Hepatitis C virus infection: Spread and Impact in the Netherlands

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The effect of hepatitis C treatment and human immunodeficiency virus (HIV) co-infection on the disease burden of hepatitis C among injecting drug users in Amsterdam

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ABSTRACT

Aims The hepatitis C virus (HCV) disease burden among injecting drug users (IDUs) is determined by HCV incidence, the long latency period of HCV, competing mortality causes, presence of co-infection and HCV treatment uptake. We examined the effect of these factors and estimated the HCV disease burden in Amsterdam. Design A Markov model was developed, incorporating HCV and human immunodeficiency virus (HIV), and parameterized with data from the Amsterdam Cohort Studies, surveillance studies and literature. Setting IDU population of Amsterdam. Measurements HCV infection simulated from its acute phase to HCV-related liver disease (i.e. decompensated cirrhosis and hepatocellular carcinoma). Findings The HCV prevalence among IDUs in Amsterdam increased to approximately 80% in the 1980s. From 2011 to 2025, the HCV-related disease prevalence will accordingly rise by 36%, from 57 cases (95% range 33–94) to 78 (95% range 43–138), respectively. In total, 945 (95% range 617–1309) individuals will develop HCV-related liver disease. This burden would have been 33% higher in the absence of HIV, resulting in 1219 cases (95% range 796–1663). In Amsterdam, 25% of HIV-negative IDUs receive successful HCV treatment, reducing the cumulative disease burden by 14% to 810 (95% range 520–1120). Further reduction of 36% can be achieved by improving treatment, resulting in 603 cases (95% range 384–851). Conclusions The hepatitis C virus burden among injecting drug users in Amsterdam has been reduced by a high competing mortality rate, particularly caused by HIV infection, and to a smaller extent by hepatitis C virus treatment. Improved hepatitis C virus treatment is expected to contribute to reduce the future hepatitis C virus disease burden.

Keywords HCV, HCV disease burden, HCV treatment, HIV co-infection, injecting drug use, mathematical model.

INTRODUCTION

Injecting drug users (IDUs) who share injecting equipment are at high risk for infection with hepatitis C virus (HCV) and other blood-borne pathogens. Since blood product screening was initiated in the Netherlands in 1991, IDUs account for the vast majority of new HCV infections nation-wide. Globally, HCV antibody prevalence in IDUs ranges from 15% to 98% [1,2]. HCV infections become chronic in about 75% of cases [3], and may lead to cirrhosis and eventually to decompensated cirrhosis or hepatocellular carcinoma (HCC) decades after infection [4]. With improved treatment since 2001, response to treatment among chronic carriers who are human immunodeficiency virus (HIV)-negative is 42–82%, depending on HCV genotype [5]. However, as HIV and HCV share transmission routes, HIV co-infection is common [1], affecting approximately 30%
of the HCV-infected IDUs in Amsterdam [6]. These co-infections are associated with a lower rate of spontaneous HCV clearance, faster HCV progression and less favourable HCV treatment outcome [7].

In Amsterdam, injecting drug use started in the late 1960s and remained common practice during the 1970s and 1980s. The prevalence of HCV antibodies among ever-injectors peaked in the 1980s, when more than 85% tested positive [3,6]. With awareness of HIV and national initiation of comprehensive harm-reduction programmes in the 1980s, risk behaviour declined among IDUs [8–10] and HCV prevalence declined, as found by the Amsterdam Cohort Studies (ACS) [6]. Amsterdam’s IDU population decreased in the 1990s due to the limited number of new injectors, mortality and selective emigration of foreign IDUs with acquired immune deficiency syndrome (AIDS) to their home countries [11].

Several studies have modelled the future disease burden of HCV for the general population [12–16] and for IDUs [17–23], some taking into account HIV infections and HCV treatment. These studies show that the prevalence of HCV-related liver disease will rise during future years. The current population of IDUs in Amsterdam is unique: injecting is no longer common [24], mortality remains high and HCV and HIV incidence have stabilized at very low rates [6]. We therefore developed a mathematical model to estimate the HCV-related disease burden, defined as the occurrence of decompensated cirrhosis or HCC, for HCV-infected populations that are in an advanced stage, using data on IDU population dynamics including the rising and declining trends of injecting behaviour over time, HCV incidence and the natural history of HCV infection. We had the unique opportunity to use longitudinal data collected since 1985 from the ACS among IDUs. We also examined the impact of HIV on the HCV disease burden: HIV-positive IDUs are at increased risk of mortality compared to HIV-negative IDUs, but effective HIV treatment has decreased this risk [25]. Several scenarios with and without HIV were explored, as well as the influence of HCV treatment on the HCV disease burden.

METHODS
Markov model

The natural history of HCV was modelled using a compartmental model representing eight health stages (Fig. 1). Individuals enter the model as IDUs at risk for acquiring HCV and HIV. To reflect the effect of ceased injecting, reduced needle-sharing and reduced risk behaviour, IDUs can switch to the former IDU compartment, in which individuals do not inject or inject safely. They can also re-enter the current IDU stage. Acute HCV-infected IDUs can spontaneously clear HCV or develop a chronic infection. Disease progression is modelled through cirrhosis, decompensated cirrhosis and HCC. HIV infection can occur at all stages. New HIV infections among individuals with decompensated cirrhosis and HCC are ignored on the assumption that new HIV infections do not cause accelerated HCV progression in these already progressed patients. The model includes two types of mortality: competing mortality (due to causes unrelated to HCV) and HCV-related mortality (by decompensated cirrhosis or HCC). The main outcome is HCV-related liver disease, defined as decompensated cirrhosis or HCC.

Model parameters

We assumed that injecting drug use started in 1960. The annual number of new injectors then increased, peaking at 570 (range 515–650) during 1975–1979 and declining thereafter (Table 1). The annual number of new injectors was estimated based on needle-exchange data and data from the central methadone register (CMR) of Amsterdam from the years 1987, 1992, 1997, 2002 and 2007, using the method of Nordt & Stohler [26]. This method assumes that the maximum number of IDUs in methadone treatment 7 years after onset of regular drug use is 27%. To check the impact of this assumption we have set this maximum to two plausible values, 14% and 41%, and estimated the incidence. The estimates did not deviate excessively from the calculated range, and therefore we assumed that it was valid to use the reported 27% by Nordt & Stohler [26] [see also supporting information S.1.1.2 (details of supporting information are given at the end of the paper)]. The estimated population served as the IDU population entering the Markov model to predict the burden of HCV. The age trend of new IDUs was obtained from ACS, an open and ongoing prospective cohort study initiated in 1985 to study the prevalence, incidence and risk factors of HIV and other blood-borne and sexually transmitted infections [27,28].

The population-specific transition rates that determine the probability to move between health stages are shown in Table 2. Data on transition rates from current IDU to former IDU ($P_{stop}$) and vice versa ($P_{start}$) and background mortality ($\mu$) were supplied by ACS. Background mortality was categorized according to age and HIV status and divided into two calendar periods (e.g. pre-1997 and 1997 onwards) as a proxy for increased survival of HIV-infected IDUs due to the introduction and widespread use of combination antiretroviral therapy in 1997. The rates for acquiring HIV and competing mortality rates for HIV-positives were derived similarly from ACS data [6]. HCV and HIV incidence for 1985 to 2005,
as published by Van den Berg et al. [6], was used to estimate the annual rate of acquiring HCV \( (P_{hc}) \) and HIV \( (P_{hv}) \) [see supporting information S.1.1.1]. We assumed that HCV was introduced to Amsterdam in 1965 and HIV in 1980. HCV incidence from 2006 to 2010 was assumed to be constant and equal to the average HCV incidence from 2001 to 2005; the same was assumed for HIV. From 2010 onwards, HCV incidence was set to zero to estimate the cumulative HCV disease burden caused by HCV infections acquired in the past. The progression rate of asymptomatic chronic HCV to cirrhosis \( (P_{cr}) \) was age-dependent, as estimated by Deuffic-Burban et al. [12, 13]. We found a low rate, as did ACS [29]. The transition rates for the development of decompensated cirrhosis \( (P_{dc}) \) and HCC \( (P_{h}) \) were derived from the literature [30–35] and the HCV-related mortality rates \( m_{dc} \) and \( m_{h} \) were derived from ACS [29]. Because HIV co-infection reduces the HCV clearance rate and accelerates HCV progression [36], the transition rates \( P_{cl}, P_{ch}, P_{cr}, P_{dc} \) and \( P_{h} \) were HIV-status-dependent (Table 3).

Analysis

The natural history of HCV in the IDU population was simulated using the R statistical package, version 2.10.1 [17]. Individuals move between health stages over 1-year time-steps, with transition rates determined by transition equations [see supporting information S.1.3]. The transition equations were constructed using the parameter estimates provided in the previous section and supporting information S.1.1. The model estimated the number of individuals in different health stages over time.
Competing mortality is defined as not hepatitis C virus (HCV)-related causes of death. The hazard rates were calculated for different age categories and two time-periods.

Studies (ACS) about risk behaviour since previous visit. Calculated as annual probability for injecting drug users (IDUs) to stop injecting (i.e. stop injecting, start methadone treatment or inject safely) based on self-reported data from IDUs in the Amsterdam Cohort Studies on human immunodeficiency virus (HIV).

Table 2 Population-specific annual transition rates supplied by the Amsterdam Cohort Studies on human immunodeficiency virus (HIV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition rate for IDU to former IDU ($P_{stop}$)</td>
<td>1960–89 0.005–0.150, ≥1990 0.010–0.200</td>
</tr>
<tr>
<td>Transition rate for former IDU to IDU ($P_{start}$)</td>
<td>0.01–0.5</td>
</tr>
</tbody>
</table>

Competing mortality for HIV-negative IDUs by age and calendar time ($\mu^{IDU}$)

<table>
<thead>
<tr>
<th>Year &lt; 1997</th>
<th>Age &lt; 30 0.001–0.006, Age 30–44 0.001–0.016, Age ≥ 45 0.002–0.021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year ≥ 1997</td>
<td>Age &lt; 30 0.001–0.006, Age 30–44 0.001–0.012, Age ≥ 45 0.001–0.020</td>
</tr>
</tbody>
</table>

Competing mortality for HIV-positive IDUs by age and calendar time ($\mu^{HIV}$)

<table>
<thead>
<tr>
<th>Year &lt; 1997</th>
<th>Age &lt; 30 0.008–0.042, Age 30–44 0.019–0.076, Age ≥ 45 0.060–0.224</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year ≥ 1997</td>
<td>Age &lt; 30 0.003–0.022, Age 30–44 0.004–0.073, Age ≥ 45 0.025–0.088</td>
</tr>
</tbody>
</table>

To account for uncertainty in parameter estimates, we set minimum and maximum values for each. Latin hypercube sampling was used to choose a parameter from the parameter space for every run [38]. In total, 1000 simulations were performed for every scenario. The results are presented as median and 95th percentile ranges. A sensitivity analysis estimating the partial rank correlation coefficient (PRCC) was performed to examine the contribution of the various parameters to variation in outcome [39] defined as the cumulative HCV-related disease burden caused by HCV infection acquired between 1960 and 2010.

Scenario studies

To examine the effect of HCV treatment on the HCV disease burden, several scenarios were studied and compared with the baseline model. First, we explored a situation without HCV treatment. Secondly, we modelled the effect of currently implemented HCV treatment. We assumed that chronically HCV-infected individuals who were HIV-negative could have received treatment since 2005 [40]. The successful HCV treatment rate is calculated as the product of treatment uptake and the percentage of those treated successfully among those receiving treatment. This transition rate, from the chronic HCV compartment to the not-HCV-infected compartment, ranged between 0.20 and 0.30. It was based on the treatment rate found by the Dutch C project [40], assuming that the success rate in the general IDU population would be lower than the rate found in the population eligible for the Dutch C project. In the third scenario, the impact of HCV treatment improvements was studied by increasing the treatment transition rates after 2012 from 0.20–0.30 to 0.50–0.60 for HIV-negatives and from zero to 0.20–0.30 for HIV-positives. In a fourth scenario, a best-case scenario, these rates were 0.90–1 and 0.50–0.60, respectively.

We also modelled the effect of HIV spread on the HCV disease burden for the various HCV treatment scenarios. In the baseline scenario, HIV was introduced in the population in 1980. In the second scenario, it was assumed that HIV was never introduced.

RESULTS

HCV disease burden

The estimated IDU population living with HCV as a percentage of the total IDU population is shown in Fig. 2. The population of injectors grew from an average of 364 individuals (95% range 307–425) during the 1960s to on average 6275 (95% range 5633–6937) during the 1980s [see supporting information S.2]. During the 1980s approximately 80% of the population was HCV-positive, while HIV prevalence was about 10%. Although the incidence of both viruses declined after 1990 [6], HCV prevalence among IDUs remained relatively high. According to our findings and ACS data, HCV prevalence among ever-injectors in 2011 is 79% (95% range 73%–89%), of whom an estimated 57 individuals (95% range 33–94) have HCV-related disease, with decompensated cirrhosis in 38 (95% range 20–70) individuals and HCC in 19 (95% range 9–35) individuals (Fig. 3). Due to the long asymptomatic phase of HCV infection, the disease burden will accordingly rise by 36% during the next decade, to 78 cases (95% range 43–138) in 2025. However, after 2025 the number of individuals living with HCV-related liver disease will again decline. The cumulative HCV disease burden resulting from infections acquired before 2010 will be 945 cases (95% range 617–1309). The case-fatality rate is 50 (95% range 36–65) per 1000 HCV infected cases.
The validity of the model was assessed by comparing the modelled HCV and HIV prevalence with prevalence data observed among ACS participants (Fig. 2). HCV prevalence data was available until the year 2004. The observed anti-HCV prevalence is slightly higher than the prevalence of chronic HCV estimated by the model. In addition, the higher observed HCV and HIV prevalence (before the year 1997) might reflect the high-risk population that was recruited; the ACS was initiated to study...
the spread of HIV and its outcome and special attention was given to include HIV-infected drug users. Consequently, the observed HIV prevalence during the 1980s and 1990s is higher than the expected prevalence in the general drug user population. The estimated prevalence is in line with the prevalence found among 200 IDUs in Amsterdam in 1996 [i.e. 25.5%, 95% confidence interval (CI) 19.7–32.3] and in 1998 (25.9%, 95% CI 19.9–32.3) [41].

The relative importance of the various parameters was examined by sensitivity analysis. It showed that outcome uncertainty is caused mainly by the competing mortality rates for HIV-negative (μ\text{H}^-) and HIV-infected (μ\text{H}^+) individuals. The HCV clearance rate (P_{\text{clH}^+}), the rate of developing cirrhosis (P_{\text{chH}^+}) and developing decompensated cirrhosis (P_{\text{dcH}^+}) for HIV-infected individuals caused little imprecision [see supporting information S.3].

**Scenario studies**

The implementation of HCV treatment can substantially reduce the disease burden. If 25% of the HIV-negative population is treated successfully for HCV, the cumulative HCV disease burden will decrease by 14% from 945 to 810 (95%, range 520–1120) in 2060, where 2060 is the year in which all the individuals who started injecting before the year 2010 have died. Further reduction of the disease burden can be achieved by improving treatment. Assuming that 55% of the HCV-positive HIV-negative IDUs and 25% of the HIV-positives is treated successfully from 2012, the cumulative burden could be reduced by 36% to 603 (95%, 384–851) (Fig. 4a). In the best-case scenario, a 47% reduction can be achieved when HCV treatment is extended to 95% for HIV-negatives and 65% for HIV-positives. When implementation of improved treatment is postponed by 1 year, 2% more individuals will develop HCV-related liver diseases.

In the hypothetical scenario in which HIV was absent, the prevalent number of IDUs living with HCV-related disease in 2011 was estimated at 59 (95%, range 37–93).

In Fig. 4, the HCV-related disease burden per calendar year for the scenario without HIV (Fig. 4b) is compared to the scenario with HIV (Fig. 4a). It shows that the number of individuals living with HCV-related liver disease rises by 33% if accelerated progression and increased competing mortality due to HIV are removed from the model. The cumulative HCV disease burden caused by HCV infections acquired before 2010 is then 1219 (95%, range 796–1663). This number falls to 978 (95%, range 637–1349) if 25% of HCV-infected IDUs are treated successfully; it drops to 460 (95%, range 288–683) if 55% are treated.

**DISCUSSION**

Given the high rate of injecting drug use in Amsterdam from the 1960s through 1980s, the local burden of
HCV-related liver disease will rise during the next decade. The subsequent introduction and spread of HIV among injectors reduced this burden due to mortality among HIV-positives, even though HIV/HCV-co-infected IDUs are at increased risk of HCV disease progression. HCV treatment can reduce the HCV disease burden, but the HCV epidemic in Amsterdam is advanced and already the IDU population has declined in numbers and HCV incidence, limiting the absolute effects of treatment success rates in this population.

Our study gains its strength from using detailed prospective data collection on HIV and HCV prevalence, incidence and clinical outcomes from the well-defined ACS over a period of 25 years. IDUs in the ACS were followed longitudinally and deaths were registered. Studies indicate that serious liver diseases will develop eventually in a large percentage of HCV-infected individuals [42–44], but they are not seen widely in ACS participants [29,45]. Our results suggest that many IDUs do not reach the age of developing HCV-related liver diseases because they die from other causes, including HIV. Furthermore, in agreement with findings from the ACS [29], a published meta-analysis found that the progression rates found in clinical settings are higher than is found in non-clinical settings, due to referral bias [44]. Only the minority of studies are performed in non-clinical settings such as the ACS.

In accordance with the findings of Davis et al. [16], we conclude that the impact of current available HCV treatment on the HCV-related disease burden is limited and implementation of new improved treatment strategies might be worthwhile, to some extent. This effect was studied by introducing HCV treatment into the model in 2005 and varying the successful treatment rate since 2012, while in the model of Davis et al. the year of introducing treatment was 2010 [16]. As a result of postponing implementation of treatment in populations that are declining in numbers, just as in Amsterdam, fewer individuals are eligible for treatment or are even alive at the time new treatment becomes available, leading eventually to a reduced benefit of implementing new treatment. This emphasizes the importance of rapid implementation when new treatment becomes available.

In growing or stable populations with ongoing risk behaviour and HCV transmission HCV treatment will be more effective than in populations that are declining in numbers. Several modelling studies have suggested that implementation of HCV treatment can lead to a substantial reduction of HCV prevalence [21,23,46], suggesting that HCV treatment could act as prevention strategy [21,23].

We were able to predict the future disease burden despite having simplified several mechanisms that play a role in its determination. Unlike most other modelling studies [12,18,20], we took into account irregular drug careers, in which IDUs stop and start injecting. Due to the importance of population dynamics, it is difficult to compare results between studies. For example, the steep decrease of injecting observed in Amsterdam since the 1980s has not occurred in Australia [18]. HCV prevalence is nevertheless lower in Australia than in Amsterdam, but the HCV disease burden is not correspondingly lower, because Amsterdam’s higher HIV prevalence makes its IDUs less likely to die of HCV-related disease. Among IDUs in Glasgow, Scotland, HCV prevalence is similarly lower than in Amsterdam, but Hutchinson and coworkers have estimated a higher HCV disease burden [20]. They conclude that ignoring HIV/HCV-co-infection causes underestimation of the HCV disease burden, whereas we conclude that it causes overestimation. These contradictory conclusions might reflect the trade-off between accelerated HCV disease progression and increased competing mortality rates for HIV-co-infected IDUs. In addition, populations may differ in risk behaviour.

A limitation of our study is that ACS participation is voluntary, possibly leading to selection bias. Furthermore, the model does not distinguish between stages of fibrosis, but assumes that the probability of developing cirrhosis is age-dependent. Moreover, we assumed that IDUs are equal in their probability to acquire HCV, irrespective of prior HCV infections. However, re-infections occur in IDUs with ongoing risk behaviour [47,48], and probability of clearance may be higher among those who have cleared previous infection [49,50]. Hence, there might be a slight overestimation of the HCV-related disease burden, although we accounted for uncertainty by performing uncertainty analysis. Furthermore, HCV and HIV data from the total drug user population living in Amsterdam are scarce and therefore model validation is a delicate issue. The model was validated by comparing the modelled results with prevalence data from the ACS and two surveillance studies among IDUs in Amsterdam in 1996 and 1998 [41].

In conclusion, we have shown that high competing mortality in the past, related to HIV, reduced the HCV disease burden in Amsterdam. HCV treatment has similarly reduced the HCV disease burden and future improvement in treatment uptake and efficacy can reduce the HCV disease burden even further, but only to a certain extent. For similar settings, with decreasing IDU populations or effective harm reduction programmes, our predictions can be interpreted as trends. Amsterdam’s IDU population is now small, with few new injectors, but changes in injecting practice or migration could trigger increased injecting and a new HCV epidemic. If so, harm reduction programmes and education about HIV and HCV might decrease the risk of HCV infection for future drug users compared to those in the 1970s and 1980s.
For today’s fast-growing IDU populations, as in central Asia [51] or in emerging HCV-risk populations, such as men who have sex with men [52], better treatment uptake can be expected to reduce substantially the future HCV disease burden and, in addition, to reduce current HCV transmission.

Declarations of interest

None.

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**Supporting information**

Additional Supporting Information may be found in the online version of this article:

**Appendix S1** Extensive description of the Markov model to estimate the burden of hepatitis C.

**Appendix S2** The population size of injecting drug users in Amsterdam, the Netherlands.

**Appendix S3** Sensitivity analysis.

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S.1. Extensive description of the Markov model to estimate the burden of Hepatitis C


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Here we give a more extensive description of the Markov model that was developed to estimate the future HCV-related disease burden among injecting drug users (IDUs) in Amsterdam. We will discuss parameter estimates, the transition matrix, simulation, Latin hypercube sampling, uncertainty analysis, and model validation.

1 Parameter Estimates

The parameter estimates were derived from data from the Amsterdam Cohort Studies on HIV infection and AIDS among IDUs, the Central Methadone Register (CMR) of Amsterdam, and the literature. The estimates are given in the Tables 1, 2, and 3 of the main text and in this section.

1.1 Annual transition rates for HCV ($P_{hcv}$) and HIV ($P_{hiv}$)

The annual transition probabilities for infection with HCV and HIV (table 1), since 1985, were derived from the Amsterdam Cohort Studies and published before by Van den Berg et al. (6). It was assumed that HCV was introduced in 1965 and HIV was introduced in 1980.

1.2 Annual number of new injectors

To estimate the number of new injectors entering the model every year, we used a method proposed by Nordt and Stohler (4), based on the assumption that the proportion of heroin users participating in substitution treatment ($S$) depends on the individual time ($t$) in years since onset of regular drug use. The approximation function is as follows:

$$S = 0.363 \times (1 - t^{-1}) \times 0.98^t$$

where

$$t > 2$$

Based on the observed number of individuals who started using heroin $x$ years ago that participate in substitution treatment during an average single day ($N_x$), the incidence of (first) regular heroin use ($I_x$) is calculated as:

$$I_x = N_x / S_x$$

In Amsterdam, all patients in methadone treatment are registered at the central methadone register (CMR). In 2007, 2383 patients participated in methadone treatment. On average, 1759 patients received methadone on a single day. Annual data were weighted by the number of methadone dosages during 2007 to estimate the distribution of the period since first regular heroin use on an average single day. The
weighted median calendar year of first regular heroin use among methadone patients was 1981 (IQR 1976-1986). Applying equation 2, the total number of new heroin users between 1965 and 2005 was 8793 individuals, and the median calendar year of starting heroin use was estimated as 1978 (IQR 1974-1983). The same method was used to estimate the incidence from the years 1987, 1992, 1997, and 2002, resulting in five predictions of the heroin incidence over time. Then, the average number of new IDUs was estimated per 5-year categories, starting in 1965. The lowest and highest 5-year estimates were used as minimum-maximum range.

On one hand this method might underestimate the incidence of heroin use, since it does not account for heroin users who temporarily lived in Amsterdam as drug tourists during the eighties. On the other hand, we estimated the number of heroin users, including users who are not necessarily injectors, resulting in an overestimate. Since we do not know what the impact of these two phenomena are on the incidence, we assumed that the incidence of new injectors is equal to the estimated incidence of heroin use. To assess the validity of the approximation formula, we changed the values of the linear scale factor. Realistic changes (i.e. changing the linear scale factor into 0.180 and and 0.545) did not result in estimates outside the range as calculated by the stated approximation formula. By performing independent latin hypercube sampling for the 5-year estimates, as explained in section 5, we accounted for uncertainty in the shape of the curve.

2 Markov Model

A deterministic model was developed to model the individual careers of IDUs regarding injecting behaviour, HCV, and HIV. First we identified eight relevant life and health stages. We distinguished between current injectors and former injectors to account for changing risk behavior. The natural history of HCV infection was divided into acute infection, chronic infection, cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma (HCC). The model is represented by the following function:

$$V_{(t+1)(a+1)} = (B_{(t,a)} + V_{(t,a)}) \times M_{(t,a)}$$  \hspace{1cm} (4)

where the population \( (V) \) at time-point \( (t+1) \) and age \( (a+1) \) is the annual number of new injectors \( (B) \) added to the population at time-point \( (t) \) and age \( (a) \) times the transition matrix \( (M) \). The model uses discrete time-steps of 1 year.

3 Transition Matrix

The transitions between the eight health stages are determined by annual transition probabilities that were derived from several data sources and dependent on several variables. The movements of individuals among health stages are expressed by a 20 x 20 transition matrix \( (M) \):
\[
M = 
\begin{pmatrix}
  m_{1-1} & m_{1-2} & 0 & 0 & m_{1-5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  m_{2-1} & m_{2-2} & 0 & 0 & m_{2-4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  m_{3-1} & 0 & 0 & m_{3-4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & m_{4-3} & m_{4-4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & m_{5-3} & 0 & m_{5-5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & 0 & 0 & m_{6-5} & m_{6-6} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & 0 & 0 & 0 & m_{7-6} & m_{7-7} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & 0 & 0 & 0 & 0 & m_{8-6} & m_{8-8} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  m_{9-1} & m_{9-2} & m_{9-3} & m_{9-4} & m_{9-5} & m_{9-6} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
  m_{10-1} & m_{10-2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{10-7} & m_{10-8} & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
  m_{11-1} & 0 & 0 & 0 & m_{11-5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{11-11} & m_{11-12} & 0 & 0 & m_{11-15} & 0 & 0 & 0 & 0 \\
  m_{12-1} & 0 & 0 & m_{12-4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{12-11} & m_{12-12} & 0 & m_{12-14} & 0 & 0 & 0 & 0 & 0 & 0 \\
  m_{13-1} & 0 & 0 & m_{13-4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{13-11} & 0 & 0 & m_{13-14} & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & m_{14-3} & m_{14-4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{14-11} & m_{14-12} & m_{14-14} & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & m_{15-3} & 0 & m_{15-5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{15-13} & 0 & m_{15-15} & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & 0 & 0 & m_{16-5} & m_{16-6} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{16-15} & m_{16-16} & 0 & 0 & 0 & 0 & 0 \\
  0 & 0 & 0 & 0 & 0 & m_{17-6} & m_{17-7} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{17-17} & 0 & 0 & 0 & 0 \\
  0 & 0 & 0 & 0 & 0 & 0 & m_{18-6} & m_{18-8} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_{18-18} & 0 & 0 & 0 & 0 \\
  m_{19-1} & m_{19-2} & m_{19-3} & m_{19-4} & m_{19-5} & m_{19-6} & 0 & 0 & 0 & 0 & 0 & m_{19-11} & m_{19-12} & m_{19-13} & m_{19-14} & m_{19-15} & m_{19-16} & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
  m_{20-1} & m_{20-2} & m_{20-3} & m_{20-4} & m_{20-5} & m_{20-6} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0
\end{pmatrix}
\]
Treatment and future burden of HCV in injecting drug users within the HIV-negative and HIV-positive groups are as follows: the supplement. The transition equations that determine the transition probabilities specific variables that are defined in the main text (Tables 1, 2, 3) and in section 1 of this supplement. The definitions of the matrix elements are given in table 2 and table 3.

The elements are determined by functions of several population- and pathogen-specific variables that are defined in the main text (Tables 1, 2, 3) and in section 1 of this supplement. The transition equations that determine the transition probabilities within the HIV-negative and HIV-positive groups are as follows:

\[
m_{1-1} = (1 - p_{hiv}) \times (1 - p_{hcv} - \mu_H^- - p_{stop})
\]
\[
m_{2-1} = (1 - p_{hiv}) \times p_{stop}
\]
\[
m_{3-1} = (1 - p_{hiv}) \times p_{hcv}
\]
\[
m_{9-1} = (1 - p_{hiv}) \times \mu_H^-
\]
\[
m_{1-2} = (1 - p_{hiv}) \times p_{start}
\]
\[
m_{2-2} = 1 - p_{start} - \mu_H^-
\]
\[
m_{9-2} = (1 - p_{hiv}) \times p_{hcv}
\]
\[
m_{3-3} = (1 - p_{hiv}) \times (1 - p_{ct} - \mu_H^-)
\]
\[
m_{9-3} = (1 - p_{hiv}) \times \mu_H^-
\]
\[
m_{2-4} = (1 - p_{hiv}) \times p_{stop}
\]
\[
m_{3-4} = (1 - p_{hiv}) \times p_{hcv}
\]
\[
m_{4-4} = (1 - p_{hiv}) \times (1 - p_{hcv} - p_{stop} - \mu_H^-)
\]
\[
m_{9-4} = (1 - p_{hiv}) \times \mu_H^-
\]
\[
m_{1-5} = (1 - p_{hiv}) \times p_{treat}^-
\]
\[
m_{5-5} = (1 - p_{hiv}) \times (1 - p_{treat}^- - p_{cr}^- - \mu_H^-)
\]
\[
m_{6-5} = (1 - p_{hiv}) \times p_{cr}^-
\]
\[
m_{9-5} = (1 - p_{hiv}) \times \mu_H^-
\]
\[
m_{6-6} = (1 - p_{hiv}) \times (1 - p_{dc}^- - p_{h}^- - \mu_H^-)
\]
\[
m_{7-6} = (1 - p_{hiv}) \times p_{h}^-
\]
\[
m_{8-6} = (1 - p_{hiv}) \times p_{h}^-
\]
\[
m_{9-6} = (1 - p_{hiv}) \times \mu_H^-
\]
\[
m_{7-7} = 1 - \mu_{dc}
\]
\[
m_{10-7} = \mu_{dc}
\]
\[
m_{8-8} = 1 - \mu_h
\]
\[
m_{10-8} = \mu_h
\]
\[
m_{11-11} = 1 - p_{hcv} - \mu_H^- - p_{stop}
\]
\[
m_{11-11} = p_{stop}
\]
\[
m_{13-11} = p_{hcv}
\]
\[
m_{19-11} = \mu_H^+
\]
\[
m_{11-12} = p_{start}
\]
\[
m_{12-12} = 1 - p_{start} - \mu_H^+
\]
\[
m_{19-12} = \mu_H^+
\]
\[
m_{14-13} = p_{cl}
\]
\[
m_{15-13} = 1 - p_{cl}^+ - \mu_H^+
\]
\[
m_{19-13} = \mu_H^+
\]
\[
m_{12-14} = p_{stop}
\]
\[
m_{13-14} = p_{hcv}
\]
\[
m_{14-14} = p_{stop} - p_{hcv} - \mu_H^+
\]
\[
m_{19-14} = \mu_H^+
\]
\[
m_{11-15} = p_{treat}^-
\]
\[
m_{15-15} = 1 - p_{treat}^- - p_{cr}^- - \mu_H^+
\]
\[
m_{16-15} = p_{cr}^+
\]
\[
m_{19-15} = \mu_H^+
\]
\[
m_{16-16} = 1 - p_{dc}^- - p_{h}^- - \mu_H^+
\]
\[
m_{17-16} = p_{h}^+
\]
\[
m_{18-16} = p_{h}^+
\]
\[
m_{19-16} = \mu_H^+
\]
\[
m_{17-17} = 1 - \mu_{dc}
\]
\[
m_{20-17} = \mu_{dc}
\]
\[
m_{18-18} = 1 - \mu_{h}
\]
\[
m_{20-18} = \mu_{h}
\]
The transition equations from the HIV-negative group to the HIV-positive group are as follows:

\[
\begin{align*}
    m_{11+1} &= p_{hiv} \times (1 - p_{hc} - \mu_H - p_{stop}) \\
    m_{13+1} &= p_{hiv} \times p_{hc} \\
    m_{14+3} &= p_{hiv} \times p_{H^+} \\
    m_{14+4} &= p_{hiv} \times \mu_H \\
    m_{15+5} &= p_{hiv} \times (1 - p_{H^+} - p_{cr} - \mu_H) \\
    m_{17+6} &= p_{hiv} \times p_{dc} \\
    m_{19+6} &= p_{hiv} \times \mu_H \\
    m_{12+1} &= p_{hiv} \times p_{stop} \\
    m_{19+1} &= p_{hiv} \times \mu_H^+ \\
    m_{15+3} &= p_{hiv} \times (1 - p_{hc} - p_{stop} - \mu_H) \\
    m_{12+4} &= p_{hiv} \times p_{stop} \\
    m_{14+4} &= p_{hiv} \times (1 - p_{hc} - p_{stop} - \mu_H) \\
    m_{11+5} &= p_{hiv} \times p_{H^+} \\
    m_{16+5} &= p_{hiv} \times p_{cr} \\
    m_{16+6} &= p_{hiv} \times (1 - p_{H^+} - p_{h} - \mu_H) \\
    m_{18+6} &= p_{hiv} \times p_{H^+}
\end{align*}
\]

The values of certain variables change with calendar time (e.g. \( P_{stop} \)), other variables are age-dependent (e.g. \( P_{cr} \)), or depend on both (e.g. \( \mu \)). Therefore, there is a transition matrix for every age and calendar year.

4 Simulation

We assumed that at time \( t = 0 \) (year 1960) the IDU population consisted of ten individuals, represented by the population matrix \( V_0 \). This population matrix contains information on the annual number of individuals per health stage and age. To calculate the size and distribution over the health stages at time \( t = 1 \) (year 1961) the age-dependent population matrix \( V_0 \) was multiplied by the age-dependent transition matrix \( M_0 \) of \( t = 0 \). Subsequently, the annual number of new injectors \( (B) \) was added to the population vector \( V_1 \), and then, this vector was multiplied by \( M_1 \), and so on, until \( t = 120 \) was reached. The annual number of new injectors is given in the main text (Table 1). The age- and calendar-year-dependent formula determining the number of IDUs in the various health stages is as follows:

\[
V_{(t+1)(a+1)} = (B + V_{(t,a)}) \times M_{(t,a)}
\]

With this simulation we estimated the age-dependent distribution of the number of IDUs over the eight health stages over time.

5 Latin hypercube sampling & Uncertainty analysis

To allow for uncertainty in the estimates needed to parameterise the model, we used Latin hypercube sampling (LHS) (1). This type of stratified Monte Carlo sampling is very efficient, using the entire parameter space. LHS enables determination of the uncertainty in outcome resulting from uncertainty in parameter estimates and to quantify the weight of this uncertainty.
We set a plausible range for each parameter used in the preceding formulas. To quantify uncertainty, 2500 values were generated for every parameter from an uniform distribution with this range. These values were combined to obtain 2500 sets of input parameters. This was done with R 2.10.1 (5) using the tgp package (2).

To calculate the sample size ($N$), we followed the empirically established formula (3):

$$N > 4/3 \times K$$

were $K$ equals the number of uncertain parameters.

To increase the significance level for sensitivity analysis, $N$ was set to 2500. We simulated how the population changed over time with respect to HCV, injecting drug use, HIV, and age, performing the operation 2500 times; thus the results can be presented as median and 95% range.

References


Table 1: The incidence of HCV and HIV over time

<table>
<thead>
<tr>
<th>Year</th>
<th>HCV</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966 - 1970</td>
<td>0.25 (0.0 - 0.50)</td>
<td></td>
</tr>
<tr>
<td>1971 - 1975</td>
<td>0.36 (0.01 - 0.70)</td>
<td></td>
</tr>
<tr>
<td>1976 - 1979</td>
<td>0.51 (0.01 - 1.00)</td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>0.51 (0.01 - 1.00)</td>
<td>0.01 (0.00 - 0.01)</td>
</tr>
<tr>
<td>1981</td>
<td>0.51 (0.01 - 1.00)</td>
<td>0.01 (0.00 - 0.02)</td>
</tr>
<tr>
<td>1982</td>
<td>0.51 (0.01 - 1.00)</td>
<td>0.02 (0.00 - 0.03)</td>
</tr>
<tr>
<td>1983</td>
<td>0.51 (0.01 - 1.00)</td>
<td>0.02 (0.00 - 0.04)</td>
</tr>
<tr>
<td>1984</td>
<td>0.51 (0.01 - 1.00)</td>
<td>0.03 (0.00 - 0.05)</td>
</tr>
<tr>
<td>1985</td>
<td>0.51 (0.01 - 1.00)</td>
<td>0.03 (0.00 - 0.06)</td>
</tr>
<tr>
<td>1986</td>
<td>0.30 (0.14 - 0.62)</td>
<td>0.07 (0.04 - 0.12)</td>
</tr>
<tr>
<td>1987</td>
<td>0.27 (0.15 - 0.47)</td>
<td>0.06 (0.04 - 0.08)</td>
</tr>
<tr>
<td>1988</td>
<td>0.24 (0.16 - 0.37)</td>
<td>0.04 (0.03 - 0.06)</td>
</tr>
<tr>
<td>1989</td>
<td>0.22 (0.16 - 0.31)</td>
<td>0.04 (0.03 - 0.05)</td>
</tr>
<tr>
<td>1990</td>
<td>0.20 (0.14 - 0.29)</td>
<td>0.03 (0.02 - 0.04)</td>
</tr>
<tr>
<td>1991</td>
<td>0.18 (0.11 - 0.27)</td>
<td>0.02 (0.02 - 0.03)</td>
</tr>
<tr>
<td>1992</td>
<td>0.15 (0.09 - 0.23)</td>
<td>0.02 (0.01 - 0.03)</td>
</tr>
<tr>
<td>1993</td>
<td>0.12 (0.08 - 0.18)</td>
<td>0.02 (0.02 - 0.03)</td>
</tr>
<tr>
<td>1994</td>
<td>0.09 (0.05 - 0.15)</td>
<td>0.02 (0.02 - 0.03)</td>
</tr>
<tr>
<td>1995</td>
<td>0.05 (0.03 - 0.13)</td>
<td>0.02 (0.02 - 0.04)</td>
</tr>
<tr>
<td>1996</td>
<td>0.04 (0.02 - 0.09)</td>
<td>0.02 (0.01 - 0.03)</td>
</tr>
<tr>
<td>1997</td>
<td>0.03 (0.02 - 0.07)</td>
<td>0.01 (0.01 - 0.02)</td>
</tr>
<tr>
<td>1998</td>
<td>0.03 (0.01 - 0.07)</td>
<td>0.01 (0.00 - 0.02)</td>
</tr>
<tr>
<td>1999</td>
<td>0.02 (0.01 - 0.07)</td>
<td>0.004 (0.00 - 0.01)</td>
</tr>
<tr>
<td>2000</td>
<td>0.02 (0.01 - 0.06)</td>
<td>0.004 (0.00 - 0.01)</td>
</tr>
<tr>
<td>2001</td>
<td>0.02 (0.01 - 0.05)</td>
<td>0.004 (0.00 - 0.01)</td>
</tr>
<tr>
<td>2002</td>
<td>0.02 (0.01 - 0.05)</td>
<td>0.004 (0.00 - 0.01)</td>
</tr>
<tr>
<td>2003</td>
<td>0.02 (0.01 - 0.05)</td>
<td>0.004 (0.00 - 0.01)</td>
</tr>
<tr>
<td>2004</td>
<td>0.02 (0.01 - 0.07)</td>
<td>0.003 (0.00 - 0.01)</td>
</tr>
<tr>
<td>2005</td>
<td>0.03 (0.01 - 0.10)</td>
<td>0.003 (0.00 - 0.02)</td>
</tr>
<tr>
<td>&gt;2006</td>
<td>0.03 (0.01 - 0.06)</td>
<td>0.004 (0.00 - 0.01)</td>
</tr>
</tbody>
</table>
Table 2: The definitions of the elements belonging to transition matrix ($M$) for transitions within the HIV-negative population and HIV-positive population

<table>
<thead>
<tr>
<th>Definition</th>
<th>HIV-negative transitions</th>
<th>HIV-positive transitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDU $\rightarrow$ IDU</td>
<td>$m_{1\leftarrow 1}$</td>
<td>$m_{11\leftarrow 11}$</td>
</tr>
<tr>
<td>IDU $\rightarrow$ former IDU</td>
<td>$m_{2\leftarrow 1}$</td>
<td>$m_{12\leftarrow 11}$</td>
</tr>
<tr>
<td>IDU $\rightarrow$ IDU with acute HCV</td>
<td>$m_{3\leftarrow 1}$</td>
<td>$m_{13\leftarrow 11}$</td>
</tr>
<tr>
<td>IDU $\rightarrow$ death</td>
<td>$m_{9\leftarrow 1}$</td>
<td>$m_{19\leftarrow 11}$</td>
</tr>
<tr>
<td>former IDU $\rightarrow$ IDU</td>
<td>$m_{1\leftarrow 1}$</td>
<td>$m_{11\leftarrow 11}$</td>
</tr>
<tr>
<td>former IDU $\rightarrow$ former IDU</td>
<td>$m_{2\leftarrow 2}$</td>
<td>$m_{12\leftarrow 12}$</td>
</tr>
<tr>
<td>IDU with acute HCV $\rightarrow$ former IDU with cleared HCV</td>
<td>$m_{4\leftarrow 3}$</td>
<td>$m_{14\leftarrow 13}$</td>
</tr>
<tr>
<td>IDU with acute HCV $\rightarrow$ (former) IDU with chronic HCV</td>
<td>$m_{5\leftarrow 3}$</td>
<td>$m_{15\leftarrow 13}$</td>
</tr>
<tr>
<td>IDU with acute HCV $\rightarrow$ death</td>
<td>$m_{9\leftarrow 3}$</td>
<td>$m_{19\leftarrow 13}$</td>
</tr>
<tr>
<td>IDU with cleared HCV $\rightarrow$ former IDU</td>
<td>$m_{2\leftarrow 4}$</td>
<td>$m_{12\leftarrow 14}$</td>
</tr>
<tr>
<td>IDU with cleared HCV $\rightarrow$ IDU with acute HCV</td>
<td>$m_{3\leftarrow 4}$</td>
<td>$m_{13\leftarrow 14}$</td>
</tr>
<tr>
<td>IDU with cleared HCV $\rightarrow$ IDU with cleared HCV</td>
<td>$m_{4\leftarrow 4}$</td>
<td>$m_{14\leftarrow 14}$</td>
</tr>
<tr>
<td>IDU with cleared HCV $\rightarrow$ death</td>
<td>$m_{9\leftarrow 4}$</td>
<td>$m_{19\leftarrow 14}$</td>
</tr>
<tr>
<td>(former) IDU with chronic HCV $\rightarrow$ IDU</td>
<td>$m_{1\leftarrow 5}$</td>
<td>$m_{11\leftarrow 15}$</td>
</tr>
<tr>
<td>(former) IDU with chronic HCV $\rightarrow$ (former) IDU with chronic HCV</td>
<td>$m_{5\leftarrow 5}$</td>
<td>$m_{15\leftarrow 15}$</td>
</tr>
<tr>
<td>(former) IDU with chronic HCV $\rightarrow$ (former) IDU with cirrhosis</td>
<td>$m_{6\leftarrow 5}$</td>
<td>$m_{16\leftarrow 15}$</td>
</tr>
<tr>
<td>(former) IDU with chronic HCV $\rightarrow$ death</td>
<td>$m_{9\leftarrow 5}$</td>
<td>$m_{19\leftarrow 15}$</td>
</tr>
<tr>
<td>(former) IDU with cirrhosis $\rightarrow$ (former) IDU with cirrhosis</td>
<td>$m_{6\leftarrow 6}$</td>
<td>$m_{16\leftarrow 16}$</td>
</tr>
<tr>
<td>(former) IDU with cirrhosis $\rightarrow$ (former) IDU with dec.cirrhosis</td>
<td>$m_{7\leftarrow 6}$</td>
<td>$m_{17\leftarrow 16}$</td>
</tr>
<tr>
<td>(former) IDU with cirrhosis $\rightarrow$ (former) IDU with HCC</td>
<td>$m_{8\leftarrow 6}$</td>
<td>$m_{18\leftarrow 16}$</td>
</tr>
<tr>
<td>(former) IDU with cirrhosis $\rightarrow$ death</td>
<td>$m_{9\leftarrow 6}$</td>
<td>$m_{19\leftarrow 16}$</td>
</tr>
<tr>
<td>(former) IDU with dec.cirrhosis $\rightarrow$ (former) IDU with dec.cirrhosis</td>
<td>$m_{7\leftarrow 7}$</td>
<td>$m_{17\leftarrow 17}$</td>
</tr>
<tr>
<td>(former) IDU with dec.cirrhosis $\rightarrow$ HCV-related death</td>
<td>$m_{10\leftarrow 7}$</td>
<td>$m_{20\leftarrow 17}$</td>
</tr>
<tr>
<td>(former) IDU with HCC $\rightarrow$ (former) IDU with HCC</td>
<td>$m_{8\leftarrow 8}$</td>
<td>$m_{18\leftarrow 18}$</td>
</tr>
<tr>
<td>(former) IDU with HCC $\rightarrow$ HCV-related death</td>
<td>$m_{10\leftarrow 8}$</td>
<td>$m_{20\leftarrow 18}$</td>
</tr>
</tbody>
</table>
Table 3: The definitions of the elements belonging to transition matrix ($M$) for transitions from the HIV-negative to the HIV-positive population

<table>
<thead>
<tr>
<th>Definition</th>
<th>Matrix elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDU → HIV+ IDU</td>
<td>$m_{11} \leftarrow 1$</td>
</tr>
<tr>
<td>IDU → HIV+ former IDU</td>
<td>$m_{12} \leftarrow 1$</td>
</tr>
<tr>
<td>IDU → HIV+ IDU with acute HCV</td>
<td>$m_{13} \leftarrow 1$</td>
</tr>
<tr>
<td>IDU → HIV+ death</td>
<td>$m_{19} \leftarrow 1$</td>
</tr>
<tr>
<td>IDU with acute HCV → HIV+ IDU with cleared HCV</td>
<td>$m_{14} \leftarrow 3$</td>
</tr>
<tr>
<td>IDU with acute HCV → HIV+ IDU with chronic HCV</td>
<td>$m_{15} \leftarrow 3$</td>
</tr>
<tr>
<td>IDU with acute HCV → death HIV+</td>
<td>$m_{19} \leftarrow 3$</td>
</tr>
<tr>
<td>IDU with cleared HCV → HIV+ former IDU</td>
<td>$m_{12} \leftarrow 4$</td>
</tr>
<tr>
<td>IDU with cleared HCV → HIV+ IDU with acute HCV</td>
<td>$m_{13} \leftarrow 4$</td>
</tr>
<tr>
<td>IDU with cleared HCV → HIV+ IDU with cleared HCV</td>
<td>$m_{14} \leftarrow 4$</td>
</tr>
<tr>
<td>IDU with cleared HCV → HIV+ death</td>
<td>$m_{19} \leftarrow 4$</td>
</tr>
<tr>
<td>(former) IDU with chronic HCV → HIV+ IDU</td>
<td>$m_{11} \leftarrow 5$</td>
</tr>
<tr>
<td>(former) IDU with chronic HCV → HIV+ (former) IDU with chronic HCV</td>
<td>$m_{15} \leftarrow 5$</td>
</tr>
<tr>
<td>(former) IDU with chronic HCV → HIV+ (former) IDU with cirrhosis</td>
<td>$m_{16} \leftarrow 5$</td>
</tr>
<tr>
<td>(former) IDU with chronic HCV → HIV+ death</td>
<td>$m_{19} \leftarrow 5$</td>
</tr>
<tr>
<td>(former) IDU with cirrhosis → HIV+ (former) IDU with cirrhosis</td>
<td>$m_{16} \leftarrow 6$</td>
</tr>
<tr>
<td>(former) IDU with cirrhosis → HIV+ (former) IDU with dec.cirrhosis</td>
<td>$m_{17} \leftarrow 6$</td>
</tr>
<tr>
<td>(former) IDU with cirrhosis → HIV+ (former) IDU with HCC</td>
<td>$m_{18} \leftarrow 6$</td>
</tr>
<tr>
<td>(former) IDU with cirrhosis → HIV+ death</td>
<td>$m_{19} \leftarrow 6$</td>
</tr>
</tbody>
</table>
S.2. The population size of injecting drug users in Amsterdam, The Netherlands


In Amsterdam, injecting drug use was introduced in the early 1960s. Introduction of HCV probably occurred by the early injectors, while HIV is spreading in the population since 1980. This graph shows the size of the population of ever-injectors and the number of IDUs who are either mono- or coinfected with HCV and HIV from 1960 to 2010. The number of ever-injectors is represented by the black line; the number of HCV-positive ever-injectors by the red line; the number of HCV/HIV-coinfected ever-injectors by the green line; and the blue line represents the number of HIV-monoinfected ever-injectors. Data is presented as median and 95% range.
S.3. Sensitivity Analysis


This figure shows the partial rank correlation coefficients (PRCCs) between the input values and the cumulative number of individuals that develop HCV-related disease (defined as decompensated cirrhosis or hepatocellular carcinoma) due to HCV infections occurring between 1960 and 2010.

We found that the key input variables that contribute most to the uncertainty in outcome are competing mortality of HIV negative individuals ($\mu^H-\$) and HIV-infected individuals ($\mu^H+$), where the probabilities of HCV clearance ($P^{H+}_{cl}$), developing cirrhosis ($P^{H+}_{ch}$), and developing decompensated cirrhosis ($P^{H+}_{dc}$) for HIV-infected individuals caused little imprecision. The significance level for most parameters was $<0.001$, except $P_{stop}$, $P_{HCV}$, $P^{H+}_{h}$ (significance level $<0.05$), and $P^{H+}_{cl}$, $P^{H+}_{ch}$, $P^{H+}_{dc}$ (not significant).

Most PRCCs have a positive value, indicating that when these parameters increase the cumulative number of individuals developing HCV-related disease will also increase. Parameters with negative PRCCs cause a decrease in outcome.

Figure 1: PRCCs between the input values and the cumulative number of individuals that develop HCV-related liver disease