HCV treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals

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ABSTRACT

Background:
Substantial reductions in HCV prevalence among people who inject drugs (PWID) cannot be achieved by harm reduction interventions such as needle exchange and opiate substitution therapy (OST) alone. Current HCV treatment is arduous and uptake low, but new highly effective and tolerable interferon-free direct-acting antiviral (DAA) treatments could facilitate increased uptake. We projected the potential impact of DAA treatments on PWID HCV prevalence in three settings.

Methods
A dynamic HCV transmission model was parameterized to three chronic HCV prevalence settings: Edinburgh, UK (25%); Melbourne, Australia (50%); Vancouver, Canada (65%). Using realistic scenarios of future DAAs (90% sustained viral response, 12 weeks duration, available 2015), we projected the treatment rates required to reduce chronic HCV prevalence by half or three-quarters within 15 years.

Results
Current HCV treatment rates may minimally impact prevalence in Melbourne and Vancouver (<2% relative reductions), but could reduce prevalence by 26% in 15 years in Edinburgh. Prevalence could halve within 15 years with treatment scale-up to 15, 40, or 76 per 1000 PWID annually in Edinburgh, Melbourne, or Vancouver, respectively (2, 13, 15-fold increases, respectively). Scale-up to 22, 54, or 98 per 1000 PWID annually could reduce prevalence by three-quarters within 15 years. Less impact occurs with delayed
scale-up, higher baseline prevalence, or shorter average injecting duration. Results are insensitive to risk heterogeneity or restricting treatment to PWID on OST. At existing HCV drug costs, halving chronic prevalence would require annual treatment budgets of USD$3.2 million in Edinburgh and ~$50 million in Melbourne and Vancouver.

**Conclusion:**

Interferon-free DAAs could enable increased HCV treatment uptake among PWID, which could have a major preventative impact. However, treatment costs may limit scale-up, and should be addressed.
INTRODUCTION

The global burden of hepatitis C virus (HCV) infection continues to rise(1, 2). The core of the HCV epidemic in the developed world occurs among people who inject drugs (PWID), who comprise the majority of new (80%) and existing (60%) cases(1). Globally, HCV seroprevalence (>60% in most countries)(3) and incidence (5-40% per annum)(4, 5) remains high among PWID. Prevention strategies, such as needle and syringe programs (NSP) and opiate substitution therapy (OST), can reduce HCV transmission, and have maintained low levels of HIV infection in many settings, but are insufficient to achieve substantial reductions in HCV prevalence(6-9). This is partly because high HCV prevalence and long injecting duration among PWID in many settings combine so the intervention coverage required for major prevalence reductions is unobtainable and unsustainable(9). Given there is no HCV vaccine, alternative strategies for HCV prevention are urgently needed.

In HIV, the demonstration that antiretroviral therapy given to HIV-infected people can prevent secondary transmission has generated considerable excitement(10) and suggestions we may have reached a tipping point for preventing HIV transmission(11). In contrast to HIV, HCV is curable and therapy is finite. Therefore, HCV treatment as prevention may provide even greater opportunity for preventing onward HCV transmission and directly reducing HCV chronic prevalence.

Mathematical modeling studies have suggested HCV treatment for PWID could be an effective(12-16) and cost-effective(17) intervention to prevent HCV transmission.
However, these studies only considered treatment with pegylated interferon and ribavirin (PEG-IFN+RBV). The feasibility of expanding this treatment regimen as a strategy for treatment as prevention is limited, given the poor tolerability and limited uptake of PEG-IFN+RBV therapy, particularly among PWID(18, 19). However, therapeutic options for HCV are evolving rapidly. Preliminary data from IFN-free direct-acting antiviral (DAA) therapy phase II trials indicates that in the near future regimens will be available with markedly reduced toxicity, high efficacy (>90% cure), improved dosing schedules (once or twice-daily) and shortened treatment duration (6-24 weeks)(20-22). Such advances indicate that a HCV treatment as prevention strategy among PWID may be feasible in the very near future.

We project the potential impact of DAA therapy on HCV prevalence in three international settings with varied prevalence.

**METHODS**

**Mathematical model**

A deterministic HCV transmission and treatment model among PWID(12) was extended to incorporate additional biological and behavioral complexity (details in figure 1 and appendix). The modeled population was stratified by infection state (uninfected, acute HCV, chronic HCV, on antiviral treatment, treatment failure), transmission risk (low/high), and current OST status (on/off). A fixed number (Φ(t)) of chronically infected PWID initiate treatment annually (or all chronic infections if fewer than Φ(t) are chronically infected), for a treatment duration of 1/ω(t). It was conservatively assumed
treatment failures (those who do not attain sustained viral response, SVR) could not be retreated due to potential resistance and reluctance to undergo further therapy.

Furthermore, at baseline few IFN+RBV treatment failures exist due to historically low treatment rates for PWID. In the base-case, PWID who are low/high risk and on/off OST are eligible for treatment; restricted treatment for only low-risk or those on OST was explored in the sensitivity analysis.

As the model is dynamic, the risk of infection or reinfection for a PWID is proportional to HCV prevalence, which changes over time. We do not assume any risk difference after treatment; reinfection risk is equal to primary infection risk. The forces of infection for each susceptible state were defined by the relative risk in that state, such that infectivity and susceptibility were altered by a factor $\Gamma$, $\Pi$, or $\Gamma \times \Pi$ if the PWID was on OST, high risk, or both, respectively. This was assumed to occur through a corresponding change in the relative frequency of transmission events with other PWID. The chance of a PWID having a transmission event with any PWID from another risk state and infectious status was proportional to the relative frequency of transmission events for PWID in that state.

Due to rapid reductions of HCV RNA levels during treatment(23), we assumed the proportion on treatment who eventually achieve SVR ($\alpha(t)$) are not infectious, whereas the remainder ($1-\alpha(t)$) remain infectious. Some evidence indicates acute infection may be associated with 2-log higher viral loads than during chronic infection(24), however no studies show increased transmissibility during this stage. Therefore, we assumed equal infectivity for the base-case, but considered a 5-fold higher transmissibility during acute
HCV in the sensitivity analysis (assuming a similar relationship between viral load and transmissibility as for HIV(25)).

**Modeling treatment scale-up and regimes**

Treatment rates, durations, and SVR were varied over time to model scale-up and new treatments (figure 2). No treatment prior to 2002 was modeled, as clinical guidance recommended against treatment of PWID (see appendix). Due to the lack of reliable treatment data before 2007, a linear scale-up to current baseline treatment rates during 2002-2007 was modeled, with baseline rates constant during 2007-2012. Prior to 2012, we assumed all treatments used PEG-IFN+RBV. We assumed a continuation of baseline treatment rates from 2012-2015, during which time triple therapy with PEG-IFN+RBV and telaprevir/boceprevir will be available(22), although due to potential contraindications/drug interactions among PWID, we assumed only half of genotype 1 patients would be eligible for triple therapy. IFN-free DAAs were assumed to become available in 2015, followed by a two-year linear scale-up in treatment (2015-2017) to ‘scaled-up’ treatment rates (implemented from 2017-2027).

**Multivariate uncertainty analyses**

To consider the effect of uncertainty in the underlying parameters, we performed a multivariate probabilistic uncertainty analysis where 1000 parameter sets were randomly sampled from setting specific parameter distributions in table 1. For each of the 1000 parameter sets, the model was calibrated to the sampled HCV chronic prevalence in 2012 and proportion on OST/high risk by varying \( \pi, \beta, \) and \( \eta \). The model was then used to
project the prevalence reductions in each setting over 15 years (2012-2027) with no
treatment scale-up, or scale-up to rates of 10, 20, 40, or 80 per 1000 PWID annually.

Additionally, the required scaled-up treatment rates to achieve prevalence reductions of
¼, ½, or ¾ within 15 years were projected. For all projections, 95% credibility intervals
(CrI) were generated from the multivariate uncertainty sampling. A linear regression
analysis of covariance (ANCOVA) was performed on the 15-year impact with scale-up to
10 per 1000 PWID annually, and the proportion of the sum-of-squares contributed by
each parameter was calculated to estimate the importance of individual parameters to the
overall uncertainty.

**Sensitivity analysis**

To evaluate the impact of individual model assumptions, univariate sensitivity analyses
were performed on projected prevalence reductions at 15 years with a treatment rate of 10
per 1000 PWID annually, using the point parameter values in **table 1**. The analysis
determined the impact of: delayed scale-up initiation (starting 2019 versus 2015), longer
scale-up duration (six versus two years), lower/higher DAA SVR (80%/100% versus
90%), increased infectivity during acute infection (5-fold infectiousness compared to
chronic infection, equal in base-case), restricting treatment to only those on OST or low
risk, shorter/longer average duration of injecting career (6/20 years versus 11 years),
shorter/longer duration on OST, no turnover from high to low risk, greater differences
between high/low risk (six times the relative risk between high/low risk versus two
times), and changes in mixing behavior between high/low risk (fully assortative versus
proportional).
Model parameterization

The model was parameterized to three international settings with a range of HCV chronic prevalence among PWID: Edinburgh, UK; Melbourne, Australia; and Vancouver, Canada. Model parameters and sources are in table 1 and appendix.

HCV antibody prevalence estimates for Edinburgh, Melbourne and Vancouver were 34%(26), 66%(19, 27), and 88%(18, 28), respectively. As 26% of individuals spontaneously clear acute infection(29), it was assumed 74% of HCV antibody positive individuals were chronically infected, resulting in HCV chronic prevalence estimates of 25% in Edinburgh, 50% in Melbourne, and 65% in Vancouver.

Death and cessation rates

PWID death rates were similar in Edinburgh (1% per year(30, 31)) and Melbourne (0.83% per year(32)), but higher in Vancouver (3% per year(33)). Site-specific unbiased estimates of the average duration of injecting until cessation are unavailable and difficult to obtain. We assumed an average injecting duration of 11 years(34), but varied this from six years up to 20 or 27 years in the uncertainty/sensitivity analyses based on seroprevalence survey data(19, 28, 35, 36).

Baseline treatment rates
Current annual numbers treated and treatment rates were estimated as: 32 PWID annually (8 per 1000 PWID) in Edinburgh, 75 PWID annually (3 per 1000 PWID) in Melbourne, and 68 PWID annually (5 per 1000 PWID) in Vancouver.

SVR rates

SVR rates for PEG-IFN+RBV were obtained from a meta-analysis of treatment among PWID (37% [95%CI 26-48%] for genotype 1, 67% [95%CI 56-78%] for genotypes 2/3)(37). Telaprevir/boceprevir with PEG-IFN+RBV increases genotype 1 SVR rates by 70% over PEG-IFN+RBV(38, 39), so a 63% SVR rate was modeled. It was assumed IFN-free DAAs will achieve 90% SVR for all genotypes with a duration of 12 weeks (20-22).

RESULTS

Base-case

Without any treatment scale-up, low chronic HCV prevalence in Edinburgh (25%) combined with switching to new DAAs and moderate baseline levels of treatment (8/1000 PWID annually) could lead to a 26% [13-45%, 95% credibility interval (CrI)] relative reduction in prevalence within 15 years. However, in Melbourne and Vancouver, higher chronic HCV prevalence (50% and 65%, respectively) combined with low current levels of treatment (<5 per 1000 PWID annually) produce little impact (<2%) on prevalence over 15 years. Figure 3 shows HCV chronic prevalence reductions over time, and figure 4 shows relative prevalence reductions at year 15 (10 years after full scale-up).
Minimal and achievable levels of treatment scale-up result in substantial impact in Edinburgh and Melbourne. Scaling-up treatment to 20 per 1000 PWID annually could result in relative prevalence reductions within 15 years of 69% [54-83% CrI] and 23% [17-32% CrI] in Edinburgh and Melbourne, respectively, but only 9% [7-15% CrI] in Vancouver. Higher treatment rates (>40 per 1000 PWID annually) are required to reduce prevalence by over >20% in Vancouver within 15 years. A scale-up to treating 80 per 1000 PWID annually could reduce HCV chronic prevalence to below 5% in Edinburgh and Melbourne, and to 30% in Vancouver, within 15 years.

**Figure 5** shows the levels of treatment necessary to reduce prevalence by ¼, ½, and ¾ within 15 years (10 years after full scale-up) in all settings. Halving current prevalence could be achieved through scaled-up treatment rates of 15 [12-19 CrI], 40 [30-50 CrI], and 76 [56-102 CrI] per 1000 PWID annually in Edinburgh, Melbourne, and Vancouver, respectively. This would require doubling treatment rates in Edinburgh (currently 32 PWID [8 per 1000] PWID annually). However, in Melbourne it would require a 13-fold scale-up (currently 75 PWID [3 per 1000 PWID] annually), and in Vancouver would require a 15-fold scale-up (currently 68 PWID [5 per 1000 PWID] annually). Reducing prevalence by ¾ would require a scale-up by: 3-fold in Edinburgh to 22 [18-27 CrI] per 1000 PWID annually, 18-fold in Melbourne to 54 [43-67 CrI] per 1000 PWID annually, and 20-fold in Vancouver to 98 [74-127 CrI] per 1000 PWID annually. This would result in HCV chronic prevalences of <10% in Edinburgh, <15% in Melbourne and <20% in Vancouver, respectively.
Uncertainty/sensitivity analysis

ANCOVA analyses indicated that uncertainty in average injecting duration contributed to the majority of variation (59%-78%) in impact at 15 years with a treatment scale-up to 10 per 1000 PWID annually. The remaining variation was due to uncertainty in baseline treatment rate in Edinburgh, baseline prevalence in Melbourne, and baseline prevalence and death rate in Vancouver.

One-way sensitivity analyses showed baseline prevalence, injecting duration, and time to scale-up initiation had the most effect on model projections at 15 years with treatment scale-up to 10 per 1000 PWID annually (figure 6, shown for Melbourne). Across the sites, if baseline chronic HCV prevalences were 5% lower, the impact of treatment scale-up increased by 24-37%, whereas if baseline prevalences were 5% higher, impact decreased by 20-27%. If the average injecting career was 20 rather than 11 years then potential impact increased by 16-53% (with greater impact at higher chronic prevalence); whereas if average injecting duration was shorter at six years impact was reduced by 29-43%. Delaying the initiation of scale-up by four years (2019 versus 2015) resulted in 7-18% less impact. Decreasing/increasing IFN-free DAA SVR rates (to 80%/100% versus 90%) correspondingly decreased/increased impact by 12 to 15%. If acute infection was associated with a 5-fold increase in transmissibility as compared to chronic infection (equal for base-case), impact was reduced by 11-16%.
Changing other assumptions regarding treatment duration or population heterogeneity (e.g., average time in OST/high risk, proportion high-risk, relative transmission risk when in OST or high-risk, mixing assumptions between low and high-risk, restricting treatment to only those on OST or low-risk) had <10% impact on projections for a scaled-up treatment rate of 10/1000 PWID annually. However, at higher treatment rates (such as 80 per 1000 PWID for Melbourne), sustaining treatment at this level would require treating the non-OST population or expanding OST coverage.

**Budgetary impact**

Previous cost-effectiveness analyses estimated the drug-only cost of triple therapy with protease inhibitors in the US at approximately USD$50,000 per course\(^{(40)}\). The cost of future IFN-free DAA regimens is unknown, but if they cost USD$50,000 [USD$25,000-75,000], then the scaled-up treatment rates necessary to halve prevalence within 15 years (15, 40, and 76 per 1000 PWID annually in Edinburgh, Melbourne, and Vancouver, respectively) would require an annual HCV treatment budget for PWID of USD$3.2 million [USD$1.6-4.7 million] in Edinburgh, USD$50.0 million [USD$25.0-75.0 million] in Melbourne, and USD$51.3 million [USD$25.7-77.0 million] in Vancouver.

**DISCUSSION**

This modeling study explored the feasibility of HCV treatment as prevention in the era of IFN-free DAA-based HCV therapy. Current levels of HCV treatment among PWID are projected to only achieve modest or negligible reductions in HCV chronic prevalence among PWID. However, scaling-up treatment could lead to substantial reductions in
HCV prevalence. In Edinburgh, a doubling of treatment rates (to 15 per 1000 PWID annually) could halve prevalence; a 3-fold increase could reduce chronic HCV prevalence to <7% within 15 years. Greater scale-up will be required in Melbourne and Vancouver where current treatment rates are lower and chronic prevalence higher, but prevalence could be halved in 15 years with treatment rates of 40 per 1000 PWID (13-fold increase from 3 per 1000 PWID annually) in Melbourne and 76 per 1000 PWID (a 15-fold increase from 5 per 1000 PWID annually) in Vancouver. A 20-fold increase from baseline treatment rates could reduce chronic prevalence to <15% and <20% in Melbourne and Vancouver, respectively, in 15 years.

Such scale-up, though considerable in Melbourne and Vancouver, has been achieved and exceeded for HIV treatment in both resource rich and poor settings(41), and even amongst PWID in some settings(42, 43). In addition, programs designed to address barriers to care among PWID have achieved yearly HCV treatment rates of 40-80 per 1000 PWID with PEG-IFN+RBV in Australia, Canada, Europe, and the United States(44-47). Moreover, scale-up of IFN-free DAA in theory will be easier to implement and have greater impact than current treatment regimes. IFN-free DAA regimens will require shorter duration and less complex monitoring(22) which in combination with higher SVR and reduced toxicity will markedly accelerate the current expansion of HCV treatment into the community, including integration with drug treatment, such as OST.

Limitations
These projections are based on a theoretical mathematical model, with several limitations. First, there is uncertainty in a number of parameters. These projections are predicated on assumptions of the effectiveness of IFN-free DAAs (based on phase II studies as evidence from large-scale evaluations are not yet available). Outcomes among PWID are unknown, but systematic reviews report similar response rates among PWID and non-PWID for IFN+RBV regimens(48, 49). Additionally, active PWID are generally younger (a meta-analysis(48) found a lower median age (38 years) for studies with HCV treatment among PWID compared to registration trials for PEG-IFN+RBV (43-45 years)) and have less advanced liver disease than the broader HCV population. We do not explicitly model HIV/HCV coinfection, as two of our settings have marginal (<1%) coinfection prevalences. However, in settings where a greater proportion of PWID are HIV/HCV coinfected, lower SVR rates may be achieved. Sensitivity analyses showed a lower SVR of 80% would still achieve substantial impact, although slightly higher treatment rates would be required to achieve specific reductions in HCV prevalence.

Furthermore, better information on average injecting duration could substantially reduce uncertainty in the projections. The average age (and injecting duration) of people in drug treatment and serological surveys in the three sites suggest injecting durations between 11 and 27 years(19, 28, 35), but unbiased estimates are unavailable. An 11 year average injecting duration was assumed(34), but if it were longer then greater impact would be achieved. Also, HCV risk and treatment uptake will vary between PWID sub-groups, relating to injecting patterns or other factors such as homelessness. However, we considered scenarios where HCV treatment is delivered only in OST or when PWID are
at “low risk” and show there is little impact on the outcome given movement between low and high risk states over an injecting career.

Second, complexities involved in treatment scale-up are not modeled. Treatment scale-up will likely be delivered in the community alongside OST, but additional interventions may be required to increase the case-finding among PWID, including health-care workforce training and interventions addressing stigma surrounding testing and treatment.

Importantly, in our model a fixed number of PWID are treated annually, so as prevalence falls an increasing proportion of infected PWID are treated. This will have implications for diagnosis and treatment retention, particularly among harder to reach PWID. However, treatment recruitment may become easier as more PWID are treated.

Third, the model assumes a stable injecting population size, which although true in the settings examined may not be applicable to all settings. For example, data from Amsterdam(50) suggests a decline in the number of injectors. In these settings, as PWID prevalence falls we would expect HCV prevalence to increase as the cohort ages, and detailed models of these settings would require age-specific information on prevalence of PWID and injecting duration to determine intervention impact.

Finally, the model incorporates current levels of OST, but did not consider the impact of scaling-up of or targeting interventions such as OST and NSP—which may additionally contribute towards reducing HCV transmission(9). As our aim was to explore the scale-up of antiviral treatment, we did not stratify the population by drug-type or explore OST
eligibility criteria. Additionally, we do not explicitly model NSP, but account for existing levels of coverage in modeling the epidemic in each setting.

**Implications and Comparison with other studies**

This is the first analysis to explore the potential of new and future direct-acting HCV antiviral therapy as prevention in a range of global prevalence settings, and supports previous modeling studies indicating HCV antiviral treatment could reduce transmission and HCV prevalence among PWID\(^\text{(12-16)}\). In contrast, mathematical models have shown scale-up of OST/NSP could have considerable impact in areas with historically low levels of OST/NSP, but in many developed countries where coverage is already high (such as our sites) the scale-up required (e.g. 80% PWID on OST or high coverage NSP for 15 years) would be unachievable and unsustainable, and would achieve less impact than modest levels of HCV treatment\(^\text{(9)}\).

Overall, the projections suggest IFN-free DAA HCV treatment as prevention is a feasible option for reducing the future burden of HCV-related disease, which is of critical public health importance given the lack of alternative effective HCV prevention strategies. HCV treatment is cost-effective, and in most settings treatment of PWID is highly cost effective\(^\text{(17)}\) primarily because of the potential prevention benefit and reduction in secondary transmission.

A question still remains, though, as to whether scaling-up is affordable – especially if the drugs are marketed at similar cost to existing therapy. Expansion will be costly, and so
any future scale-up of HCV treatment for prevention will require drug-price reform, especially for lower and middle income settings, but possibly also for developed countries that require high treatment rates.


FIGURE LEGENDS

Figure 1. Model schematic showing the HCV disease transmission and treatment states (A) and behavioral states (B). The model includes compartments for uninfected PWID ($X_{j,k}$), acutely infected PWID ($A_{j,k}$), chronically infected PWID ($C_{j,k}$), PWID on antiviral treatment ($T_{j,k}$), and PWID treatment failures ($F_{j,k}$) (A). Additionally, the population was stratified by risk (low/high, $j=0$ or 1, respectively), and OST (off/on, $k=0$ or 1, respectively) (B). New PWID enter the model at a constant rate ($\theta$) as uninfected, off OST, and either low or high risk. Uninfected PWID can become acutely infected with HCV, where a proportion ($\delta$) of individuals spontaneously clear their acute infection after a duration of time ($1/\psi$), and return to the uninfected compartment. Those who do not spontaneously clear the acute infection ($1-\delta$) progress to chronic infection, where they are eligible for antiviral treatment. As PWID are unlikely to be diagnosed during acute infection, it was assumed PWID are not treated during the acute stage. If treated, a proportion ($\alpha(t)$) achieve SVR and return to the uninfected compartment. Those who do not attain SVR ($1-\alpha(t)$) move to the treatment failure compartment where they cannot be retreated. PWID exit all compartments due to permanent cessation of drug use ($\mu_1$) or death due to drug or non-drug related causes ($\mu_2$). The base-case analysis assumed PWID transition between high/low risk stages, as well as on/off OST. More details in appendix.

PWID=people who inject drugs, SVR=sustained viral response, OST=opiate substitution therapy.

Figure 2. Treatment scenario in the base-case analysis (scale-up and changing drug treatments over time). We assume no treatment of PWID prior to 2002. From 2002, a
five year linear scale-up (2002-2007) to baseline treatment rates (8 per 1000 PWID annually in Edinburgh, 3 per 1000 PWID annually in Melbourne, and 5 per 1000 PWID annually in Vancouver) was implemented. For all treatments during 2002-2012, it was assumed PWID were treated with PEG-IFN+RBV. We assume treatment rates remain steady from 2012-2015, but that telaprevir/boceprevir is given to half of genotype 1 patients. In 2015, it was projected that IFN-free DAAs will be available, such that SVR rates will increase (to 90%) and a two year scale-up will occur (2015-2017) followed by full ‘scaled-up’ treatment rates from 2017 onwards. PEG-IFN=pegylated interferon, RBV=ribavirin, IFN-free DAAs=interferon free direct-acting antivirals, G1=genotype 1, PWID=people who inject drugs.

**Figure 3. Chronic prevalence over time in (A) Edinburgh, (B) Melbourne, and (C) Vancouver.** Simulations show no scale-up from baseline, or scale-up to 10, 20, 40, or 80 per 1000 PWID treated annually. We assume no treatment prior to 2002, a linear scale-up to baseline treatment rates during 2002-2007, and baseline treatment rates during 2007-2012. A linear scale-up from baseline to scaled-up rate during 2015-2017 was modeled. HCV prevalence data points shown for comparison with 95% confidence intervals.

**Figure 4. Relative prevalence reductions at 15 years (by 2027) with no treatment scale-up (8/1000 PWID annually in Edinburgh, 3/1000 PWID annually in Melbourne, and 5/1000 PWID annually in Vancouver) and four treatment rate scenarios (10, 20, 40, and 80 per 1000 PWID annually).** Bars indicate the mean relative
prevalence reductions, with whiskers representing the 95% credibility interval for the simulations.

**Figure 5.** Annual scaled-up treatment rate required to reduce prevalence by \( \frac{1}{4}, \frac{1}{2}, \text{ or } \frac{3}{4} \) in Edinburgh, Melbourne, and Vancouver within 15 years (by 2027). Bars (and numbers) indicate the mean value, with whiskers representing the 95% credibility interval.

**Figure 6.** Results from the one-way sensitivity analyses; percent change from the base-case scenario of the predicted relative prevalence reduction at 15 years in Melbourne with scaled-up treatment rate of 10/1000 PWID annually (from a baseline rate of 3/1000 PWID annually). For the base-case, all chronically infected PWID (high/low risk or on/off OST) were eligible for treatment. OST=opiate substitution therapy, mo=months.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Edinburgh, UK point value (sampling bounds)</th>
<th>Melbourne, Australia point value (sampling bounds)</th>
<th>Vancouver, Canada point value (sampling bounds)</th>
<th>Units</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV chronic prevalence among PWID in 2012</td>
<td>Vary π</td>
<td>25% (22-28%)</td>
<td>50% (47-53%)</td>
<td>65% (63-67%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PWID population size (used to calculate baseline treatment rate)</td>
<td>4,240</td>
<td>25,000</td>
<td>13,500</td>
<td></td>
<td>-</td>
<td>E: (26, 36) M: (19) V: (18, 28) Sampled from a uniform distribution</td>
</tr>
<tr>
<td>Baseline treatment rate (from 2007 onward)</td>
<td>Vary</td>
<td>8 (4-12)</td>
<td>3 (1.5-4.5)</td>
<td>5 (2.5-7.5)</td>
<td>per 1000 PWID per year</td>
<td>E: [HCV treatment database(54), unpublished] M: [Victorian Department of Health unpublished figures and NSP survey(27)] V: [CHASE(18), unpublished] Sampled from a uniform distribution</td>
</tr>
<tr>
<td>Proportion genotype 1</td>
<td>μ2</td>
<td>1%</td>
<td>0.83%</td>
<td>3%</td>
<td>per year</td>
<td></td>
</tr>
<tr>
<td>Death rate</td>
<td>μ2</td>
<td>1%</td>
<td>0.83%</td>
<td>3%</td>
<td>per year</td>
<td>E: [HCV treatment database(54), unpublished] M: [Victorian Department of Health unpublished figures and NSP survey(27)] V: [CHASE(18), unpublished 1999-2010] Sampled from a Poisson distribution</td>
</tr>
<tr>
<td>Proportion PWID on OST</td>
<td>Vary β</td>
<td>57% (50-64%)</td>
<td>48% (44-52%)</td>
<td>45% (43-47%)</td>
<td>-</td>
<td>E: [NESI(36), unpublished] M: (19, 52) V: (33) Sampled from a uniform distribution</td>
</tr>
<tr>
<td>Duration on OST</td>
<td>12/γ</td>
<td>8 (4-12)</td>
<td>6.5 (3.25-8.75)</td>
<td>7 (3.5-10.5)</td>
<td>months</td>
<td>E: (31) M: (57) V: (58) Sampled from a uniform distribution</td>
</tr>
<tr>
<td>Proportion PWID high risk</td>
<td>Vary φ</td>
<td>33% (27-39%)</td>
<td>17% (14-20%)</td>
<td>64% (62-66%)</td>
<td>-</td>
<td>E: (36, 59) M: [MIX(60), unpublished] V: (33) Sampled from a uniform distribution</td>
</tr>
<tr>
<td>Duration high risk</td>
<td>12/κ</td>
<td>14 (7-21)</td>
<td>13 (6.5-19.5)</td>
<td>38 (19-57)</td>
<td>months</td>
<td>E: (9, 61) M: [MIX(60), unpublished] V: [UHRI(33), unpublished] Sampled from a uniform distribution</td>
</tr>
<tr>
<td>Proportion spontaneously clear</td>
<td>12/δ</td>
<td>6 (3-9)</td>
<td>6 (3-9)</td>
<td>6 (3-9)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Duration of acute stage</td>
<td>12/ψ</td>
<td>11 (6-20)</td>
<td>11 (6-27)</td>
<td>11 (6-23)</td>
<td>years</td>
<td>(34, 35) See appendix for details. Sampled from a triangular distribution</td>
</tr>
<tr>
<td>SVR</td>
<td>a(t)</td>
<td>37% (26-48)</td>
<td>37% (26-48)</td>
<td>37% (26-48)</td>
<td>-</td>
<td>(37) Sampled from a uniform distribution (37) Sampled from a uniform distribution</td>
</tr>
<tr>
<td>SVR</td>
<td>α(t)</td>
<td>37% (26-48)</td>
<td>37% (26-48)</td>
<td>37% (26-48)</td>
<td>-</td>
<td>(37) Sampled from a uniform distribution (37) Sampled from a uniform distribution</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>52/α(t)</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>weeks</td>
<td>(38, 39) Weighted estimate based on stopping rules Estimated (22)</td>
</tr>
<tr>
<td>Relative risk for acquiring HCV on OST</td>
<td>Γ</td>
<td>0.41 (0.21-0.82)</td>
<td>0.41 (0.21-0.82)</td>
<td>0.41 (0.21-0.82)</td>
<td>-</td>
<td>(8) Sampled from a lognormal distribution.</td>
</tr>
<tr>
<td>Relative risk for high risk</td>
<td>Π</td>
<td>3.6 (1.5-8.7)</td>
<td>3.6 (1.5-8.7)</td>
<td>1.4 (1-2.1)</td>
<td>-</td>
<td>E: (8, 59) M: [55], assumed equal to Edinburgh V: (28) Sampled from a lognormal distribution</td>
</tr>
</tbody>
</table>
Table 1. Model parameters and sources

- Used to estimate the infection rate, π (Vary π and fit to the HCV chronic prevalence). Note that π is not the incidence rate.
- PWID population size was used to calculate baseline treatment rate per 1000 PWID. Hence, for the model projections, the new injector entry rate (θ) was varied to fit to a total PWID population size of 1000.
- From 2008/2009 NESI survey excluding those who attended a survey recruitment site for methadone.
- Defined as proportion PWID experiencing unstable housing (8, 28, 55, 59).
- When SVR rates vary by genotype, calculated using a weighted estimate based on population genotype distribution and SVR.
- When treatment durations vary by genotype, calculated using a weighted estimated based on genotype distribution, SVR, and treatment duration.
- Calculated based on early stopping rules and proportion achieving early viral response. SVR=sustained viral response; PEG-IFN= pegylated interferon; RBV=ribavirin; G1=genotype 1; G2/3=genotypes 2 or 3; DAA= direct acting antivirals; OST=opiate substation therapy; PWID=people who inject drugs.
Figure 1. Model schematic showing the HCV disease transmission and treatment states (A) and behavioral states (B). The model includes compartments for uninfected PWID (Xj,k), acutely infected PWID (Aj,k), chronically infected PWID (Cj,k), PWID on antiviral treatment (Tj,k), and PWID treatment failures (Fj,k) (A). Additionally, the population was stratified by risk (low/high, j=0 or 1, respectively), and OST (off/on, k=0 or 1, respectively) (B). New PWID enter the model at a constant rate (θ) as uninfected, off OST, and either low or high risk. Uninfected PWID can become acutely infected with HCV, where a proportion (δ) of individuals spontaneously clear their acute infection after a duration of time (1/ψ), and return to the uninfected compartment. Those who do not spontaneously clear the acute infection (1-δ) progress to chronic infection, where they are eligible for antiviral treatment. As PWID are unlikely to be diagnosed during acute infection, it was assumed PWID are not treated during the acute stage. If treated, a proportion (α(t)) achieve SVR and return to the uninfected compartment. Those who do not attain SVR (1-α(t)) move to the treatment failure compartment where they cannot be retreated. PWID exit all compartments due to permanent cessation of drug use (μ1) or death due to drug or non-drug related causes (μ2). The base-case analysis assumed PWID transition between high/low risk stages, as well as on/off OST. More details in appendix.

PWID=people who inject drugs, SVR=sustained viral response, OST=opiate substitution therapy.
Figure 2. Treatment scenario in the base-case analysis (scale-up and changing drug treatments over time).

We assume no treatment of PWID prior to 2002. From 2002, a five year linear scale-up (2002-2007) to baseline treatment rates (8 per 1000 PWID annually in Edinburgh, 3 per 1000 PWID annually in Melbourne, and 5 per 1000 PWID annually in Vancouver) was implemented. For all treatments during 2002-2012, it was assumed PWID were treated with PEG-IFN+RBV. We assumed treatment rates remain steady from 2012-2015, but that telaprevir/boceprevir is given to half of genotype 1 patients. In 2015, it was projected that IFN-free DAAs will be available, such that SVR rates will increase (to 90%) and a two year scale-up will occur (2015-2017) followed by full 'scaled-up' treatment rates from 2017 onwards. PEG-IFN=pegylated interferon, RBV=ribavirin, IFN-free DAAs=interferon free direct-acting antivirals, G1=genotype 1, PWID=people who inject drugs.
Figure 3. Chronic prevalence over time in (A) Edinburgh, (B) Melbourne, and (C) Vancouver. Simulations show no scale-up from baseline, or scale-up to 10, 20, 40, or 80 per 1000 PWID treated annually. We assume no treatment prior to 2002, a linear scale-up to baseline treatment rates during 2002-2007, and baseline treatment rates during 2007-2012. A linear scale-up from baseline to scaled-up rate during 2015-2017 was modeled. HCV prevalence data points shown for comparison with 95% confidence intervals.
Figure 4. Relative prevalence reductions at 15 years (by 2027) with no treatment scale-up (8/1000 PWID annually in Edinburgh, 3/1000 PWID annually in Melbourne, and 5/1000 PWID annually in Vancouver) and four treatment rate scenarios (10, 20, 40, and 80 per 1000 PWID annually). Bars indicate the mean relative prevalence reductions, with whiskers representing the 95% credibility interval for the simulations.
Figure 5. Annual scaled-up treatment rate required to reduce prevalence by ¼, ½, or ¾ in Edinburgh, Melbourne, and Vancouver within 15 years (by 2027). Bars (and numbers) indicate the mean value, with whiskers representing the 95% credibility interval.
279x215mm (300 x 300 DPI)
Figure 6. Results from the one-way sensitivity analyses; percent change from the base-case scenario of the predicted relative prevalence reduction at 15 years in Melbourne with scaled-up treatment rate of 10/1000 PWID annually (from a baseline rate of 3/1000 PWID annually). For the base-case, all chronically infected PWID (high/low risk or on/off OST) were eligible for treatment. OST=opiate substitution therapy, mo=months.

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SUPPLEMENTARY INFORMATION

Mathematical model
We use a dynamic, deterministic, compartmental model of HCV transmission and treatment among people who inject drugs (PWID). The model included compartments for uninfecteds ($X_{i,j}$), acutely infected ($A_{i,j}$), chronically infected ($C_{i,j}$), on antiviral treatment ($T_{i,j}$), and treatment failures ($F_{i,j}$). Additionally, the PWID population was stratified by risk (low/high, $j=0$ or 1, respectively), and OST (off/on, $k=0$ or 1, respectively). We track changes in the populations over time, $t$.

New injectors enter the susceptible PWID population at a rate ($\theta$), a proportion of which ($\varphi$) enter as high risk, and the remainder ($1-\varphi$) entering as low risk. We assume all PWID are not on OST when initiating injecting, but can subsequently be recruited into OST at a rate ($\beta$). PWID remain on OST for a duration ($1/\gamma$). Low risk PWID can move to high risk at a rate ($\eta$), and remain high risk for a duration ($1/\kappa$). We fit both $\beta$ and $\eta$ such that the proportion on OST or high risk remains constant throughout the simulation and equal to the proportions entering each state.

Uninfected PWID can become acutely infected with HCV, where a proportion ($\delta$, 26%) of individuals spontaneously clear their acute infection after a duration of time ($1/\psi$, approximately 0.5 years$^3$), and return to the uninfected compartment. Those who do not spontaneously clear the acute infection ($1-\delta$) progress to chronically infected, where they are eligible for antiviral treatment. As PWID are unlikely to be diagnosed during acute infection, we assumed PWID are not treated during the acute stage. If treated, a proportion ($\alpha(t)$) achieve SVR and return to the uninfected compartment. Those who do not attain SVR ($1-\alpha(t)$) move to the treatment failure compartment. We conservatively assumed treatment failures cannot be retreated because baseline treatment rates are low, so few PWID previously treated with PEG-IFN+RBV would be eligible for retreatment with DAAs. If retreatment were allowed, the impact projections would be more than our base-case. PWID exit all compartments due to permanent cessation of drug use ($\mu_1$) or death due to drug or non-drug related causes ($\mu_2$).

We neglected immunity in the model due to the lack of strong data surrounding the presence of immunity (either following spontaneous clearance or successful treatment), and because previous analyses have shown that incorporating immunity has minimal impact on model projections$^3,4$.

The full model equations are as follows, for low risk PWID not on OST:

$$\frac{dX_{0,0}}{dt} = \theta(1-\varphi) - \lambda_{0,0}X_{0,0} + \delta\psi A_{0,0} + \alpha(t)\omega(t)T_{0,0} + \kappa X_{1,0} + \gamma X_{0,1} - (\mu_1 + \mu_2 + \beta + \eta)X_{0,0}$$

$$\frac{dA_{0,0}}{dt} = \lambda_{0,0}X_{0,0} - \psi A_{0,0} + \kappa A_{1,0} + \gamma A_{0,1} - (\mu_1 + \mu_2 + \beta + \eta)A_{0,0}$$

$$\frac{dC_{0,0}}{dt} = (1-\delta)\psi A_{0,0} - f(C_{0,0},t) + \kappa C_{1,0} + \gamma C_{0,1} - (\mu_1 + \mu_2 + \beta + \eta)C_{0,0}$$

$$\frac{dT_{0,0}}{dt} = f(C_{0,0},t) - \omega(t)T_{0,0} + \kappa T_{1,0} + \gamma T_{0,1} - (\mu_1 + \mu_2 + \beta + \eta)T_{0,0}$$

$$\frac{dF_{0,0}}{dt} = (1-\alpha(t))\omega(t)T_{0,0} + \kappa F_{1,0} + \gamma F_{0,1} - (\mu_1 + \mu_2 + \beta + \eta)F_{0,0}$$

For low risk PWID on OST:

$$\frac{dX_{0,1}}{dt} = -\lambda_{0,1}X_{0,1} + \delta\psi A_{0,1} + \alpha(t)\omega(t)T_{0,1} + \kappa X_{1,1} + \beta X_{0,0} - (\mu_1 + \mu_2 + \gamma + \eta)X_{0,1}$$

$$\frac{dA_{0,1}}{dt} = \lambda_{0,1}X_{0,1} - \psi A_{0,1} + \kappa A_{1,1} + \beta A_{0,0} - (\mu_1 + \mu_2 + \gamma + \eta)A_{0,1}$$

$$\frac{dC_{0,1}}{dt} = (1-\delta)\psi A_{0,1} - f(C_{0,1},t) + \kappa C_{1,1} + \beta C_{0,0} - (\mu_1 + \mu_2 + \gamma + \eta)C_{0,1}$$

$$\frac{dT_{0,1}}{dt} = f(C_{0,1},t) - \omega(t)T_{0,1} + \kappa T_{1,1} + \beta T_{0,0} - (\mu_1 + \mu_2 + \gamma + \eta)T_{0,1}$$
\[
\frac{dF_{0,1}}{dt} = (1 - \alpha(t))\omega(t)T_{0,1} + \kappa F_{1,1} + \beta F_{0,0} - (\mu_1 + \mu_2 + \gamma + \eta)F_{0,1}
\]

For high risk PWID not on OST:
\[
\begin{align*}
\frac{dX_{1,0}}{dt} &= \theta \varphi - \lambda_{1,0}X_{1,0} + \delta \psi A_{1,0} + \alpha(t)\omega(t)T_{1,0} + \eta X_{0,0} + \gamma X_{1,1} - (\mu_1 + \mu_2 + \beta + \kappa)X_{1,0} \\
\frac{dA_{1,0}}{dt} &= \lambda_{1,0}X_{1,0} - \psi A_{1,0} + \eta A_{0,0} + \gamma A_{1,1} - (\mu_1 + \mu_2 + \beta + \kappa)A_{1,0} \\
\frac{dC_{1,0}}{dt} &= (1 - \delta)\psi A_{1,0} - f(C_{1,0}, t) + \eta C_{0,0} + \gamma C_{1,1} - (\mu_1 + \mu_2 + \beta + \kappa)C_{1,0} \\
\frac{dT_{1,0}}{dt} &= f(C_{1,0}, t) - \omega(t)T_{1,0} + \eta T_{0,0} + \gamma T_{1,1} - (\mu_1 + \mu_2 + \beta + \kappa)T_{1,0} \\
\frac{dF_{1,0}}{dt} &= (1 - \alpha(t))\omega(t)T_{1,0} + \eta F_{0,0} + \gamma F_{1,1} - (\mu_1 + \mu_2 + \beta + \kappa)F_{1,0}
\end{align*}
\]

For high risk PWID on OST:
\[
\begin{align*}
\frac{dX_{1,1}}{dt} &= -\lambda_{1,1}X_{1,1} + \delta \psi A_{1,1} + \alpha(t)\omega(t)T_{1,1} + \eta X_{0,1} + \beta X_{1,0} - (\mu_1 + \mu_2 + \gamma + \kappa)X_{1,1} \\
\frac{dA_{1,1}}{dt} &= \lambda_{1,1}X_{1,1} - \psi A_{1,1} + \eta A_{0,1} + \beta A_{1,0} - (\mu_1 + \mu_2 + \gamma + \kappa)A_{1,1} \\
\frac{dC_{1,1}}{dt} &= (1 - \delta)\psi A_{1,1} - f(C_{1,1}, t) + \eta C_{0,1} + \beta C_{1,0} - (\mu_1 + \mu_2 + \gamma + \kappa)C_{1,1} \\
\frac{dT_{1,1}}{dt} &= f(C_{1,1}, t) - \omega(t)T_{1,1} + \eta T_{0,1} + \beta T_{1,0} - (\mu_1 + \mu_2 + \gamma + \kappa)T_{1,1} \\
\frac{dF_{1,1}}{dt} &= (1 - \alpha(t))\omega(t)T_{1,1} + \eta F_{0,1} + \beta F_{1,0} - (\mu_1 + \mu_2 + \gamma + \kappa)F_{1,1}
\end{align*}
\]

where \(f(C_{i,j}, t)\) is the number of PWID initiated onto treatment per year from each chronic infection compartment, \(C_{i,j}\). A fixed total number (\(\Phi(t)\)) of chronically infected PWID are initiated onto treatment per year in the population, with a treatment duration of 1/\(\omega(t)\). Treatments are allocated proportionally to the eligible groups. If \(\Phi(t)\) is greater than the number of eligible chronic infections, all eligible chronic infections are treated.

For example, if all chronically infected PWID are eligible for treatment (low/high risk and on/off OST), then
\[
\begin{align*}
\Phi(t) \left( \frac{C_{i,j}}{C_{0,0} + C_{1,0} + C_{0,1} + C_{1,1}} \right) & \quad \text{if } \Phi(t) < (C_{0,0} + C_{1,0} + C_{0,1} + C_{1,1}) \\
\Phi(t) & \quad \text{if } \Phi(t) \geq (C_{0,0} + C_{1,0} + C_{0,1} + C_{1,1})
\end{align*}
\]

Alternatively, if only PWID on OST are eligible for treatment, then \(f(C_{i,0}, t) = 0\) and
\[
\begin{align*}
\Phi(t) \left( \frac{C_{i,1}}{C_{0,0} + C_{1,0} + C_{0,1} + C_{1,1}} \right) & \quad \text{if } \Phi(t) < (C_{0,1} + C_{1,1}) \\
\Phi(t) & \quad \text{if } \Phi(t) \geq (C_{0,1} + C_{1,1})
\end{align*}
\]

The forces of infection for each susceptible state were defined by the relative risk in that particular state, such that infectivity and susceptibility was altered by a factor \(\Gamma, \Pi, \text{ or } \Gamma \times \Pi\) if the PWID was on OST, high risk, or high risk and on OST, respectively. This was assumed to occur through a corresponding change in the relative frequency of transmission events with other PWID. The chance of a PWID having a transmission event with any PWID from another risk state (high/low risk or on/off OST) and infectious status was proportional to the relative frequency of
transmission events for PWID in that state. Due to the rapid reduction in viral loads during treatment\(^5\), we assumed that during treatment the proportion who will eventually achieve SVR (\(\alpha(t)\)) are not infectious, whereas the remainder (1-\(\alpha(t)\)) remain infectious. For the base-case analysis, we assume equal transmissibility from the acute stage as compared to the chronic stage (\(\Xi=1\)), but explore increased transmissibility during the acute stage (\(\Xi>1\)) in the sensitivity analysis. The forces of infection for the base-case (assuming proportional mixing) were defined by:

\[
\begin{align*}
\lambda_{0,0} &= \pi \left( \Omega_{0,0} + \Gamma \Omega_{0,1} + \Pi \Omega_{1,0} + \Gamma \Pi \Omega_{1,1} \right) / \Omega_{0,0} + \Lambda_{0,0} + \Gamma (\Omega_{0,1} + \Lambda_{0,1}) + \Pi (\Omega_{1,0} + \Lambda_{1,0}) + \Gamma \Pi (\Omega_{1,1} + \Lambda_{1,1}) \\
\lambda_{0,1} &= \Gamma \lambda_{0,0} \\
\lambda_{1,0} &= \Pi \lambda_{0,0} \\
\lambda_{1,1} &= \Gamma \Pi \lambda_{0,0} \\
\end{align*}
\]

where

\[
\Omega_{ij,k} = \Xi A_{ij,k} + C_{ij,k} + (1 - \alpha(t)) T_{ij,k} + F_{ij,k}
\]

and

\[
\Lambda_{ij,k} = \alpha(t) T_{ij,k} + X_{ij,k}.
\]

For the sensitivity analysis examining fully assortative mixing between low and high risk PWID, the following forces of infection were used:

\[
\begin{align*}
\lambda_{0,0} &= \pi (\Omega_{0,0} + \Gamma \Omega_{0,1}) / \Omega_{0,0} + \Lambda_{0,0} + \Gamma (\Omega_{0,1} + \Lambda_{0,1}) \\
\lambda_{0,1} &= \Gamma \lambda_{0,0} \\
\lambda_{1,0} &= \Pi \lambda_{0,0} \\
\lambda_{1,1} &= \Gamma \Pi \lambda_{0,0} \\
\end{align*}
\]

Parameters

Edinburgh parameters were obtained from the Needle and Exchange Surveillance Initiative (NESI) surveys 2007\(^6\), 2008/2009\(^7\), and 2010 (unpublished), and the Scottish HCV treatment database\(^8\). Melbourne estimates were taken from Melbourne injecting drug use (MIX) and Networks cohorts\(^9, 10\), and NSP survey estimates from 2002-2011\(^11, 12\). Vancouver parameters were determined from the Community Health and Safety Evaluation (CHASE) and Urban Health Research Initiative (UHRI) cohorts\(^13-15\).

Total number of PWID

We estimate there are 4,241 [3,276-5,681 95% CI] PWID in Edinburgh (calculated by using previous estimates\(^16\) and inflating by a factor of 1.3 based on subsequent Bayesian analysis of Scotland PWID estimates\(^17\)). Melbourne has approximately 25,000 PWID, estimated from the number of OST clients\(^18\) and self-reported OST treatment uptake\(^18, 19\). In Vancouver, the number of PWID has been estimated at 13,500 [10,000-15,000 95% CI]\(^20\).

High risk

We used unstable housing as a measure of ‘high-risk’, as it has been associated with HCV incidence in Vancouver (RR 1.4 [1.0-2.1, 95% confidence interval])\(^15\) and Scotland/UK (RR 3.6 [1.5-8.7, 95% confidence interval])\(^21, 22\). No population characteristics have yet been associated with HCV incidence in Melbourne. Although unstable housing has been associated with a higher risk of HCV acquisition, it was not statistically significant, possibly due to a lack of power in the study\(^9\). We therefore assume a high risk population in Melbourne approximate in size to that of the unstable housing fraction (17% [14-20%, 95% confidence interval], unpublished data from MIX\(^10\) cohort), with the relative risk comparable to that seen in the UK (RR 3.6), as it was the highest risk ratio reported for unstable housing across the cities.

OST
The reduction in HCV susceptibility and infectivity on OST was determined from a recent meta-analysis of pooled UK data\textsuperscript{22}, which showed a relative risk of 0.41 [0.21-0.82, 95% confidence interval] while on OST. We note that not all studies have shown this effect. For example, a meta-analysis by Hagan et al.\textsuperscript{23} found a relative risk of acquiring HCV of 0.60 (0.35, 1.03) for PWID on OST, but the effect did not reach statistical significance.

**Injecting duration**

Site-specific estimates of the average duration of injecting until long-term cessation are unavailable and difficult to obtain due to bias. Longitudinal surveys of PWID recruited from drug treatment sites tend to over-represent active injectors with a longer duration of injecting, whereas general population surveys over-represent ex-injectors with short periods of injecting. Sweeting et al.\textsuperscript{24}, combined UK population surveys and other information on PWID in order to adjust for sample biases, subsequently estimating 11 years from initiation to permanent cessation. We therefore use 11 years as the average injecting duration until cessation point value in all the sites. For Edinburgh, the cross-sectional NESI survey reported a median injecting duration of 8 years\textsuperscript{6,7} (with a 32 year median age of survey participant). Other longitudinal surveys — that may be subject to recruitment bias — estimate longer average duration. For example, the Edinburgh Addiction Cohort estimated a median duration of injecting of 5 years for people unexposed to OST (with 30% ceasing within one year) and 20 years for people with longer exposure to OST\textsuperscript{25}. Therefore we sample from a wide uncertainty interval for the uncertainty and sensitivity analyses.

For the UK, we sample from the range reported in Sweeting et al.\textsuperscript{24} of 6-20 years (using a triangular distribution with 11 years as the mean). For Melbourne, the median injecting duration reported in the Australian NSP survey (from which we estimated HCV prevalence) is approximately 15 years\textsuperscript{11} (with a median survey age of 35), 7 years higher than that reported in Edinburgh in the NESI survey. Hence, we increase the upper range by 7 years for Melbourne as compared to Edinburgh (sampling from 6-27 years, mode 11, triangular distribution). For Vancouver, the median injecting duration reported in the VIDUS cohort (from which we estimated HCV prevalence) was 11 years at baseline\textsuperscript{15} (with a median age of 34), hence we increase the upper sampling range by 3 years as compared to Edinburgh, sampling from 7-23 years (mode 11, triangular distribution).

**Treatment prior to 2002**

Clinical guidance in the UK, Europe, US, and Australia recommended against treatment of PWID prior to 2002\textsuperscript{26-29}. Therefore, we model no treatment of PWID before 2002.

**Simulation Methods**

All equations were solved using MATLAB (version R2010a), using the inbuilt ordinary differential equation solver ODE45, a variable timestep solver based on a Runge-Kutta formula. Simulations were performed on a MacBook Pro with a 2.33 GHz Intel Core 2 Duo processor, running OS 10.7.5.
References


