THE NECESSITY OF A TREATMENT SCALE-UP TO IMPACT HCV TRANSMISSION IN IN PEOPLE WHO INJECT DRUGS IN MONTRÉAL: A MODELLING STUDY

Anthony Cousien[1,2,3], Pascale Leclerc[3], Carole Morissette[3], Julie Bruneau[4], Elise Roy[5], Viet Chi tran[6], Yazdan Yazdanpanah[1,2,7], Joseph Cox[3,8]

[1]IAME, UMR 1137, INSERM, F-75018 Paris, France
[2]IAME, UMR 1137, Univ Paris Diderot, Sorbonne Paris Cité, F-75018 Paris, France
[3]Direction régionale de santé publique du Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Ile-de-Montréal, 1301 rue Sherbrooke est, Montréal, Québec, Canada H2L 1M3
[4]Centre de recherche, Centre hospitalier de l'Université de Montréal (CRCHUM), 900 Saint-Denis, Montréal, Québec, Canada H2X 0A9.
[5]Faculté de médecine et des sciences de la santé, Université de Sherbrooke, Campus Longueuil, 150 place Charles-Le Moyne, Longueuil, Québec, Canada J4K 0A8.
[6]Laboratoire Paul Painlevé UMR CNRS 8524, UFR de Mathématiques, Université des Sciences et Technologies Lille 1, Cité Scientifique, Villeneuve d'Ascq, France.
[7]Service des Maladies Infectieuses et Tropicales, Hôpital Bichat Claude Bernard, Paris, France
[8]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Purvis Hall, 1020 Pine Avenue West, Montreal, Quebec, Canada H3A 1A3; Chronic Viral Illness Service, McGill University Health Centre, 3650 Saint Urbain, Montreal, Quebec, Canada H2X 2P4

Corresponding author :
Joseph COX
Public Health Department
CIUSSS du Centre-Sud-de-l'Île-de-Montréal
1301, rue Sherbrooke est
Montréal (Québec) H2L 1M3
(514) 528-2400, poste 3630; (514) 528-2452 (fax)
jcox@santepub-mtl.qc.ca

Word count: 5,472

Number of tables: 1

Number of figures: 3

ABBREVIATIONS

HCV: Hepatitis C virus
PWID: People who inject drugs
DAA: Direct-acting antiviral
TasP: Treatment as Prevention
PY: Persons-years
SVR: Sustained virological response
HCC: Hepatocellular carcinoma
HIV: Human immunodeficiency virus
$CAD: Canadian dollars
EASL: European Association for the Study of the Liver
INESS: Québec Institute for Excellence in Health and Social Services
ANRS: French Agence Nationale de Recherche sur le Sida et les hépatites virales

KEYWORDS

Dynamic model; HCV elimination; treatment initiation criteria; cascade of care; direct-acting antiviral;

people who inject drugs

CONFLICT OF INTERESTS

Julie Bruneau has received travel grants and honoraria from Boehringher Ingelheim, Merck, Gilead; Joseph Cox has received unrestricted grants and honoraria from Brisol-Myers Squibb, Gilead, ViiV Healthcare; Yazdan Yazdanpanah has received travel grants, honoraria for presentations at workshops and consultancy honoraria from Abbott, Brisol-Myers Squibb, Gilead, Merck, Pfizer, Tibotec, ViiV Healthcare. All other authors declare that they have no conflicts of interest.

FINANCIAL SUPPORT

The PhD of Anthony Cousien is funded by the French Agence Nationale de Recherches sur le Sida et les hépatites virales (ANRS), grant number 95 146. This study was funded by the Strategic Training Program in Transdisciplinary Research on Public Health Interventions: Promotion, Prevention and Public Policy (4P), a partnership of the Institute of Population and Public Health and the Institute of Health Services and Policy Research of the Canadian Institutes of Health Research (CIHR) and the Québec Population Health Research Network.

AUTHOR'S CONTRIBUTION

Anthony Cousien, Viet Chi Tran and Yazdan Yazdanpanah built and implemented the model; Julie Bruneau, Anthony Cousien, Joseph Cox and Pascale Leclerc contributed to the acquisition of data; Julie Bruneau, Anthony Cousien, Joseph Cox, Pascale Leclerc, Carole Morissette, Elise Roy and Yazdan Yazdanpanah contributed to the analysis and interpretation of the results. Anthony Cousien and Joseph Cox drafted the article. Julie Bruneau, Pascale Leclerc, Carole Morissette, Elise Roy, Viet Chi Tran and Yazdan Yazdanpanah reviewed the paper; all of the authors gave final approval of the version to be published.

ABSTRACT

Background & aims: HCV transmission remains high in people who inject drugs (PWID). New direct-acting antivirals (DAAs), highly effective and more tolerable than previous regimens, make a "Treatment as Prevention" (TasP) strategy more feasible. This study assesses how improvements in the cascade of care could impact hepatitis C burden among PWID in Montréal.

Methods: We used a dynamic model to simulate HCV incidence and prevalence after 10 years, and cirrhosis complications after 10/40 years. Eight scenarios of improved cascade of care were examined.

Results: Using the current cascade of care, new DAAs, and baseline incidence and prevalence of 22.1/100 person-years (PY) and 53.1%, the estimated HCV incidence and prevalence at 10 years were 9.4/100PY and 55.8%. Increasing the treatment initiation rate from 5%/year initially to 20% years resulted in large decreases in incidence (6.4/100PY), prevalence (36.6%), and cirrhosis complications (-18%/-37% after 10/40 years). When restricting treatment to fibrosis level ≥ F2 instead of F0 (reference scenario), such decreases in HCV occurrence were unreachable. Improving the whole cascade of care led to the greatest effect by halving the incidence and prevalence at 10 years and the number of cirrhosis complications after 40 years.

Conclusions: The current level of treatment access in Montréal is limiting a massive decrease in hepatitis C burden among PWID. A substantial treatment scale-up, regardless of fibrosis level, is necessary. Improving the rest of the cascade of care is necessary to optimize a TasP strategy and control the HCV epidemic, but only once this treatment scale-up is achieved.

INTRODUCTION

Drug injection is the main transmission route for hepatitis C virus (HCV) in high income countries (1). The number of people who inject drugs (PWID) in the past six months in Montréal is estimated to be 4,000 (2). According to regional surveillance data (SurvUDI network), approximately 70% of this population has been exposed (antibody positive) to HCV (3) and the number of new infections remains high: 22.1/100 persons-years (PY) for the 2010-2013 period (unpublished SurvUDI data).

Access to HCV treatment remains limited in this population. Several components of the HCV cascade of care may explain poor treatment uptake. During 2003-2011, 23% of the infected PWID reported they were not aware of their infection; among those who were aware, 45% reported a physician consultation in the past 6 months, and 12% initiated HCV treatment (3). There may be reluctance on the part of physicians to initiate antiviral treatment in PWID (4). Precarious living conditions and other co-morbidities (e.g., psychiatric disorders) may have been identified as barriers to treatment initiation (5). Also, uncontrolled substance use often constitutes a treatment barrier and many physicians prefer to treat PWID who participate in opiate substitution programs (4). Until recently, the standard antiviral treatment regimen for HCV (dual therapy pegylated interferon plus ribavirin) was associated with numerous challenges. The regimen required a treatment duration of 24 to 48 weeks and the sustained virological response (SVR) rate was only 45% for genotype 1, (6, 7), the most common genotype in Montréal (8). Moreover, this treatment regimen required weekly injections of peginterferon, and was associated with severe adverse events such as rash, anemia and/or depression (6, 7).

However, since 2014 direct-acting antiviral (DAA) molecules for HCV treatment are increasingly available. These treatments are more effective (>90% SVR for all genotypes), shorter (12 weeks), less restrictive as oral regimens, and they cause few or no adverse events (9-14). This recent advances in the HCV therapeutic area provides an interesting opportunity to eliminate HCV infection in this population. The successful treatment of infected individuals could limit the transmission of the virus to current or future injecting partners and prevent the occurrence of serious health outcomes such as end-stage liver disease. However, if a “Treatment as Prevention” (TasP) strategy is to work, it will require enhancements in the “HCV cascade of care”, including increased HCV testing, linkage to HCV care,

improved liver fibrosis assessment, greater HCV treatment uptake, and improved adherence and cure of HCV (15).

In this paper, we used a previously developed dynamic stochastic model for HCV transmission in PWID (16) to estimate the impact of a TasP strategy on HCV transmission and related morbidity when varying the components of the HCV cascade of care among PWID.

METHODS

Dynamic modeling was used to simulate HCV transmission and natural history. Details about the model and related parameters are provided below and elsewhere (16).

Model

The starting population is Montréal's active (i.e., injection, past 6 months) PWID population, with an estimated size of 4,000 individuals (2). Due to limited data regarding the evolution of the population size of PWID in Montréal, the population size is assumed constant in time: each dead PWID is replaced in the model by another non-infected PWID. A previously described model of HCV transmission was used to estimate the impact of a TasP strategy (16). Briefly, it is a stochastic individual-based model including the social network of PWID (i.e., people who inject together), and the background risk of HCV infection between injecting partners (17) (see Appendix A1).

Figure 1 describes the transition chart of the model for HCV transmission and care. Figure 2 presents the natural history of HCV infection; two complications can occur in cirrhosis: decompensation and hepatocellular carcinoma (HCC), which can lead to death. Finally, the model includes rates of permanent or sustained injection cessation and general mortality (i.e., non-HCV-related mortality) which also depends on the injecting status (active or inactive, i.e. after cessation of injection) of PWID overtime.

Parameters

Key parameters are presented in Table 1. Where possible we used regional data reflecting the local context. SurvUDI, a bio-behavioural surveillance system for HCV and HIV infections among PWID in Eastern Central Canada and targeting hard-to-reach PWID, provided most of the estimates for model parameters. Eligibility criteria included age 14 years and older, injecting at least once within the past six months, and speaking French or English (3). Particularly, the contact rate β was fitted by Approximate Bayesian Computation (or ABC) to reproduce, during the first year of simulation, the incidence observed in Montreal for active PWID participating in SurvUDI for the 2010-2013 period, i.e. 22/100PY. ABC is a bayesian method used to infer some parameters of a model without likelihood estimation (18). Details about the method are provided in Appendix A1. Other parameters were

derived from the scientific literature. Appendix A2 provides details and underlying assumptions for the model.

Outcomes

The outcomes of interest were: occurrence of HCV infection (average incidence and prevalence after 10y) and related morbidity (average number of cirrhosis complications avoided over 10 and 40y). The outcomes were estimated for whole PWID populations (active plus inactive injectors) except incidence, for which only active PWID are at risk of infection. In addition, for each scenario, the mean numbers of treatments initiated (and completed unless the individual dies during the treatment) over 40y were estimated (see Appendix A4).

Scenarios

Using 8 different scenarios, we estimated the impact of improvements in the HCV cascade of care on HCV occurrence and morbidity in the Montréal PWID population. One thousand epidemic trajectories were simulated to derive the effects of each of the eight following scenarios:

S1 (reference): The current HCV cascade of care using the new DAAs (for all stages of liver fibrosis). Mean time from the end of acute hepatitis C to detection: 2y; mean time from detection to linkage to care: 1.7y; annual loss to follow-up rate: 10.2%/y; treatment initiation rate (when linked to care): 5%/y; SVR rates: 81% (90% for new DAAs in clinical trials minus a 10% decrease to account for the difference between real-world and clinical trial contexts, see Appendix A1); duration of the treatment: 12 weeks.

S2: S1 with an improvement in the mean time to detection of chronic HCV from 2y to 0.5y (1y after the infection, due to the 6 months of acute hepatitis C in the model), and corresponding to annual testing, as supported by AASLD guidelines (19).

S3: S1 with an improvement in linkage to care, with a mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y

S4: S1 with an improvement in adherence to treatment. In this scenario, we improved the SVR rate of 81% to the level demonstrated in clinical trials, i.e. 90%.

S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care.

S6: Improvement in treatment initiation rate from 5%/y to 20%/y when linked to care.

S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care.

S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 only. Due to the high cost of the new DAAs (55,000$CAD (20)), there may be a reluctance to treat people with minimal fibrosis (F0/F1 fibrosis scores) (19). Therefore, simulations were performed based on treatment initiation at fibrosis scores between F2 and F4, i.e., 100% of the PWID with moderate or severe fibrosis were treated (vs. 5% of all PWID without cirrhosis complications in S1) while those with F0 and F1 were excluded from treatment.

Sensitivity analysis

We performed a deterministic univariate sensitivity analysis by varying the parameter values based on the uncertainty interval (e.g., 95% confidence interval) if available, or by using values from other studies. Due to the uncertainty about the number of injecting partners, we also varied this parameter to cover the range of likely values in the literature (between 3 and 15) (16). The details of theses analyses are provided in Appendix A6.

RESULTS

Figure 3 presents boxplots representing the prevalence and incidence distributions after 10y, and the proportion of cirrhosis complications avoided over 10 and 40y, for each scenario compared with S1, the reference. In addition, the reader can refer to Appendices 4, 5 and 6 for the evolution of the outcomes over time, the cumulative number of treatments needed for each scenario and the impact of each scenario on the disposition of PWID in the cascade of care after 10 years, respectively.

HCV transmission in the population

In the reference scenario S1, the mean incidence and prevalence estimates after 10y were 9.4/100PY [95% confidence interval: 9.2; 9.7] and 55.8% [55.6; 55.9], respectively. Improved testing in S2, linkage to care in S3 or adherence to treatment in S4, each taken separately, led to similar incidence estimates of 9.3/100PY [9.1; 9.6], 9.1/100PY [8.8; 9.3] and 9.2/100PY [9.0; 9.5], respectively. S2, S3

and S4 also led to similar prevalence estimates: 54.7% [54.6; 54.9], 53.2% [53.1; 53.4] and 54.5% [54.4; 54.7]. Improvements in the treatment initiation rate, from 10%/y to 20%/y in S5 and S6 led to a decrease in HCV occurrence with incidence estimates of 8.1/100PY [7.9; 8.3] and 6.4/100PY [6.2; 6.6], respectively. Similarly, prevalence estimates decreased for S5 and S6: 47.5% [47.3; 47.6] and 36.6% [36.4; 36.7]. The combined scenario S7 (representing improvements in the whole cascade of care) was the most effective with the incidence dropping to 4.3/100PY [4.2; 4.4] and prevalence to 24.0% [23.9; 24.2] after 10y. Finally, when restricting treatment to F2-F4 fibrosis scores in S8, the incidence and prevalence estimates were 7.3/100PY [7.1; 7.5] and 44.3% [44.1; 44.5], respectively.

Chronic hepatitis C complications

Compared with the reference scenario S1, improved testing in S2, had almost no impact resulting in 0% [-1; 2] and 1% [0; 3] of cirrhosis complications avoided over 10 and 40y, respectively. Improved linkage to care in S3, and adherence to treatment in S4, had moderate effects in the long term, with 2% [1; 4] and 1% [-1; 3] of complications avoided after 10y and 6% [5; 7] and 6% [5; 7] after 40y. Improvements in the treatment initiation rate from 10%/y in S5 and to 20%/y in S6, resulted in the avoidance of 7% [6; 9] and 18% [17; 20] of complications after 10y, respectively, while greater decreases were observed after 40y: 21% [20; 22] and 37% [36; 38]. The combined scenario S7 demonstrated a decrease of 30% [29; 32] after 10y, and 54% [53; 54] after 40y, in the number of cirrhosis complications. Finally, treating only F2-F4 fibrosis levels in S8 led to a decrease of 44% [43; 45] and 49% [48; 50] in complications after 10 and 40y, respectively.

Sensitivity analysis

The tornado graphs in Appendix A6 present variations in outcomes assuming the conditions of S1 while considering parameter uncertainty levels. The parameters determined to be most sensitive (top 10) in outcome estimation are presented for each outcome. For the incidence after 10 years, the most sensitive parameters were the mean time to cessation of injection (with a variation in the reference scenario S1 of -6.0/100 p.y, +3.9/100 p.y.), the treatment initiation rate (-1.3/100 p.y., 1.7/100 p.y.) and the infection rate per infectious injecting partner (-1.6/100 p.y., 1.1/100 p.y.). The most sensitive parameters for the prevalence after 10 years were the treatment initiation rate (-8.3%, +8.7%) and the

mean time to cessation of injection (-9.0%, +5.1%). Finally, for the number of cirrhosis complications within 10 years, estimates were most sensitive to the transition rate from F2/F3 to F4 (-18%, +22%), the fibrosis distribution in the population (-28%, +0%) and the decompensation rate (-10%, +15%). For cirrhosis complications after 40 years, estimates were most sensitive to the following parameters: the treatment initiation rate (-21%, +37%), the transition rate from F2/F3 to F4 (-29%, +26%) and the transition rate from F0/F1 to F2/F3 (-15%; +11%).

In other sensitivity analyses, the trends of our results remained unchanged when we varied the number of injecting partners. In addition, we also simulated the 8 scenarios with the lower and upper bounds of the mean time to cessation of injection used in the univariate sensitivity analysis (4.7 years and 14 years), due to the large impact on prevalence and incidence. The trends observed for the various scenarios were relatively unchanged.

INTERPRETATION

We used an individual-based model to simulate the evolution of HCV infection among active PWID in Montréal while varying the cascade of care. Model parameters were primarily informed by local data. The results showed, compared with the current cascade of HCV care, that the best approach to curtail ongoing HCV transmission and future cirrhosis complications in this population, is to improve access to treatment. By increasing the treatment initiation rate from 5%/y to 10%/y and 20%/y, prevalence at 10y decreased from 55.8% to 47.5% and 36.6%, respectively. Similarly, incidence rates at 10y dropped from 9.4/100PY to 8.1/100PY and 6.4/100PY, respectively. In addition, the number of cirrhosis complications decreased by 21% and 37% over 40y using 10%/y and 20%/y treatment initiation rates. Conversely, improved testing, linkage to care or adherence to treatment alone, led to minimal decreases in disease burden. However, combining these improvements with a higher treatment initiation rate permitted a decrease of almost 50% in the prevalence and incidence at 10y and the number of cirrhosis complications over 40y. Finally, by restricting treatment to patients with moderate and severe fibrosis (S8), the impact on HCV transmission was considerably lower compared to S7 (no fibrosis restriction, treatment initiation of 20%/y), even in the optimistic case where 100% of the eligible individuals were treated. However, there was a greater impact on the reduction in the number of cirrhosis complications in the short term: -44% (10y). Nevertheless, both scenarios S7 and S8 would require a similar number of treatment courses over 10y; approximately 1,500, see Appendix A4.

These results show, that even in the context of new DAAs, a large decrease in the disease burden using TasP, first requires greater access to treatment for PWID once they are diagnosed and linked to care. When this treatment scale-up is achieved, improvements in other parts of the cascade of care could result in additional benefits for both HCV transmission and morbidity/mortality. Without this treatment scale-up, increased testing or linkage to care would be of limited benefit; these patients would not initiate antiviral treatment before several years, all while experiencing ongoing fibrosis progression. This approach would be inconsistent with recent statements from the European Association for the Study of the Liver (EASL) (21) where screening of PWID is promoted in part to improve access to

treatment, but also to reduce transmission. For the same reason, while treatment initiation restricted to fibrosis scores ≥ F2 would reduce liver related morbidity, it would also delay treatment for many other infected PWID. This would effectively allow for several years of ongoing HCV transmission before individuals reach treatment eligibility. This restriction may be justified as it targets treatment to those most in need in whom liver complications are more imminent. However, from a public health perspective, the treatment of patients in the absence of liver disease (low fibrosis scores) is most important to reduce HCV occurrence, and consequently the disease burden over the long-term.

In other settings, modeling studies using different models showed that even a small increase in treatment availability for PWID can result in a large decrease in HCV transmission in the context of highly effective antivirals (22-24), particularly in a low prevalence context (24). However, these models did not integrate the entire cascade of care, and thus did not identify the specific steps in the cascade that have the largest impact on the course of the HCV epidemic. In Montréal, this appears to be treatment initiation once PWID are diagnosed and linked to care.

In our sensitivity analysis, the mean time to cessation of injection and the infection rate per infected injecting partner were sensitive parameters for estimating HCV incidence (see Appendix A6). These results suggest that improvements in primary and secondary prevention interventions aimed at reducing the harms of substance use (e.g., delayed initiation of injection drug use, provision of clean injection equipment, opioid substitution therapies, and supervised injection facilities) would complement a TasP strategy. A previous modeling study in the United Kingdom demonstrated the importance of combining risk reduction measures with a treatment scale-up to achieve a high decrease in HCV prevalence (25). In our model, the current situation of risk reduction measures in Montréal was implicitly included in the infection rate per infected partner values and the time to cessation of injection; the heterogeneity with respect to harm reduction uptake was neglected. Estimating the impact of these preventive public health strategies, in addition to variations in the HCV cascade of care, would require a more complex model including injecting drug use initiation, injection equipment distribution programs, opioid substitution therapies/programs, and supervised injection facilities, expected soon in Montréal (26). Further investigation is needed to incorporate them in the model.

This study has several limitations. First, the network model is static and relatively simple compared with those for PWID in other countries using chain referral sampling (17). The paucity of data about the network dynamic and topology constrained us, and the development of a more realistic model would require field studies on PWID networks. Also, for simplicity, the model did not explicitly include other comorbidities common in PWID such as HIV infection (3). While current recommendations promote an individual-based treatment decision for PWID (19, 27), treatment is probably preferentially initiated in PWID with advanced levels of fibrosis. However, in our reference scenario, the treatment initiation is independent of the fibrosis score. Finally, with the high cost of the new DAAs (around 55,000$ Canadian for a 12-week course (20)), extended access to these antivirals for the PWID population would mean increased costs for the health system (see Appendix A4 for the number of completed treatment courses needed for each scenario). Under the current situation, the cost of the introduction of the new DAAs for the public health insurance system in Québec is estimated to be 45 million Canadian dollars for the first three years after introduction (28). Future modeling works could consider including health care costs to estimate the costs of a TasP strategy.

Our study also has several strengths. The large amount of local data available through ongoing regional surveillance work (SurvUDI and the Notifiable Disease Reporting System of the Montréal Public Health Department) and numerous past and current epidemiological studies (8, 29-31) ensures the model reflects the current situation of HCV infection and care for PWID in Montréal. Also, the model included the entire cascade of care for chronic hepatitis C with testing, linkage to care and treatment. To conclude, TasP could lead to a large decrease in chronic hepatitis C burden among PWID in Montréal. The success of this strategy rests on first expanding access to antiviral treatment to PWID already engaged in HCV care. From a public health perspective, access to antiviral treatment is a priority focus in improving the HCV cascade of care. Limiting treatment to moderate to severe fibrosis, while effective in circumventing cirrhosis complication in the short-term, would do little to curtail ongoing HCV transmission in this population. Coupling greater treatment access with ongoing improvements in the HCV cascade of care would ultimately result in less HCV occurrence and disease burden in Montreal. Regardless, elimination of HCV infection in this population would not be expected to occur in the short to mid-term. Such an ambitious objective would require a “TasP+”

strategy, which would foster a commitment to greater treatment access as well as harm reduction services. Such a strategy would be in line with the recent Québec Institute for Excellence in Health and Social Services (INESSS) recommendations, which recommended to progressively lower (over several years) the fibrosis threshold for access to DAAs to together with harm reductions measures improvements (32), making possible for Quebec to be the first province in Canada where a true TasP+ programmatic intervention could occur. In future work, a more sophisticated model could help evaluate the impact of a “TasP+” strategy; it would consider ongoing improvements in the HCV cascade of care while also determining the health care investment needed to eliminate HCV infection among PWID.

ACKNOWLEDGMENTS

The authors would like to thank: the working group previously involved in the model development: Sylvie Deuffic-Burban, Jean-Stéphane Dhersin and Marie Jauffret-Roustide; Robert Allard and Emilie Maurais for their helpful advice during this study; Lucie Bédard, Caty Blanchette, Christine Savard and Claude Tremblay from the Montréal Public Health Department for their help in parameter estimation using SurvUDI data and the Notifiable Disease Reporting System data; and the scientific advisory board of this project: Elisabeth Avril, Patrizia Carrieri, Elisabeth Delarocque-Astagneau, Véronique Dorée, Albert Herszkowicz, Christine Larsen, Gilles Pialoux, Philippe Sogni, and Elisabeta Vergu.

The PhD of Anthony Cousien is funded by the French Agence Nationale de Recherches sur le Sida et les hépatites virales (ANRS), grant number 95 146. This study was funded by the Strategic Training Program in Transdisciplinary Research on Public Health Interventions: Promotion, Prevention and Public Policy (4P), a partnership of the Institute of Population and Public Health and the Institute of Health Services and Policy Research of the Canadian Institutes of Health Research (CIHR) and the Québec Population Health Research Network.

Numerical results presented in this paper were carried out using the regional computational cluster supported by Université Lille 1, CPER Nord-Pas-de-Calais/FEDER, France Grille, CNRS. We would like to thank the technical staff of the CRI-Lille 1 center.

REFERENCES

1. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011 Aug 13;378(9791):571-83.
2. Leclerc P, Vandal AC, Fall A, Bruneau J, Roy E, Brissette S, et al. Estimating the size of the population of persons who inject drugs in the island of Montreal, Canada, using a six-source capture-recapture model. Drug Alcohol Depend. 2014 Sep 1;142:174-80.
3. Leclerc P, Morissette C, Tremblay C, Roy É. Le volet montréalais du Réseau SurvUDI: Direction de la santé publique, Agence de la santé et des services sociaux de Montréal; 2011.
4. Myles A, Mugford GJ, Zhao J, Krahn M, Wang PP. Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada. Can J Gastroenterol. 2011 Mar;25(3):135-9.
5. Moirand R, Bilodeau M, Brissette S, Bruneau J. Determinants of antiviral treatment initiation in a hepatitis C-infected population benefiting from universal health care coverage. Can J Gastroenterol. 2007 Jun;21(6):355-61.
6. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001 Sep 22;358(9286):958-65.
7. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, Jr., et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002 Sep 26;347(13):975-82.
8. Bernier L, Willems B, Delage G, Murphy DG. Identification of numerous hepatitis C virus genotypes in Montreal, Canada. J Clin Microbiol. 1996 Nov;34(11):2815-8.
9. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon S, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 may 16;368(20):1878-87.
10. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014 May 15;370(20):1889-98.
11. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014 May 15;370(20):1879-88.
12. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17;370(16):1483-93.
13. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014 May 22;370(21):1973-82.
14. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1604-14.
15. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V, 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. PLoS One. [Research Support, N.I.H., Extramural]. 2014;9(7):e101554.
16. Cousien A, Tran VC, Deuffic-Burban S, Jauffret-Roustide M, Dhersin J-S, Yazdanpanah Y. Impact of a treatment as prevention strategy on hepatitis C virus transmission and on morbidity in people who inject drugs. arXiv preprint arXiv:150602987. 2015.
17. Rolls DA, Daraganova G, Sacks-Davis R, Hellard M, Jenkinson R, McBryde E, et al. Modelling hepatitis C transmission over a social network of injecting drug users. J Theor Biol. 2012 Mar 21;297:73-87.
18. Marin J-M, Pudlo P, Robert CP, Ryder RJ. Approximate Bayesian computational methods. Statistics and Computing. 2012;22(6):1167-80.
19. AASLD, IDSA, IAS–USA. Recommendations for testing, managing, and treating hepatitis C. 2014 [June 2015]; Available from: http://www.hcvguidelines.org/fullreport.

20. Régie de l'assurance maladie du Québec. Liste de médicaments. 2015 [July 2015]; Available from: http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/medicaments/liste-medicaments55.pdf.
21. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. Journal of hepatology. [Practice Guideline]. 2014 Feb;60(2):392-420.
22. Hellard M, Rolls DA, Sacks-Davis R, Robins G, Pattison P, Higgs P, et al. The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. Hepatology. [Research Support, Non-U.S. Gov't]. 2014 Dec;60(6):1861-70.
23. Hellard ME, Jenkinson R, Higgs P, Stoove MA, Sacks-Davis R, Gold J, et al. Modelling antiviral treatment to prevent hepatitis C infection among people who inject drugs in Victoria, Australia. Med J Aust. 2012 Jun 8;196(10):638-41.
24. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatology. 2013 Nov;58(5):1598-609.
25. Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. [Research Support, Non-U.S. Gov't]. 2013 Aug;57 Suppl 2:S39-45.
26. Communiqué de la ministre déléguée à la Réadaptation, à la Protection de la jeunesse et à la Santé publique. Québec2015 [July 2015]; Available from: http://www.msss.gouv.qc.ca/documentation/salle-de-presse/ficheCommunique.php?id=950.
27. Myers RP, Shah H, Burak KW, Cooper C, Feld JJ. an update on the management of chronic hepatitis c: 2015 consensus guidelines from the canadian association for the study of the liver. Can J Gastroenterol Hepatol. 2015;29(1):19-34.
28. Institut national d'excellence en santé et en services sociaux. Avis au ministre pour la mise à jouer des listes de médicaments du 2 juin 2014. 2014; Available from: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Juin_2014/_AvisMinistre_WEB_innovateurs_2014_06.pdf.
29. Roy E, Boudreau JF, Boivin JF. Hepatitis C virus incidence among young street-involved IDUs in relation to injection experience. Drug Alcohol Depend. 2009 Jun 1;102(1-3):158-61.
30. Roy E, Haley N, Leclerc P, Sochanski B, Boudreau JF, Boivin JF. Mortality in a cohort of street youth in Montreal. JAMA. 2004 Aug 4;292(5):569-74.
31. De P. Using social networks to better conceptualize risk fro bloodborne viruses among injection drug users. Montréal, Canada: McGill university; 2007.
32. Avis au Ministre de l'Institut National d'Excellence en Santé et Services Sociaux pour la mise à jour des listes de médicaments2015.

Table 1 Key parameters of the model

Parameter	Value	References
Population size	4,000	(2)
Average number of injecting partners during the injecting career	12	Derived from (31)
Initial distribution (HCV infection and cascade of care)		
Susceptible with high risk	10.10%	SurvUDI, 2012-2014, unpublished data
Susceptible with low risk	36.80%	
Acute hepatitis C	0%*	
Non-detected chronic hepatitis C	8.40%	SurvUDI, 2012-2014, unpublished data
Detected, non-linked to care chronic hepatitis C	24.40%	
Detected and linked to care chronic hepatitis C	15.30%	
Under treatment	0.40%	
Non-responders after treatment	4.60%	
Initial distribution in the natural history model		
F0/F1	61.1%	(Private communication, J. Bruneau)
F2/F3	23.3%	
F4	15.6%	
Decompensated cirrhosis	0%*	
HCC	0%*	
Infection rate by injecting partner in Susceptible (low risk)	0.025 y^{-1}partner^{-1}	Fitted by Approximate Bayesian Computation (ABC) to have a 22.1/100 p-y baseline incidence (SurvUDI, 2010-2013)
Mean time from the end of acute hepatitis C to detection	2.0y	Derived from SurvUDI, 2012-2014, unpublished data
Mean time before linkage to care	1.7y	Derived from Notifiable Disease Reporting System of the Montréal Public Health Department
Loss to follow-up rate	10.3%/y	Derived from SurvUDI, 2012-2014, unpublished data
Treatment initiation rate when linked to care	5%/y	Approximate value derived from SurvUDI, 2012-2014, based on current number of people under treatment (0.4%)
Treatment: incoming DAAs regimens		
Duration	12 weeks	(9-14)

SVR rate – treatment naive - all genotypes- clinical trials	90%	¿ ¿

*Hypothesis
PWID: people who inject drugs; SVR: sustained virological response

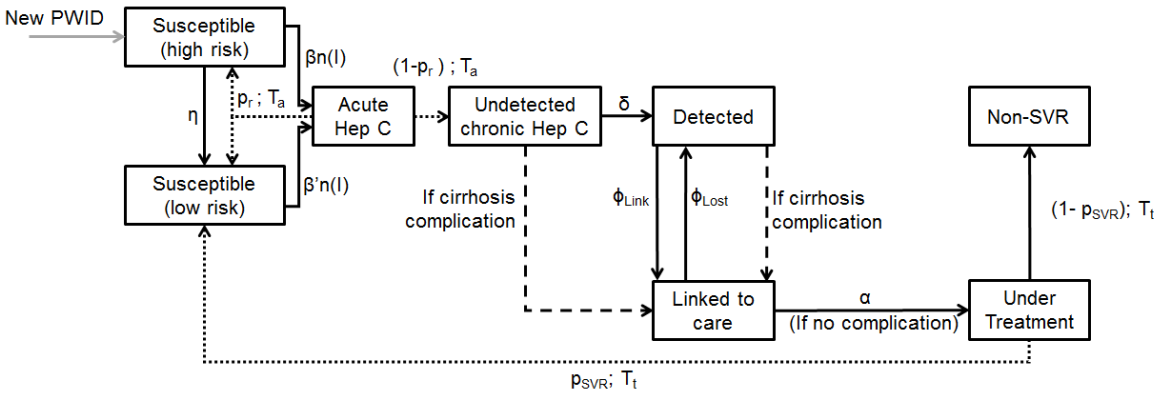


Figure 1 Transition chart of the model for HCV infection and care. New PWID enters the population as "Susceptible (high risk)" during all the simulation period to keep a constant population size (i.e each death in the population implies the arrival of a new PWID). Plain arrows correspond to transitions occurring according to exponential probability distributions. Dashed lines correspond to transitions occurring after a fixed time with a given probability. Dotted lines correspond to transitions related to the natural history model. An individual is considered as Detected if he/she has an HCV antibody positive test. An individual is considered as Linked to care if he/she had one or more consultation related to his/her HCV infection in the past 6 months (with the first link to care corresponding to the first positive RNA test, see Appendix A2).

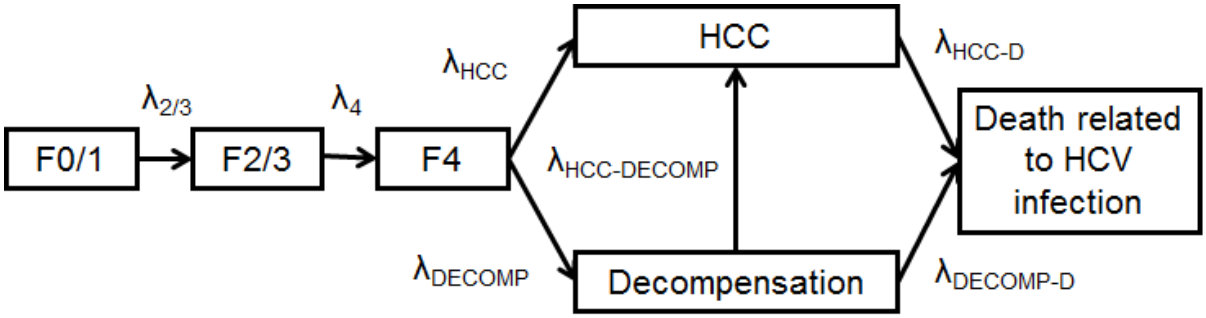


Figure 2 Transition chart for the natural history of chronic hepatitis C. All transitions occur according to exponential probability distributions. Metavir fibrosis scores F0 and F1 (respectively F2 and F3) were gathered in a F0/1 (respectively F2/3) state.

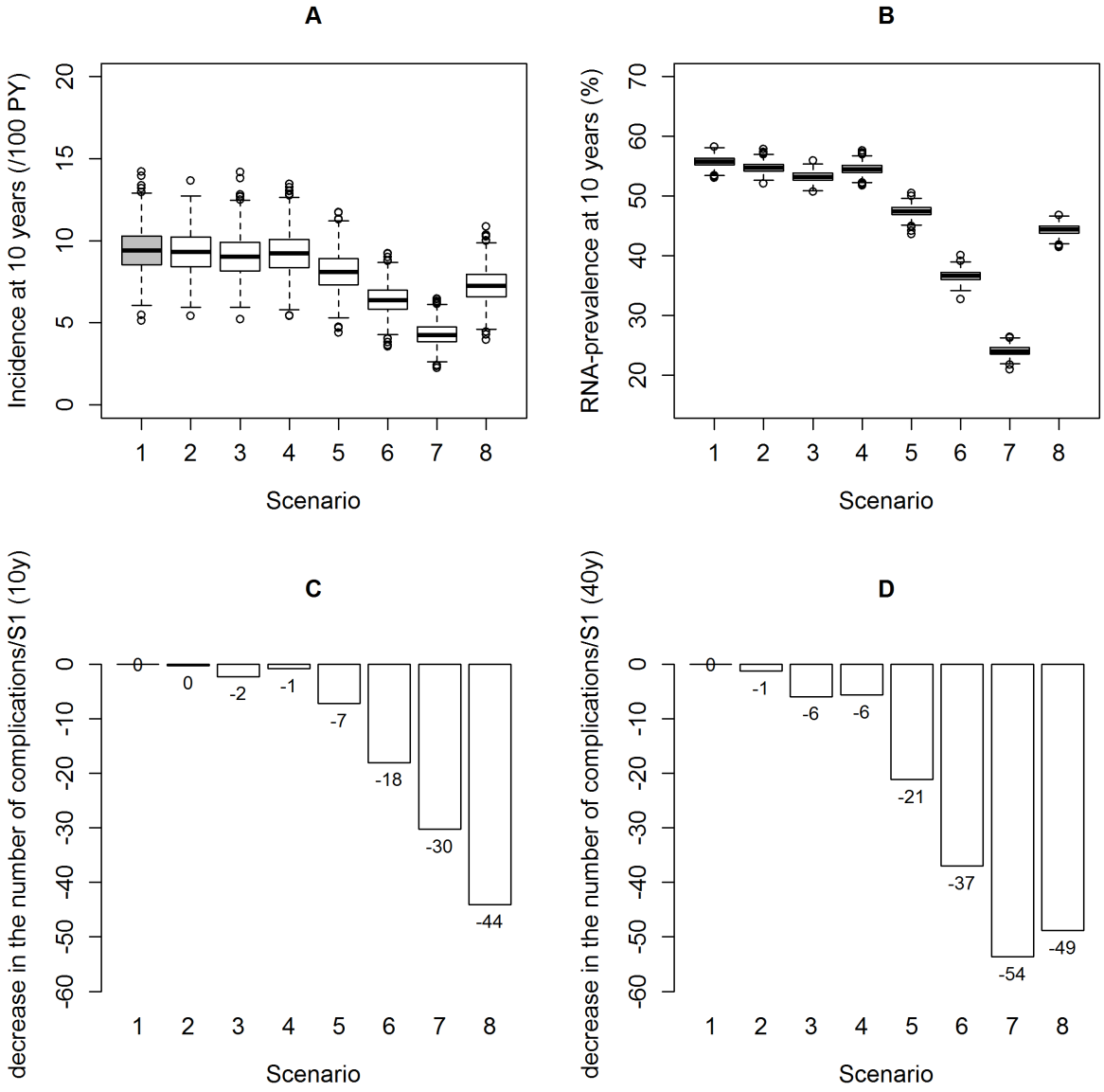


Figure 3 Results according to various HCV cascade of care scenarios; 1,000 simulations. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). S1 (reference): The current HCV cascade of care using the new DAAs. S2: S1 with an improvement in the mean time to detection of chronic HCV from 2y to 0.5y. S3: S1 with an improvement in linkage to care, with a decrease in mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y. S4: S1 with an improvement in adherence to treatment, i.e. we improved the SVR rate of 81% to the level demonstrated in clinical trials, i.e. 90%. S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care. S6: Improvement in the treatment initiation rate from 5%/y to 20%/y when linked to care. S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care; no fibrosis criteria for treatment initiation. S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 only.

SUPPLEMENTATARY MATERIAL

A1: SOCIAL NETWORK

The social network of our population was defined as the network of injecting partners (i.e. people who inject together) to take into account the background risk of HCV infection between injecting partners (1). Due to a lack of data about the global topography of this network in Montréal, we used an Erdös-Rényi model (2), which can be calibrated using data on the individual-centered network. In this model, each dyad of PWID is linked with a constant probability p, which can be estimated from the size of the whole population N and the average number of injection partners expected $\acute{d}$ noting that $p=\acute{d}/(N-1)$.

A2: MODEL PARAMETERS

The parameters necessary for running the model were mainly provided by SurvUDI data, or by the literature. They are presented in Table A1. We preferentially used data from regional studies when available. Hypotheses underlying some parameter values are detailed below. To assess the impact of these hypotheses on our simulations, we performed several sensitivity analyses (see the main text and supplementary material S2).

Mean number of injecting partners: in his PhD thesis (3), De, P. detailed a study about the social network of people who inject drugs (PWID) in Montréal. We estimated the average number of injecting partners as the product of the average number of PWID in the individual-centered network, the average proportion of PWID with whom the individual reported having injected, the turnover rate (by month) of the network and the average length (in months) of the injecting career from (Fazito *et al.* (4)) providing an estimate of 12 injecting partners per PWID.

Chronic HCV prevalence and initial distribution of susceptible PWID: according to SurvUDI data, 72% of active (in the last 6 months) PWID in Montréal are HCV antibody positive, and based on the proportion of antibody positive individuals among whom RNA can be detected (5), the initial prevalence of chronic hepatitis C is 53%.

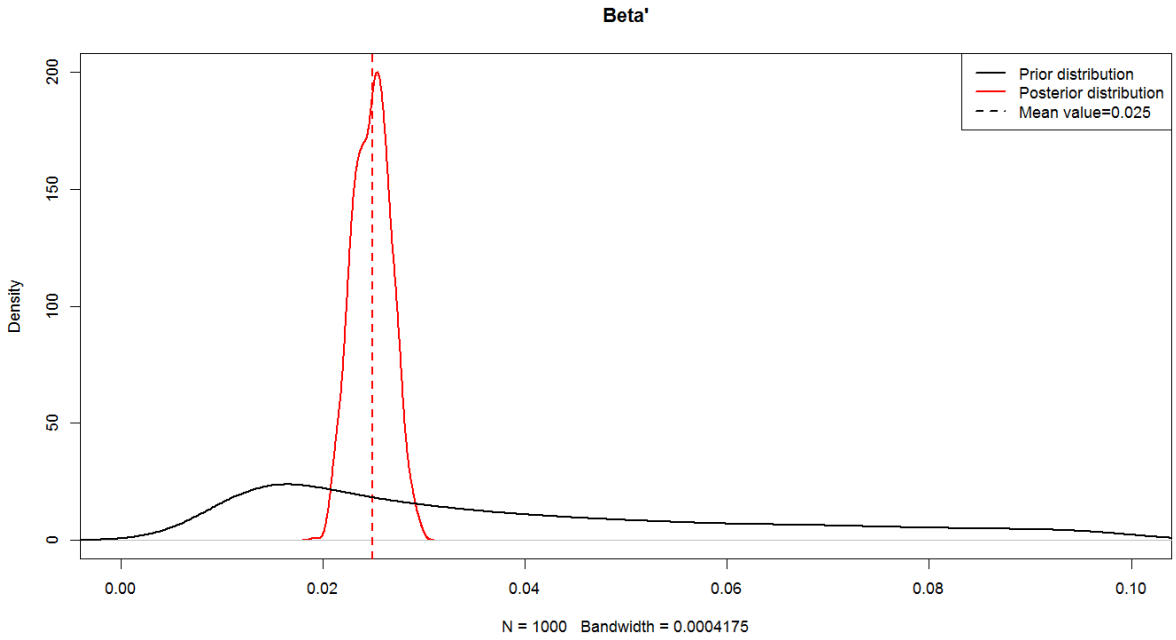
Initial number of acute hepatitis C infections in the PWID population: due to short duration of acute hepatitis (6 months), we assumed that the baseline proportion of active PWID with an acute hepatitis C infection was negligible.

Initial distribution in the natural history model: due to the lack of data about this parameter, we used the distribution of patients followed at the Centre hopitalier de l'université de Montréal (CHUM) for their chronic hepatitis C infection and reporting inject drug use (private communication, J. Bruneau).

Infection rate by injecting partner: this rate was fitted to obtain an incidence of 22.1/100 person-years (p.y) during the first year of simulation in the reference scenario. This value corresponds to the estimate found in SurvUDI for the 2010-2013 period. The method used was Approximate Bayesian Computation (6).

Briefly, the main idea of ABC is to fit the (possibly a set of) parameter(s) θ of a model thanks to simulations and computation of a (possibly set of) statistic(s) $s_i, i=1,\ldots,N$ that are compared to the observed values on the data s_{obs}. More precisely, we drawn a model parameter sample $\theta_i, i=1,\ldots,N$ in a prior probability distribution. The models are simulated with these parameters is used to obtain the corresponding simulated statistics $s_i, i=1,\ldots,N$. Each parameter value is then weighted by $W_i = K_\delta(s_i - s_{obs})$, where K_δ is a smoothing kernel with tolerance threshold δ. The weighted sample $(\theta, W_i / \sum_{i=1}^{N} W_i), i=1,\ldots,N$ gives the posterior probability distribution. We used a variant of the ABC algorithm with linear adjustement to correct θ_i given the other simulations: supposing a linear relation between θ and S, each θ_i is replaced by $\theta_i^* = \theta_i - b(s_i - s_{obs})$, with b estimated by linear regression. This variant allows for a tighter posterior distribution. For more details about ABC, the reader can refer to (6, 7).
For our model, we estimated the contact rate β, using a log-transformed uniform prior distribution on [0.01, 0.1], and the incidence observed in SurvUDI survey (22.1/100PY) as target statistic. We performed 25,000 simulations of the model with a tolerance threshold corresponding to 10% of the total number of simulations. Prior and posterior distribution, as well as prior and posterior incidence, are presented in the Figure below.

A.



B.

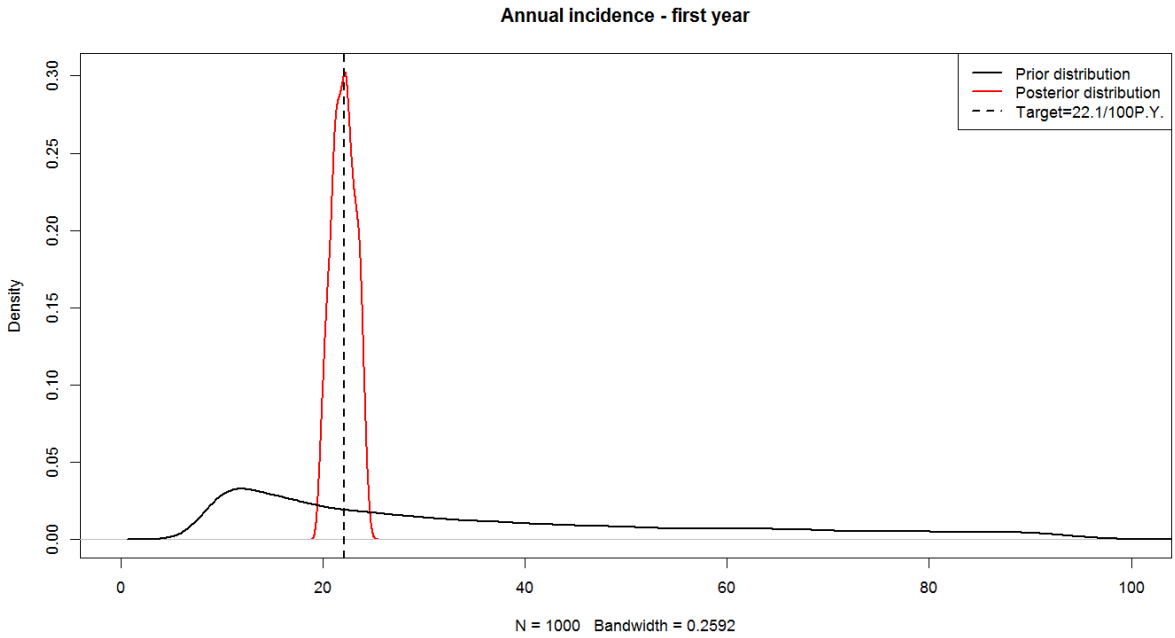


Figure S1 Prior and posterior distribution for the infection rate per injecting partner and the annual incidence in ABC estimation.

This parameter was also fitted to correspond to changes in the initial set of parameters (mean number of injecting partners and the mean duration before the cessation of injection) in the sensitivity analyses (Appendix A3).

Mean duration of the high risk period after injection initiation, relative risk of infection during this period and mortality rates of active PWID: we used estimates based on PWID in studies among street youth of Montréal (8).

Mean time from the end of acute hepatitis C infection to detection: this time was derived from the time of the last test in SurvUDI for the 2012-2014 period. The details of the method are given in (9).

Mean time to linkage to care: we assumed that after detection, the first consultation for an individual related to his/her HCV infection is measured by the occurrence of a HCV RNA-test. It occurs after a mean duration of 1.7 years according to Notifiable Disease Reporting System of the Montréal Public Health Department.

Loss to follow-up rate: according to SurvUDI data, 10.2% of the PWID detected have seen a physician for hepatitis C infection in the past year. Due to our definition of linkage to care (a consultation in the previous 6 months), we considered that these PWID were lost to follow-up during the year, and thus we estimated the annual loss to follow-up rate to 10.2%/y.

Treatment initiation rate when linked to care: using SurvUDI data, the current proportion of PWID under treatment at the time of the study was estimated to be 0.4% during the 2012-2014 period. If we assume that this proportion remains stable over the short term, knowing that the standard of care during this time period was the peg-interferon + ribavirin with treatment durations of between 24 and 48 weeks (10), and knowing that the initial distribution in the “Detected and linked to care chronic hepatitis C” state is 15.3%, approximately 5% of the compartment (i.e. 0.8%) will be treated during the year.

Mortality of inactive PWID: due to the lack of data, we used mortality of the general population in Québec (10).

Ratio of the effectiveness in the real-world situation to the efficacy in clinical trials: in absence of data about the effectiveness of new DAAs after approval and market availability, we estimated this ratio based on dual-therapy peg-interferon + ribavirin. We used the following sustained virological response (SVR) rates as clinical trials values: 50% for genotypes 1/4 and 80% for genotypes 2/3 (10); and as real-world values for PWID: 42.9% for genotypes 1/4 and 73.1% for genotypes 2/3 (11). Using the genotype distribution of (12), we estimated this ratio to be 0.90.

Mean duration before the cessation of injection: due to the absence of data about PWID in Montréal, we used estimates from Fazito *et al.* for North America (4).

Table A1 parameters of the model

Parameter	Value	References
Population size	4,000	(13)
Average number of injecting partners during the injecting career	12	Derived from (3)
Initial distribution (HCV infection and cascade of care)		
Susceptible with high risk	10.10%	SurvUDI, 2012-2014, unpublished data
Susceptible with low risk	36.80%	
Acute hepatitis C	0%*	SurvUDI, 2012-2014, unpublished data
Non-detected chronic hepatitis C	8.40%	
Detected, non-linked to care chronic hepatitis C	24.40%	
Detected and linked to care chronic hepatitis C	15.30%	
Under treatment	0.40%	
Non-responders after treatment	4.60%	
Initial distribution in the natural history model		
F0/F1	61.1%	(Private communication, J. Bruneau)
F2/F3	23.3%	
F4	15.6%	
Decompensated cirrhosis	0%*	
HCC	0%*	
Infection rate by injecting partner in Susceptible (low risk)	0.025 $y^{-1}$$partner^{-1}$	Fitted by ABC to have a 22.1/100 p-y baseline incidence (SurvUDI, 2010-2013)
Relative risk of infection in Susceptibles (high risk)	3	(8)
Mean duration of the high-risk period, i.e. Susceptibles (high risk)	4 y	
Mean duration of acute hepatitis C	0.5 y	(14)
Probability of spontaneous recovery	26%	

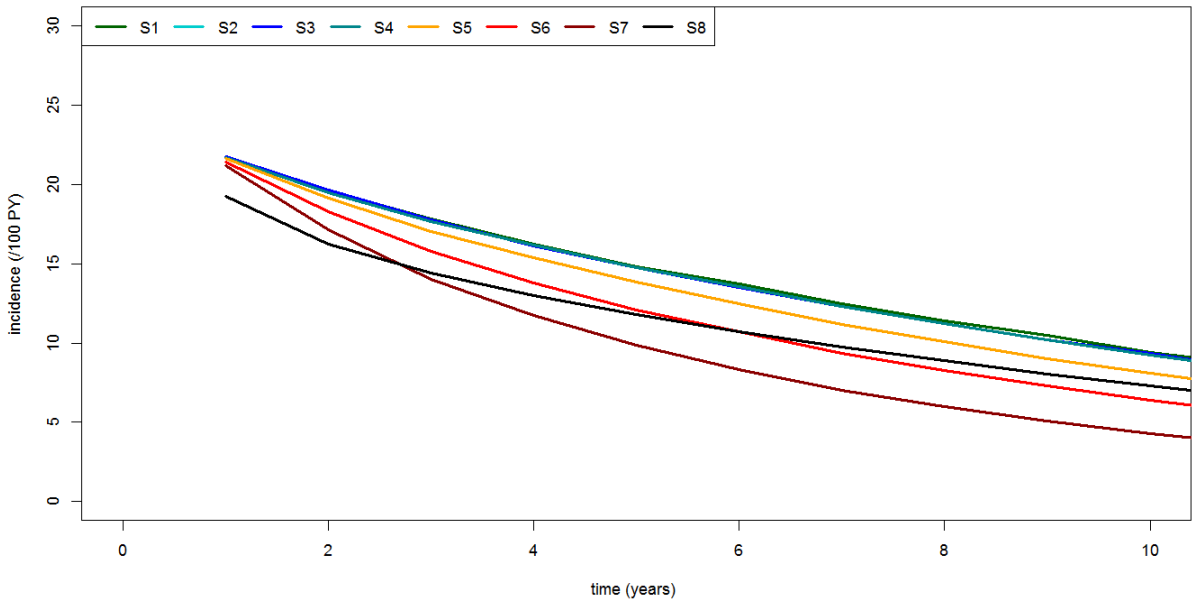
Mean time from the end of acute hepatitis C to detection	2.0y	¿ ¿ ¡	Derived from SurvUDI, 2012-2014, unpublished data
Mean time before linkage to care	1.7y		Derived from Notifiable Disease Reporting System of the Montréal Public Health Department
Loss to follow-up rate	10.3%/y		Derived from SurvUDI, 2012-2014, unpublished data
Treatment initiation rate when linked to care	5%/y		Approximate value derived from SurvUDI, 2012-2014, based on current number of people under treatment (0.4%)
Treatment: incoming DAAs regimens			
Duration	12 weeks	¿ ¿	(15-20)
SVR rate – treatment naive - all genotypes- clinical trials	90%	¿ ¿	
Annual mortality among active PWID	18.4/1000		(21)
Annual mortality among inactive PWID	7.5/1000		(10)
Ratio of the effectiveness in real life to the efficacy in clinical trials	0.90		Derived from (10-12)
Mean duration before the cessation of injection	9.5y		(4)
Transition rate from F0/F1to F2/F3	0.052/y	¿ ¿	(22)
Transition rate from F2/F3 to F4	0.054/y	¿ ¿	
Transition rate from F4 to Decompensated cirrhosis	0.04/y	¿	(23, 24)
Transition rate from F4 to HCC	0.021/y	¿	
Transition rate from Decompensated cirrhosis to Death related to HCV	0.306/y	¿	
Transition rate from HCC to Death related to HCV	0.433/y	¿	
Transition rate from Decompensated cirrhosis to HCC	0.21/y	¿	
Relative risk after a SVR			
Decompensated cirrhosis	0.08	¿ ¿	(25)
HCC	0.27	¿ ¿	

*Hypothesis

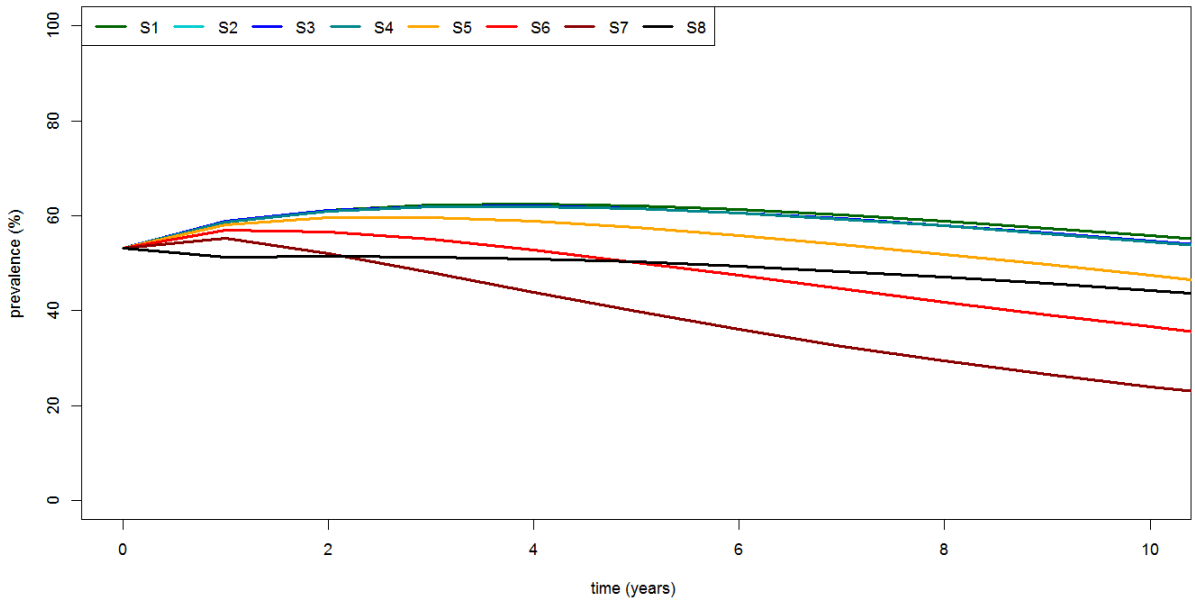
PWID: people who inject drugs; SVR: sustained virological response; HCC: hepatocellular carcinoma

A3: EVOLUTION OF THE INCIDENCE, PREVALENCE AND NUMBER OF CIRRHOSIS COMPLICATIONS PER SCENARIO

A.



B.



C.

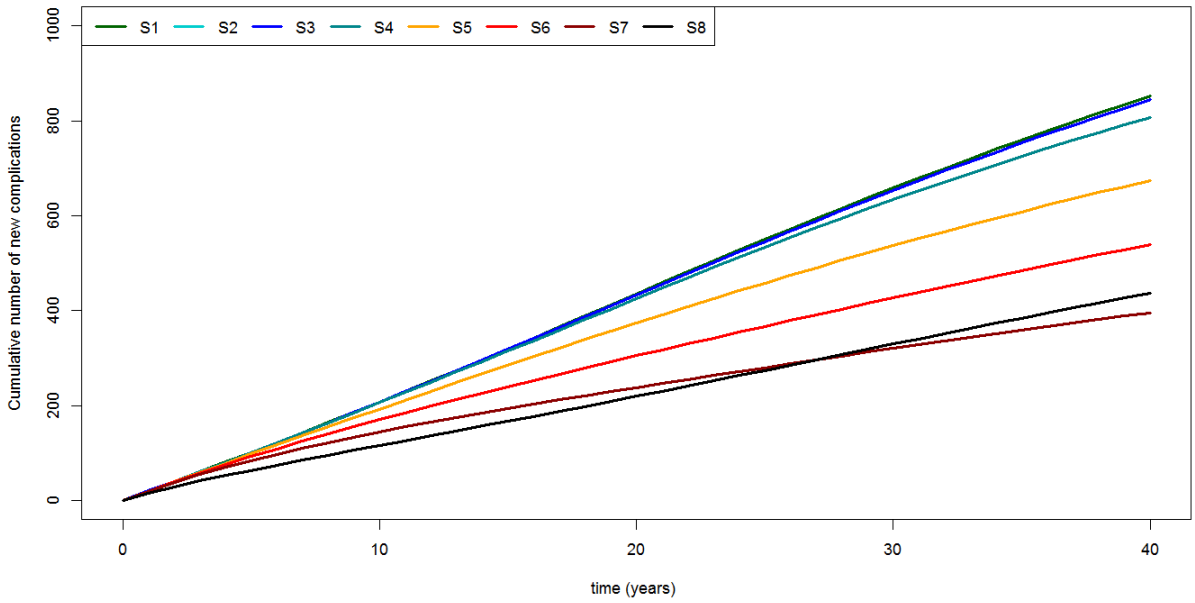


Figure S2 Evolution of A) the incidence of HCV in the population over the first 10 years, B) the prevalence of HCV infection over the first 10 years and C) the number of new cirrhosis complications over the first 40 years.

A4: EVOLUTION OF THE NUMBER OF TREATMENTS PER SCENARIO

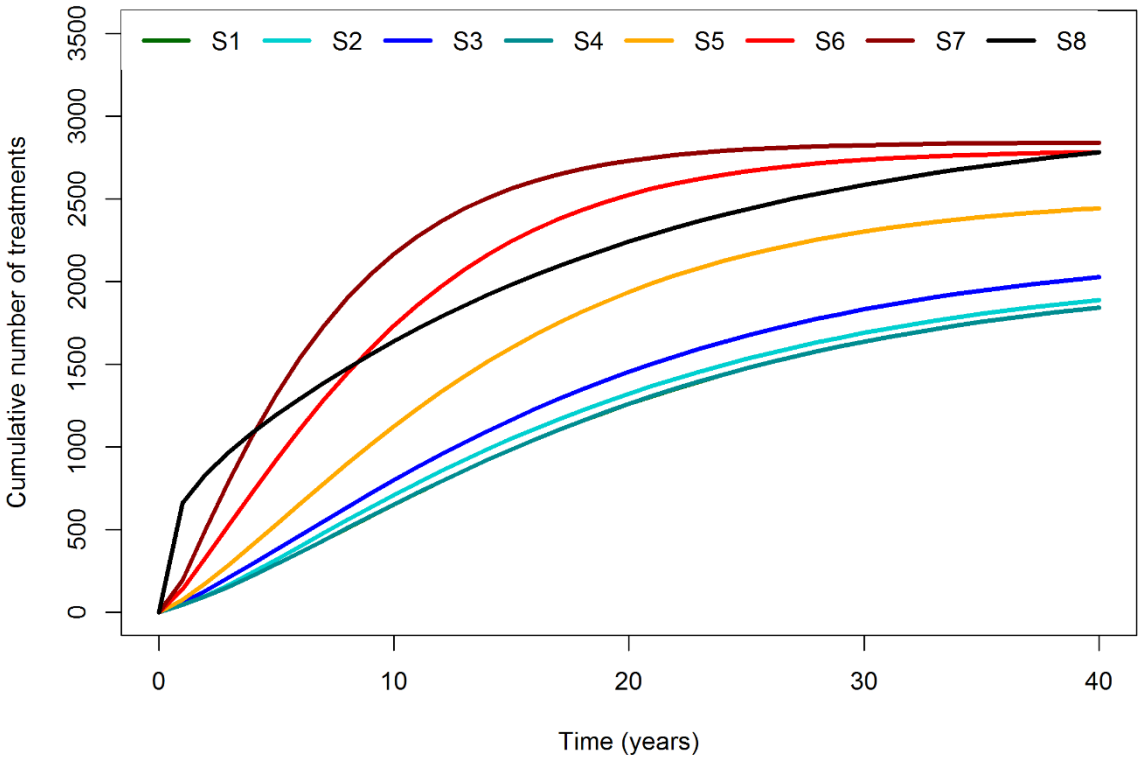


Figure S3 Cumulative number of treatments initiated in each scenario over 40 years of simulation

A5: DISTRIBUTION IN THE CASCADE OF CARE AFTER 10 YEARS

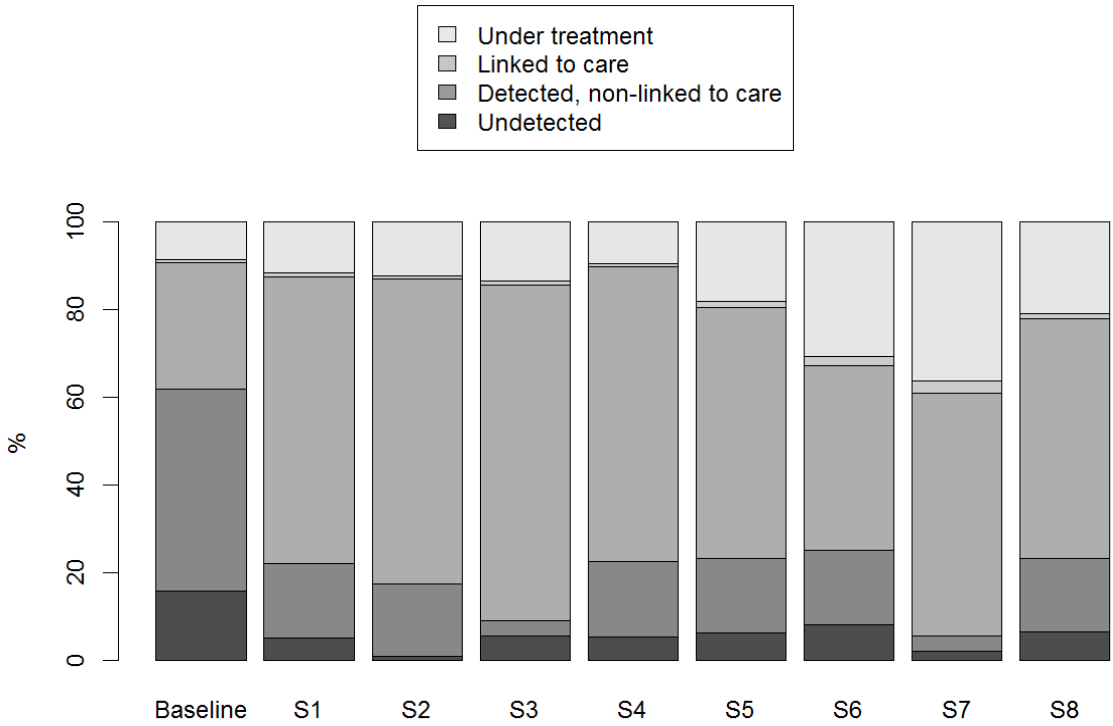


Figure S4 Distribution of the PWID population in the HCV cascade of care at baseline and after 10 years in the 8 scenarios. S1 (reference): current cascade of care with the new DAAs; S2: improvement in testing; S3: improvement in linkage to care; S4: improvement in adherence to treatment; S5: moderate improvement in the treatment initiation rate; S6: high improvement in the treatment initiation rate; S7: combined S2, S3, S4 and S6; S8: systematic treatment initiation when linked to care, but only for F2-F3-F4 fibrosis scores.

A6: SENSITIVITY ANALYSES

Univariate sensitivity analysis – parameters ranges

In the univariate sensitivity analysis, the values of selected parameters were varied based on their uncertainty intervals (see Table A2). When unavailable, we used values from other settings or assumptions. Explanations for some of these assumptions are given below.

Initial fibrosis distribution in infected PWID was estimated for people infected by drug injection, but not necessarily for those who were active injectors. It also assumes a first evaluation has been done and thus a population that may be more advanced relative to HCV care access. We made this initial distribution vary using less severe fibrosis scores.

In our main analysis, the risk of infection per infectious partner was assumed to remain the same after a SVR. Due to the possible cessation of drug injection and the possible treatment of infectious partners during the time elapsed before being treated, the reinfection rate is actually lower than the primary infection rate in our model: over the first 10 years of simulations, the incidence of primary infection in the reference scenario is 16.0/100 p.y. meanwhile the incidence of reinfection after a SVR is 4.9/100 p.y. However, in the literature, the annual reinfection rate ranges between 2% and 4% (11). Despite the conservative nature of our estimate, we used a relative risk of 0.5 after a SVR in the sensitivity analysis.

Table A2 Values of the parameters used in the univariate sensitivity analysis

Parameters	Base case value	Range in sensitivity analysis	References
Initial distribution in the natural history model			
F0/F1	61.1%	75*	
F2/F3	23.3%	15*	
F4	15.6%	10*	
Infection rate (per infectious injecting partner) among Susceptibles (low risk)	0.025/y	0.022 – 0.027	From ABC estimation
Mean duration of the high-risk period, i.e. Susceptibles (high risk)	4.0 y	1.0 -4.0	(26)
Relative risk of reinfection after SVR	1	0.5-1*	
Time between chronic infection and detection	2.0 years	0.5 – 7.8	(27)
Average time before linkage to carev / Loss to follow-up rate	1.7 y / 14%/y	0.5 – 4 / 2.6 – 15	(9)
Annual mortality among active PWID mortality	18.4/1000	13.8 – 23.8	(28, 29)
Annual mortality among inactive PWID mortality	7.5/1000	7.0 - 8.0*	
Average duration of injecting career	9.5 years	4.7 - 14	(4)
Transition rate from F0/F1 to F2/F3	0.052/y	0.031 - 0.074	(22)
Transition rate from F2/F3 to F4	0.054/y	0.025 – 0.101	
Transition rate from F4 to Decompensated cirrhosis	0.04/y	0.032 – 0.052	(23, 24)
Transition rate from F4 to HCC	0.021/y	0.017 – 0.028	
Transition rate from Decompensated cirrhosis to Death related to HCV	0.306/y	0.129 – 0.395	
Transition rate from HCC to Death related to HCV	0.433/y	0.319 – 0.499	
Transition rate from Decompensated cirrhosis to HCC	0.021/y	0.017 – 0.028	

*Hypothesis

PWID: people who inject drugs; SVR: sustained virological response; HCC: hepatocellular carcinoma

The tornado graphs in Figure S2 present variations in outcomes under the conditions of S1 while considering parameter uncertainty levels. The parameters most sensitive (top 10) in outcome estimation are presented for each outcome. For the incidence after 10 years, the most sensitive parameters were the mean time to cessation of injection (with a variation in the reference scenario S1 of -6.0/100 p.y, +3.9/100 p.y.), the treatment initiation rate (-1.3/100 p.y., 1.7/100 p.y.) and the infection rate per infectious injecting partner (-1.6/100 p.y., 1.1/100 p.y.). The most sensitive parameters for the prevalence after 10 years were the treatment initiation rate (-8.3%, +8.7%) and the mean time to cessation of injection (-9.0%, +5.1%). Finally, for the number of cirrhosis complications within 10 years, estimates were most sensitive to the transition rate from F2/F3 to F4 (-18%, +22%), the fibrosis distribution in the population (-28%, +0%) and the decompensation rate (-10%, +15%). For cirrhosis complications after 40 years, estimates were most sensitive to the following parameters: the treatment initiation rate (-21%, +37%), the transition rate from F2/F3 to F4 (-29%, +26%) and the transition rate from F0/F1 to F2/F3 (-15%; +11%).
Results of the other sensitivity analyses are presented in Figures S3 to S6. The trends of our results remained unchanged when we varied the number of injecting partners. In addition, we also simulated the 8 scenarios with the lower and upper bounds of the mean time to cessation of injection used in the univariate sensitivity analysis (4.7 years and 14 years), due to the large impact on prevalence and incidence. The trends observed for the various scenarios were relatively unchanged.

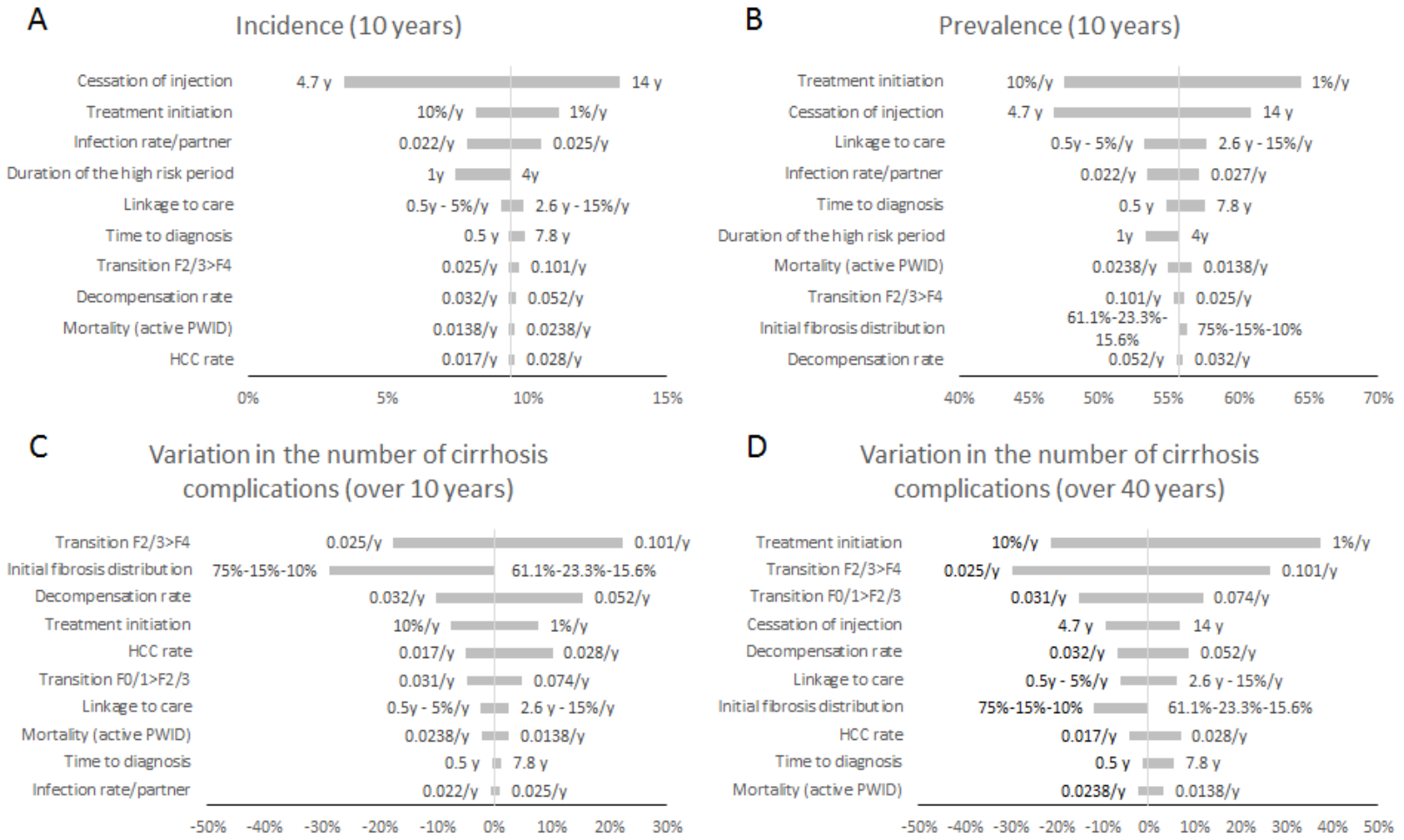


Figure S4 Tornado graphs representing variations in outcomes while considering parameter uncertainty demonstrating the top 10 most sensitive parameters in the model (using the reference scenario (S1)). The corresponding parameters values are given on the charts. A. Incidence at 10 years; B. Prevalence at 10 years; C. Variation in the proportion of new cirrhosis complications over 10 years, compared with the reference scenario (S1); D. Variation in the proportion of new cirrhosis complications over 40 years, compared with the reference scenario (S1).

Mean number of 3 injecting partner

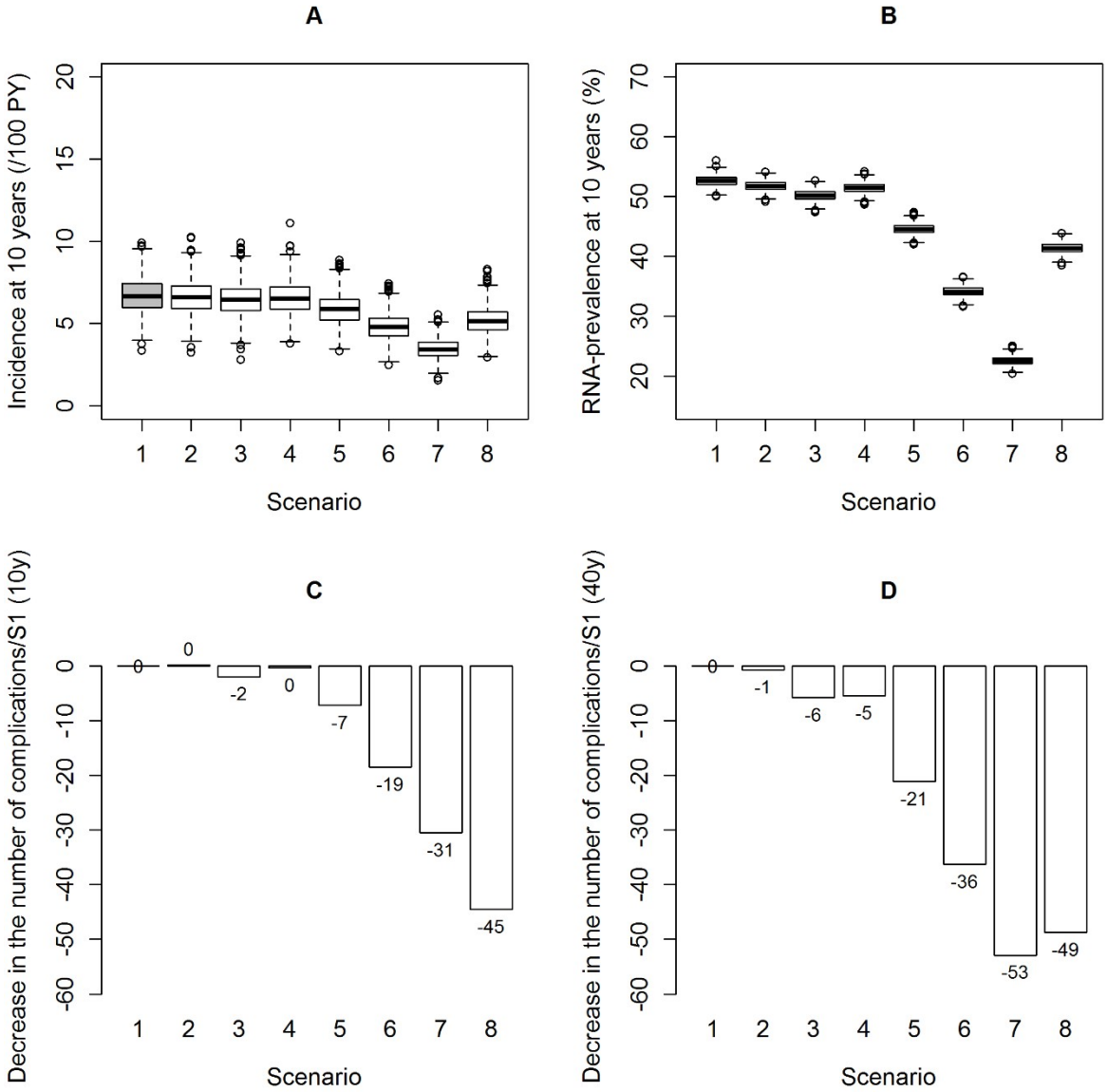


Figure S5 Results according to scenario based on 1,000 simulations, with a mean number of 3 injecting partners. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). The infection rate per infectious partner with this set of parameters was estimated to be 0.098/y using Approximate Bayesian Computation to have an initial incidence of 22.1/100 p.y. S1 (reference): The current HCV cascade of care using the new DAAs. S2: S1 with an improvement in the mean time to detection of chronic HCV from 2y to 0.5y. S3: S1 with an improvement in linkage to care, with a mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y. S4: S1 with an improvement in adherence to treatment, i.e. we improved the SVR rate of 81% to the level demonstrated in clinical trials, i.e. 90%. S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care. S6: Improvement in treatment initiation rate from 5%/y to 20%/y when linked to care. S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care. S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 only.

Mean number of 15 injecting partner

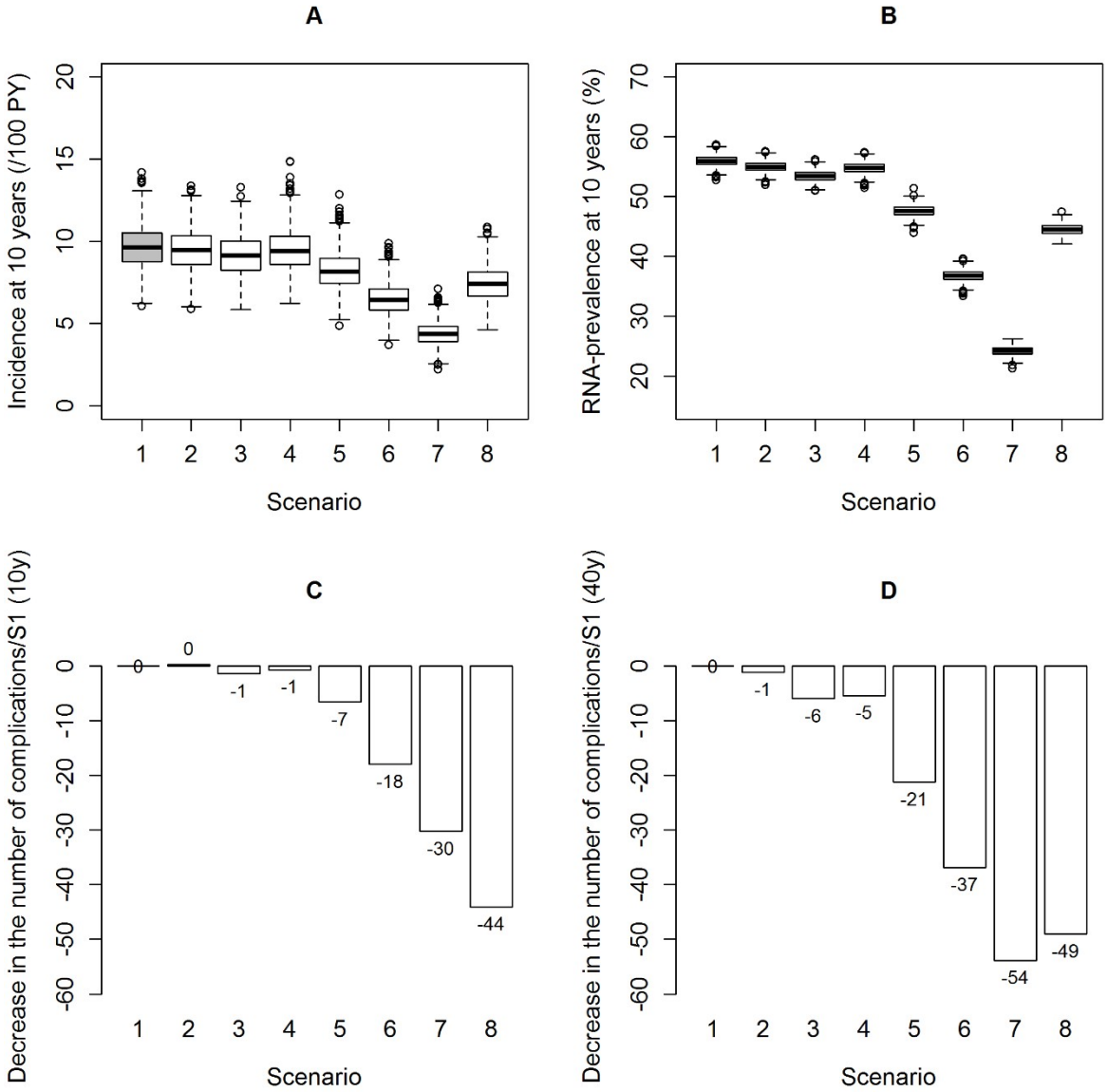


Figure S6 Results according to scenario based on 1,000 simulations, with a mean number of 15 injecting partners. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). The infection rate per infectious partner with this set of parameters was estimated to be 0.020/y using Approximate Bayesian Computation to have an initial incidence of 22.1/100 p.y. S1 (reference): The current HCV cascade of care using the new DAAs. S2: S1 with an improvement in the mean time to detection of chronic HCV from 2y to 0.5y. S3: S1 with an improvement in linkage to care, with a decrease in mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y. S4: S1 with an improvement in adherence to treatment, i.e. we improved the SVR rate of 81% to the level demonstrated in clinical trials, i.e. 90%. S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care. S6: Improvement in the treatment initiation rate from 5%/y to 20%/y when linked to care. S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care; no fibrosis criteria for treatment initiation. S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 only. S1 (reference): The current HCV cascade of care using the new DAAs. S2: S1 with an

improvement in the mean time to detection of chronic HCV from 2y to 0.5y. S3: S1 with an improvement in linkage to care, with a mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y. S4: S1 with an improvement in adherence to treatment, i.e. we improved the SVR rate of 81% to the level demonstrated in clinical trials, i.e. 90%. S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care. S6: Improvement in treatment initiation rate from 5%/y to 20%/y when linked to care. S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care. S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 only.

Mean duration before cessation of injection 4.7 years

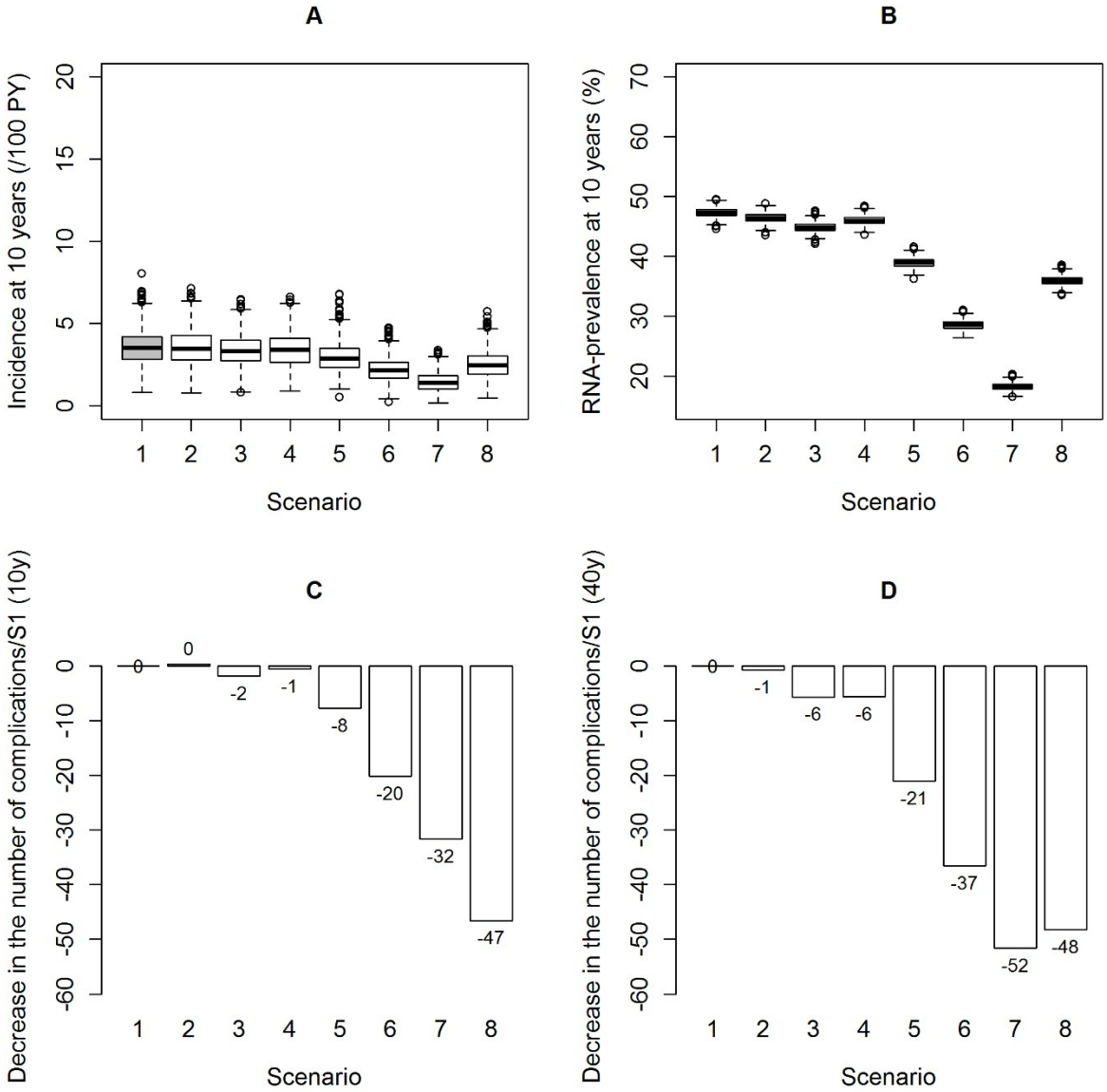


Figure S7 Results according to scenario based on 1,000 simulations, with a mean duration of the injecting career of 4.7 years. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). The infection rate per infectious partner with this set of parameters was estimated to be 0.026/y using Approximate Bayesian Computation to have an initial incidence of 22.1/100 p.y. S1 (reference): The current HCV cascade of care using the new DAAs. S2: S1 with an improvement in the mean time to detection of chronic HCV from 2y to 0.5y. S3: S1 with an improvement in linkage to care, with a decrease in mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y. S4: S1 with an improvement in adherence to treatment, i.e. we improved the SVR rate of 81% to the level demonstrated in clinical trials, i.e. 90%. S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care. S6: Improvement in the treatment initiation rate from 5%/y to 20%/y when linked to care. S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care; no fibrosis criteria for treatment initiation. S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 S1 (reference): The current HCV cascade of care using the new DAAs. S2:

S1 with an improvement in the mean time to detection of chronic HCV from 2y to 0.5y. S3: S1 with an improvement in linkage to care, with a mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y. S4: S1 with an improvement in adherence to treatment, i.e. we improved the SVR rate of 81% to the level demonstrated in clinical trials, i.e. 90%. S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care. S6: Improvement in treatment initiation rate from 5%/y to 20%/y when linked to care. S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care. S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 only.

Mean duration before cessation of injection 14 years

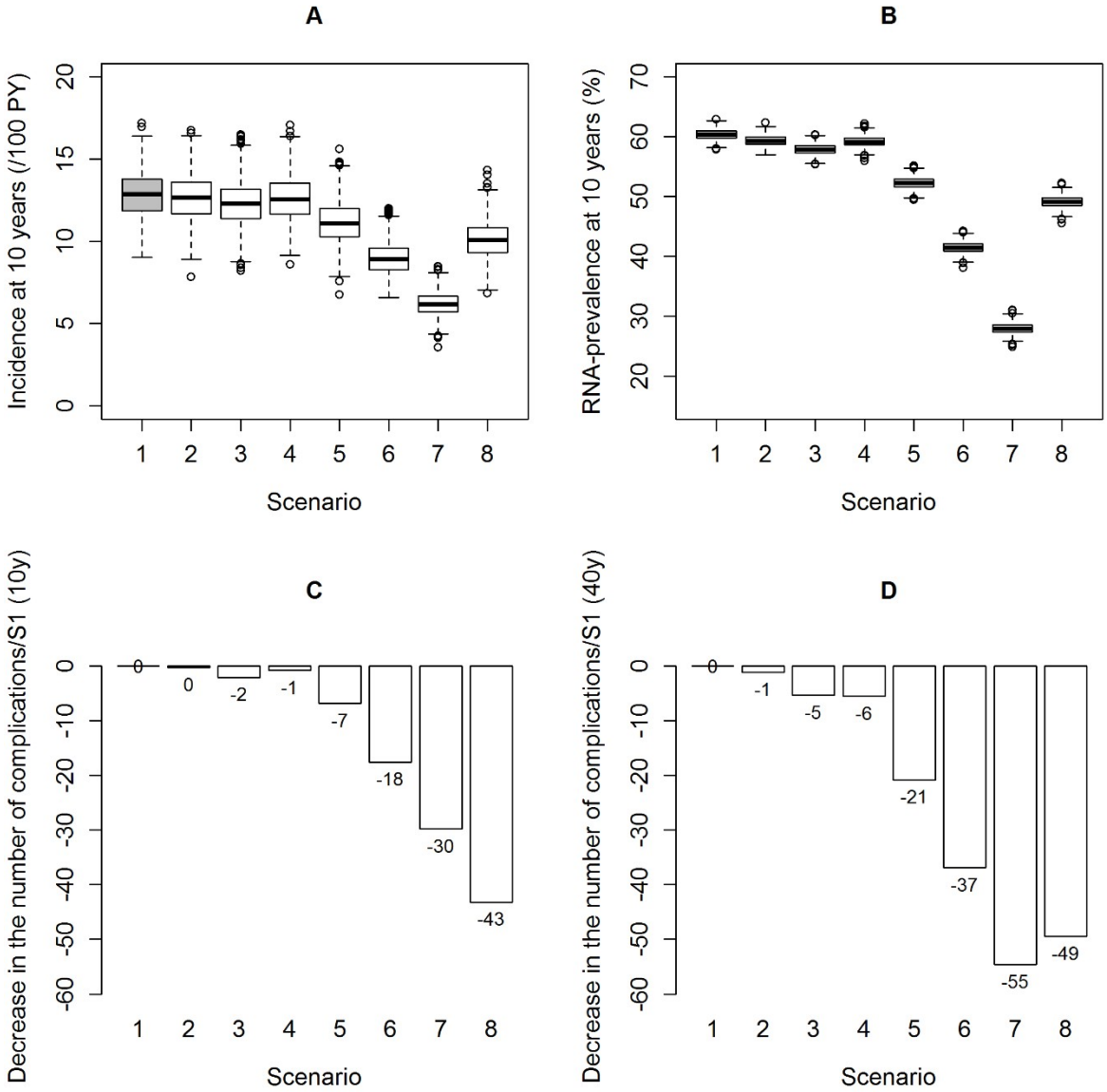


Figure S8 Results according to scenario based on 1,000 simulations, with a mean duration of the injecting career of 14 years. A. Boxplots of the incidence at 10 years; B. Boxplots of the prevalence at 10 years; C. Proportion of cirrhosis complications avoided after 10 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)); D. Proportion of cirrhosis complications avoided after 40 years (mean percentage of new cirrhosis complications avoided, compared with the reference scenario (S1)). The infection rate per infectious partner with this set of parameters was estimated to be 0.024/y using Approximate Bayesian Computation to have an initial incidence of 22.1/100 p.y. S1 (reference): The current HCV cascade of care using the new DAAs. S2: S1 with an improvement in the mean time to detection of chronic HCV from 2y to 0.5y. S3: S1 with an improvement in linkage to care, with a decrease in mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y. S4: S1 with an improvement in adherence to treatment, i.e. we improved the SVR rate of 81% to the level demonstrated in clinical trials, i.e. 90%. S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care. S6: Improvement in the treatment initiation rate from 5%/y to 20%/y when linked to care. S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care; no fibrosis criteria for treatment initiation. S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 S1 (reference): The current HCV cascade of care using the new DAAs. S2:

S1 with an improvement in the mean time to detection of chronic HCV from 2y to 0.5y. S3: S1 with an improvement in linkage to care, with a mean time to linkage to care from 1.7y to 0.5y and a loss to follow-up rate from 10.2%/y to 5%/y. S4: S1 with an improvement in adherence to treatment, i.e. we improved the SVR rate of 81% to the level demonstrated in clinical trials, i.e. 90%. S5: S1 with an improvement in treatment initiation rate from 5%/y to 10%/y when linked to care. S6: Improvement in treatment initiation rate from 5%/y to 20%/y when linked to care. S7: Combined scenarios S2, S3, S4 and S6 to determine the impact of improvements in the entire cascade of care. S8: S1 with an initiation of HCV treatment at fibrosis levels F2-F3-F4 only.

A7: WIDTH OF THE CONFIDENCE INTERVALS

Trajectories in a stochastic, individual-based model converge in probability to the solution of a differential equation system when the population size N goes to infinity (30). We can calculate a central limit theorem, which shows the convergence rate is in $1/\sqrt{N}$ (31). Here, N =4,000. From this convergence we can deduce asymptotic normality results for the outputs of the model (prévalence, incidence and number of complications) which are simple functions of the epidemic trajectory. Thus, the standard deviation is in $1/\sqrt{N}$.

For our simulations, we did n =1 000 Monte-Carlo replications of these outputs. The width of the confidence intervals is thus in $C/\sqrt{n}$, with C a constante. This explains the confidence intervals are tigth. These confidence intervals correspond to the set of parameters of the main analysis, they don't take into account the uncertainty related to these parameters. The latter, which relies on the parameters estimation, was studied in sensitivity analysis.

REFERENCES

1. Rolls DA, Daraganova G, Sacks-Davis R, Hellard M, Jenkinson R, McBryde E, et al. Modelling hepatitis C transmission over a social network of injecting drug users. J Theor Biol. 2012 Mar 21;297:73-87.
2. Erdős P, Rényi A. On Random Graphs. I. Publicationes Mathematicae. 1959;6:290–7.
3. De P. Using social networks to better conceptualize risk fro bloodborne viruses among injection drug users. Montréal, Canada: McGill university; 2007.
4. Fazito E, Cuchi P, Mahy M, Brown T. Analysis of duration of risk behaviour for key populations: a literature review. Sex Transm Infect. 2012 Dec;88 Suppl 2:i24-32.
5. Trubnikov M, Yan P, Archibald C. Estimated prevalence of Hepatitis C virus infection in Canada, 2011. Canada Communicable Disease Report. 2014;40(19):429.
6. Marin J-M, Pudlo P, Robert CP, Ryder RJ. Approximate Bayesian computational methods. Statistics and Computing. 2012;22(6):1167-80.
7. Blum MG, Tran VC. HIV with contact tracing: a case study in approximate Bayesian computation. Biostatistics. [Research Support, Non-U.S. Gov't]. 2010 Oct;11(4):644-60.
8. Roy E, Boudreau JF, Boivin JF. Hepatitis C virus incidence among young street-involved IDUs in relation to injection experience. Drug Alcohol Depend. 2009 Jun 1;102(1-3):158-61.
9. Cousien A, Tran VC, Deuffic-Burban S, Jauffret-Roustide M, Dhersin J-S, Yazdanpanah Y. Impact of a treatment as prevention strategy on hepatitis C virus transmission and on morbidity in people who inject drugs. arXiv preprint arXiv:150602987. 2015.
10. NICE. PegInterferon alfa and ribavirin for the treatment of mild chronic hepatitis C2006.
11. Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis. 2013 Aug;57 Suppl 2:S80-9.
12. Bernier L, Willems B, Delage G, Murphy DG. Identification of numerous hepatitis C virus genotypes in Montreal, Canada. J Clin Microbiol. 1996 Nov;34(11):2815-8.
13. Leclerc P, Vandal AC, Fall A, Bruneau J, Roy E, Brissette S, et al. Estimating the size of the population of persons who inject drugs in the island of Montreal, Canada, using a six-source capture-recapture model. Drug Alcohol Depend. 2014 Sep 1;142:174-80.
14. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. 2006 Jan;13(1):34-41.
15. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17;370(16):1483-93.
16. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014 May 15;370(20):1889-98.
17. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014 May 15;370(20):1879-88.
18. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014 Jan 16;370(3):211-21.
19. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1604-14.
20. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon S, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 may 16;368(20):1878-87.
21. Roy E, Haley N, Leclerc P, Sochanski B, Boudreau JF, Boivin JF. Mortality in a cohort of street youth in Montreal. JAMA. 2004 Aug 4;292(5):569-74.
22. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008 Aug;48(2):418-31.
23. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. JAMA. 2003 Jul 9;290(2):228-37.

24. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Empirically calibrated model of hepatitis C virus infection in the United States. Am J Epidemiol. 2002 Oct 15;156(8):761-73.
25. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol. 2010 Mar;8(3):280-8, 8 e1.
26. Sutton AJ, Gay NJ, Edmunds WJ, Hope VD, Gill ON, Hickman M. Modelling the force of infection for hepatitis B and hepatitis C in injecting drug users in England and Wales. BMC Infect Dis. 2006;6:93.
27. Martin NK, Hickman M, Miners A, Hutchinson SJ, Taylor A, Vickerman P. Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons. BMJ Open. 2013;3(8).
28. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. Bull World Health Organ. 2013 Feb 1;91(2):102-23.
29. Miller CL, Kerr T, Strathdee SA, Li K, Wood E. Factors associated with premature mortality among young injection drug users in Vancouver. Harm Reduct J. 2007;4:1.
30. Tran VC. Une ballade en forêts aléatoires: Université Lille 1; 2014.
31. Andersson H, Britton T. Stochastic epidemic models and their statistical analysis: Springer Science & Business Media; 2012.