal	Analysis of SNAP data	
High-risk parameters							
Percentage of PWID that are high-risk[b] in 2009 (%)	14.5	13.0, 16.2			Normal	Analysis of SNAP data	
Rate that PWID move from high to low-risk per year	0.47	0.3, 0.6			Normal	Analysis of SNAP data	
Rate ratio for acquiring HCV if high risk[b] compared to if low risk	3.2	2.1, 5.0			Log-normal	Analysis of SNAP data	
Proportion of PWID doing like-with-like mixing by risk status (0 means random mixing and 1 means full like-with-like mixing)				0–0.5	Uniform		No data so wide range assumed
Proportion of PWID doing like-with-like mixing by duration of injecting (0				0.4–0.8	Uniform	Analysis of SNAP data.	Fit to give 87.3% of PWID injecting ≥3 yrs inject with PWID injecting ≥3 yrs

means random mixing and 1 means full like-with-like mixing)							
Intervention parameters							
Year MAT started in Perry County				1990–2000	Uniform		
Rate leave MAT/SSP per 100pyrs[c]				132–352	Uniform	Analysis of SNAP data.	Gives 3.5 – 9 months on MAT/SSP.
Coverage of MAT in 2009 (%)	4.7	3.8, 5.8			Normal	Analysis of SNAP data.	Used to find the recruitment rate onto MAT

Abbreviations – PWID: people who inject drugs; HCV: hepatitis C virus; SNAP: Social Networks Among Appalacian People; MAT: medication-assisted treatment; SSP: syringe service programs; 95%CI: 95% confidence interval; 95%CrI: 95% credible interval. [a]The range for PWID population size is +/-20% of the estimated 700 PWID. [b]High-risk is defined as sharing works in the past 6 months. [c]The recruitment rate onto SSP calibrated for the different intervention scenarios – no SSP at baseline in Perry County.

Table 3: Model parameters and calibration data with uncertainty bounds (usually 95% confidence intervals) for San Francisco.

Parameter	Mean	95%CI	Point estimate	Range	Distribution	Source	Notes
PWID and HCV related parameters							
HCV antibody prevalence in 1999 among 15-29yr olds (%)	60.8	53.9, 67.5			Normal	[35]	
HCV antibody prevalence in 1999 among 30-49yr olds (%)	93.4	92.1, 94.6			Normal	[35]	
HCV antibody prevalence in 1999 among 50+ yrs old (%)	96.3	94.3, 98.7			Normal	[35]	Used to calibrate HCV transmission risk per year (among low-risk PWID not on MAT/SSP) in those aged < 30 **(**0.39; 95%CrI: 0.26-0.58) and in those aged ≥ 30 (0.14; 95%CrI: 0.08-0.28)
HCV incidence per 100pyrs in 2001 (< 30yrs)	25.1	18.7, 32.9			Normal	[32]	Used to calibrate HCV transmission risk per year (given above).
Proportion of PWID that start injecting between 15 – 24 yrs old			0.7586		N/A	[34]	Little uncertainty so point estimate used. Calibrated to data on age of first injection from UHS[34] and size estimates
Proportion of PWID that start injecting between 25-29 yrs old			0.1247		N/A	[34]	Little uncertainty so point estimate used. Calibrated to data on age of first injection from UHS[34] and size estimates
Proportion of PWID that start injecting between 30-49 yrs old			0.1167		N/A	[34]	Little uncertainty so point estimate used. Calibrated to data on age of first injection from UHS[34] and size estimates
Number of years in 15-24 yrs age group			7.2 years		N/A	UHS data[34]	15-24 year old PWID stay <10 years in first age group because on average enter at older age than 15
Number of years in 25-29yrs age group			5.0 years		N/A	UHS data[34]	
Number of years in 30-49yrs age group			20.0 years		N/A	UHS data[34]	
Population size of PWID aged 15-29 yrs old				3,052–8,048	Uniform	[25]	
Population size of PWID aged 30+ yrs old				10,988–28,970	Uniform	[25]	
Percentage of 30+yr old PWID that are 30-49 (%)				42.5–52.9	Uniform	[25]	Population size estimates[25] and re-analysis of UHS data to get proportion of 30+ that are 30-49 years old. Used to calibrate the rate that individuals initiate injecting per year
Overall drug and non-drug related mortality rate per year (%)	0.91				Poisson	[65]	
Temporary cessation rate per year for 15-29 yr olds	0.16	0.1, 0.2			Uniform	[36]	

Relapse rate to injecting per year for 15-29yr olds	0.56	0.4, 0.7			Uniform	[36]	
Relapse rate to injecting per year for 30+yr olds	0.30	0.2, 0.6			Uniform	[36]	
Years prior to 2017 when decrease in PWID initiation rate started				10–30	Uniform		Recruitment into injecting thought to have reduced in past but uncertain so large range
Percentage of mixing being like-with-like by age among those aged < 30 (%)				54–62	N/A		Range used to determine proportion of PWID doing like-with-like mixing by age (0 means random mixing and 1 means full like-with-like mixing) (0.0004-0.46)
High risk parameters							
Percentage of PWID that are high risk[a] pre-2002 (%)	61.1	58.7, 63.5			Normal	Analysis of UFO data	
Percentage of PWID that are high risk[a] post-2002 (%)	48.3	43.9, 52.6			Normal	Analysis of UFO data	
Rate that PWID move from high to low risk per year	1.6	1.3, 1.9			Normal	Analysis of UFO data	
Rate ratio for acquiring HCV if high risk[a] compared to if low-risk	1.6	1.3, 2.1			Log-normal	Analysis of UFO data	
Proportion of PWID doing like-with-like mixing by risk status (0 means random mixing and 1 means full like-with-like mixing)				0–0.5	Uniform		No data so wide range assumed
Intervention parameters							
Year MAT started in San Francisco			2000		Point estimate		Coverage low before 2000 (UFO data)
Rate leave MAT/SSP per year	1.0	0.7, 1.6			Normal	[37]	This gives 0.99 years (7.5 – 18 months on MAT/SSP)
Coverage of MAT in 2004 (%)	2.6	1.8, 3.7			Normal	Analysis of UFO data.	Used to find the recruitment rate onto MAT.
Coverage of MAT in 2015 (%)	12.2	10.3, 14.4			Normal	Analysis of UFO data.	Used to find the recruitment rate onto MAT.
Coverage of SSP in 1997 among 15-29yr olds (%)	70.6	52.5, 84.9			Normal	Analysis of NHBS data	UHS data from 1997 has similar coverage to NHBS data from 2012, with NHBS data used to give coverage by age. Used to find the recruitment rate onto SSP for different age groups.
Coverage of SSP in 1997 among 30-49yr olds (%)	86.0	81.0, 90.1			Normal	Analysis of NHBS data	UHS data from 1997 has similar coverage to NHBS data from 2012, with NHBS data used to give coverage by age. Used to find the recruitment rate onto SSP for different age groups.
Coverage of SSP in 1997 among 50+ yrs old (%)	88.1	83.7, 91.6			Normal	Analysis of NHBS data	UHS data from 1997 has similar coverage to NHBS data from 2012, with NHBS data used to give coverage by age. Used to find the recruitment rate onto SSP for different age groups.

Abbreviations – PWID: people who inject drugs; HCV: hepatitis C virus; NHBS: National HIV Behavioural Surveillance; UHS: Urban Health Study; MAT: medication-assisted treatment; SSP: syringe service programs; 95%CI: 95% confidence interval; 95%CrI: 95% credible interval. [a]High-risk is defined as sharing works in the past 6 months.

Table 4: Median and 95% credible intervals for the baseline projections, illustrative examples and treatment scale-up required for reaching WHO/ U.S. National Academies of Sciences, Engineering and Medicine elimination targets.

	Perry County, Kentucky		San Francisco	
	Median	**95% CrI**	**Median**	**95%CrI**
Baseline projections				
Incidence in 2017 (/100pyrs)	21.3	10.2, 39.2	12.9	8.9, 18.4
Prevalence in 2017 (%)	59.5	39.0, 75.0	75.5	66.6, 85.7
Treatment rates needed to decrease incidence by 90% by 2030				
Number of PWID needing treatment each year				
Without full HR[a]	58	30, 99	1574	940, 2319
With full HR[a]	22	0, 52	1418	840, 2092
Percentage of chronically infected PWID needing treatment in the first year (%)				
Without full HR[a]	12.6	10.5, 16.5	9.3	7.9, 11.1
With full HR[a]	4.7	0, 9.0	8.3	7.2, 9.9

Abbreviations: 95%CrI: 95% credible interval; WHO: World Health Organisation; PWID: People who inject drugs; HR: Harm reduction; MAT: Medication assisted treatment; SSP: Syringe Service Provision. [a]Full HR is full harm reduction – 50% coverage of MAT and 84% coverage of SSP (scaled-up in Perry County only).