

## SUPPLEMENTARY INFORMATION

### S1: MODEL DETAILS AND PARAMETERS ESTIMATIONS

Table S1 summarizes the values of the parameters we used in the model and the hypotheses we made.

#### *Network*

For the Erdős-Rényi graph, the only parameter needed is the average number of injecting partners.

Wylie *et al.* found that Canadian PWID had a median of 3.5 injecting partners for a period of 30 days (1). Sacks-Davis *et al.* reported a median number of 3 injecting partners/PWID, in Melbourne, with a median duration of 3 years for a partnership (2). Murray *et al.* estimated the annual number of injecting partners to be 6 in Australia (3). Due to the lack of data about network dynamics over the long term, we assumed that PWID had an average of 6 injecting partners for the whole period. We varied this parameter from 3 to 15 in a sensitivity analysis.

#### *Population*

*Size of the population:* we assumed a population of 10,000 PWID.

*Proportion of current PWID:* we considered a population that consisted exclusively of current PWID, at the beginning of each simulation.

From this point forward, we use the name of the state of the model in Figure 1 to describe the percentage of people in this state.

*Initial distribution in the model:* from ANRS-Coquelicot study for the year 2011 (unpublished).

In details, we estimated the seroprevalence in PWID to be 65.9%. Knowing that viral ARN is present in 65% of seropositive individuals PWID (4), we had a viral prevalence of 42.8%. Thus the percentage of uninfected PWID initially is  $S+S'=57.2\%$ . In our population, 5.4% of individuals were in their first year of injection, and we assumed that they were all susceptible to infection. Since  $S+S'=57.2\%$ , Thus  $S=5.4\%$  and  $S'=51.8\%$ . Due to the short duration of acute hepatitis C (6 months), we assumed that the

number of acute hepatitis C cases at a given moment was negligible:  $A=0\%$ . In ANRS-Coquelicot, 21.4% of infected people, which represent 42.8% of the whole population, were unaware of their infection, thus  $NDC=9.2\%$ . 33.7% of those who were aware of their infection, i.e. the remaining 33.6% of the whole population, were not linked to care, thus  $DCNL=11.3\%$ ; 47.6% were linked to care, but not treated, so  $DCL=16.0\%$ ; 6.4% were linked and currently undergoing treatment, thus  $T=2.2\%$ ; and 12.3% had a previous unsuccessful or interrupted treatment, so  $Non-SVR=4.1\%$ .

To avoid that all the initially treated people stop their treatment at the same time and ensure a smooth trajectory at the beginning of the simulations, we drew a past time under treatment for individual in T in a uniform distribution (between 0 and  $T_1$ ).

*Distribution in the natural history model:* we found no estimation of the distribution of chronically infected PWID according to Metavir Score for the whole infected group for the French PWID population. However, Melin *et al.* provide an estimate at the initiation of treatment, so we assumed that these two distributions were similar (5).

We assumed that at the beginning of each simulation, the number of cirrhosis complications was negligible.

We required that in the initial population an individual in a state had a fibrosis score coherent with his state, i.e. no cirrhosis complications in NDC, DCNL, DCL (as we assumed that any individual with complications would always be linked to care), no F2-F3-F4 in DCNL (because we assumed people in these stages would get treated); and no fibrosis score  $<F2$  in T and Non-SVR because in the base case PWID were only treated according to current guidelines - between scores F2 and F4.

*Proportion of men,  $p_M$ :* the proportion of men in PWID, 74.5%, was given by ANRS-Coquelicot study.

### ***Transitions and care***

*Infection rate per infectious contact in S (high risk),  $\beta$ , and in S' (low risk),  $\beta'$ :* We fitted these rates using approximate Bayesian computation (ABC) from some statistics calculated on the ANRS-Coquelicot population. The detailed methods are given in Supplementary Information S2.

*Duration of acute hepatitis,  $T_a$ , and probability of spontaneous recovery,  $p_r$ :* Micallef *et al.* provided an estimated  $p_r=26\%$  of spontaneous recovery during the  $T_a=0.5$  years of acute hepatitis (6).

*Testing rate in chronic hepatitis C,  $\delta$* : We found no direct estimation of the testing rate in the literature. However, the ANRS-Coquelicot study contains data sufficient to derive the rates for active PWID and inactive PWID. From this point forward, we define “active PWID” as the PWID that injected in the past month, and “inactive PWID” as the PWID that did not inject in the past month. We used these two groups as a proxy for current PWID, and former PWID (see Supplementary Information S3). We found a mean duration between infection and diagnosis of  $1/\delta=1.25$  years for current PWID and  $1/\delta=1.45$  years for former PWID.

*Linkage to care rate,  $\phi_{Link}$ , and loss to follow up rate,  $\phi_{Lost}$* : we found no data about loss to follow-up for chronically HCV-infected PWID in France. However, the doctoral thesis work of Dr. Bakhao Ndiaye provides this rate among HIV-infected PWID (7). We assumed that the rate was similar for both HIV and HCV. Therefore, the annual probability of loss to follow up was 13.8/100 person-year. The linkage to care rate,  $\phi_{Link}$ , was estimated at 0.39 by ABC (see Supplementary Information S2), corresponding to an average duration of  $1/0.39=2.6$  years before an individual links to care.

*Treatment*: For incoming DAAs regimens, we used a  $e=90\%$  SVR rate for a 12-week treatment (8-15). In order to take into account the lower effectiveness of treatment in real life compared to the efficacy of the same regimen in clinical trials, we applied a ratio  $r=90.3\%$  to the SVR rate. This ratio corresponds to the ratio of the effectiveness in an observational study to the efficacy in clinical trials of the dual therapy in Melin *et al.* (5) (if we consider a SVR rate of 45% for genotype 1 and 80% for genotype 2/3 in clinical trials (16) in bitherapy peg-interferon + ribavirin).

*Cessation of drug use rate,  $\theta$* : in the absence of data on a French PWID population, we used Scottish data to get the mean duration between first injection and cessation of drug use:  $1/\theta=13.9$  years (17, 18).

*Non-HCV mortality,  $\mu$* : For mortality of PWID, Lopez *et al.* estimated the annual mortality rate to be 0.0077 per years ( $y^{-1}$ ) for men and 0.0054  $y^{-1}$  for women among heroin, cocaine and crack cocaine users (19).

For former-PWID, we found no data. We hypothesized that mortality among former-PWID was similar to the mortality of adults >20 years in the general population, which was  $\mu=0.0113 \text{ y}^{-1}$  for men and  $\mu=0.0098 \text{ y}^{-1}$  for women in 2011 (20, 21).

### Natural history parameters

Estimates of the transition rates between stages F0/1, F2/3 and F4 specific to PWID were available in Thein *et al.* (22). For complications and HCV-related death rates, we found no estimate for a PWID population, but Salomon *et al.* provided an estimate of HCV-related cirrhosis rates for the general population (23, 24). We found no estimate of the HCC rate in decompensated cirrhosis  $\lambda_{HCC-Decomp}$ , so we assumed that  $\lambda_{HCC-Decomp} \approx \lambda_{HCC}$ .

**Table S1** Parameters for the model

Parameter	Value	References
Population size	10,000*	
Initial distribution in the IBM		
<i>Susceptible with high risk (S)</i>	5.4%	} ANRS-Coquelicot
<i>Susceptible with low risk (S')</i>	51.8%	
<i>Acute hepatitis C (A)</i>	0%*	
<i>Non-diagnosed chronic hepatitis C (NDC)</i>	9.2%	} ANRS-Coquelicot
<i>Diagnosed, non-linked to care chronic hepatitis C (DCNL)</i>	11.3%	
<i>Diagnosed and linked to care chronic hepatitis C (DCL)</i>	16.0%	
<i>Under treatment (T)</i>	2.2%	
<i>Non-responders after treatment (Non-SVR)</i>	4.1%	
Initial distribution in the natural history model		
<i>F0/F1</i>	35%	} (5)
<i>F2/F3</i>	51%	
<i>F4</i>	14%	
<i>Decompensated cirrhosis</i>	0%*	
<i>HCC</i>	0%*	
% Men among current PWID ( $p_M$ )	75.5%	ANRS-Coquelicot
Number of injecting partners per PWID ( $\bar{d}$ )	6*	See Supplementary Information S1
Infection rate by injecting partner in S' ( $\beta'$ )	0.01 $\text{y}^{-1}\text{partner}^{-1}$	See Supplementary Information S2

Relative risk of infection in S ( $\beta/\beta'$ )	3	}	(25)
Duration of high risk period ( $1/\eta$ )	1 y		
Duration of acute hepatitis C ( $T_a$ )	0.5 y	}	(6)
Probability of spontaneous recovery ( $p_r$ )	26%		
Average time from chronic infection to diagnosis ( $1/\delta$ )			
<i>Current PWID</i>	1.25 y	}	Derived from ANRS-Coquelicot data (See Supplementary Information S3)
<i>Former PWID</i>	1.45 y		
Average time before linkage to care ( $1/\phi_{Link}$ )	2.6 y		See Supplementary Information S2
Loss to follow-up rate ( $\phi_{Lost}$ )	14%/y		(7)
Treatment: incoming DAAs regimens			
<i>Duration (<math>T_t</math>)</i>	12 weeks	}	(8-10, 12-14, 26-28)
<i>SVR rate (<math>p_{SVR}</math>) – treatment naive - all genotypes- clinical trials</i>	90%		
Ratio of the effectiveness in real life to the efficacy in clinical trials ( $r$ )	0.903		(5)
Mortality ( $\mu$ )			
<i>Current PWID - men</i>	0.0077 y <sup>-1</sup>	}	(19)
<i>Current PWID - women</i>	0.0054 y <sup>-1</sup>		
<i>Former PWID - men</i>	0.0114 y <sup>-1</sup>	}	(20, 21)
<i>Former PWID - women</i>	0.0098 y <sup>-1</sup>		
Duration of injecting career ( $1/\theta$ )	13.9 y		(17, 18)
Transition rate F0/F1 → F2/F3 ( $\lambda_{2/3}$ )	0.052 y <sup>-1</sup>	}	(22)
Transition rate F2/F3 → F4 ( $\lambda_4$ )	0.054 y <sup>-1</sup>		
Transition rate F4 → Decompensated cirrhosis ( $\lambda_{Decomp}$ )	0.04 y <sup>-1</sup>	}	(23, 24)
Transition rate F4 → HCC ( $\lambda_{HCC}$ )	0.021 y <sup>-1</sup>		
Transition rate Decompensated cirrhosis → Death related to HCV ( $\lambda_{Decomp-M}$ )	0.306 y <sup>-1</sup>		
Transition rate HCC → Death related to HCV ( $\lambda_{HCC-M}$ )	0.433 y <sup>-1</sup>		
Transition rate Decompensated cirrhosis → HCC ( $\lambda_{Decomp-HCC}$ )	0.021 y <sup>-1</sup>		

\* Hypothesis

IBM: Individual-based model

SVR: Sustained virological response

PWID: People who inject drugs

y<sup>-1</sup>: per year

HCC: Hepatocellular carcinoma

DAA: Direct-acting antiviral

HCV: Hepatitis C virus

## **S2: ESTIMATING THE INFECTION RATE $\beta$ AND THE LINKAGE TO CARE RATE $\phi_{Link}$ BY APPROXIMATE BAYESIAN COMPUTATION (ABC)**

For sophisticated models where likelihood can be numerically intractable, methods based on likelihood fail to provide good estimates for parameters. Approximate Bayesian Computation (ABC) is a computational method used to infer some parameters without likelihood estimation (29).

We denote by  $\theta$  the set of parameters to derive and  $X$  the set of observed data.

### **Reminder: Bayesian inference**

To clearly understand the motivation of ABC, we begin with a quick reminder about the main principle of Bayesian inference. The main idea of the Bayesian inference is to consider  $\theta$  as a random variable with a probability distribution.

Let  $\pi(\theta)$  be the *prior distribution* of the parameters. The prior distribution is chosen to reflect the uncertainty around  $\theta$  before any data is observed. Ideally, the variable must be the most informative possible (for example, a choice for the parameter  $p$  of an Erdős–Rényi model can be a beta distribution).

Let  $L(\theta, X)$  be the likelihood of  $\theta$  given the data  $X$  in the model. This likelihood corresponds to the information given by the data.

The *posterior distribution* of the parameters is defined as the distribution of  $\theta$  taking into account the available data, i.e.  $p(\theta|X)$ . According to Bayes theorem, it is given by:

$$p(\theta|X) \propto L(\theta, X)\pi(\theta)$$

Where  $\propto$  means that the two quantities are proportional. The posterior distribution is more informative than the prior distribution and we expect a tighter distribution. Bayesian inference aims at estimating this distribution and its mean or median can be chosen as estimates of the parameter  $\theta$ .

### **Main idea of ABC**

The key point of Bayesian inference is the computation of the likelihood  $L(\theta, X)$ . However, for a complex model, this may be intractable. The main idea of ABC is to 1) catch information from the

observed data by replacing the posterior distribution by the target distribution  $p(\theta|S(X))$  (called the *partial posterior distribution*), where  $S$  is a vector of summary statistics of the data (for example, the number of edges or the number of triangles of the graph); and 2) use the generative model to avoid any likelihood-like computation.

Let  $s_{obs}$  be the value of  $S(X)$  in the data. ABC aims to approximate  $L(\theta|s_{obs})$  by considering simulations for which  $S$  is close to  $s_{obs}$ .

The basic form of the ABC is thus based on a rejection algorithm, and implemented as follows:

1. Generate  $N$  random draws  $(\theta_i, s_i)$ ,  $i = 1, \dots, N$  in the joint law of  $(\theta, S)$ . The parameter  $\theta_i$  is generated from the prior distribution  $\pi$ , and the vector of summary statistics  $s_i$  is calculated for the  $i$ th data set that is simulated from the model with parameter  $\theta_i$ .
2. Associate to the  $i$ th simulation, the weight  $W_i = K_\delta(s_i - s_{obs})$ , where  $\delta$  is a tolerance threshold and  $K_\delta$  a (possibly multivariate) smoothing kernel.
3. The distribution  $\sum_{i=1}^N W_i \delta_{\theta_i} / \sum_{i=1}^N W_i$  in which  $\delta_\theta$  denotes the Dirac mass at  $\theta$ , approximates the target distribution.

In our study, we used an improved version of this rejection algorithm, based on linear adjustments of the parameters: we assumed a linear link between  $\theta$  and  $S$  for observations under the tolerance threshold, i.e.  $\theta$  can be approximated by a function of the form  $a + bS$ , and  $\theta_i$  is replaced by:

$$\theta_i^* = \theta_i - b(s_i - s_{obs}),$$

The slope  $b$  is estimated by regressions of  $\theta_i$  on  $s_i$  with  $N$  simulations, using the package ‘‘abc’’ (30) of the statistical software R (31).

### Application of ABC

We have two parameters of interest:  $\beta'$  the injection rate per infectious edge in the network for an experienced PWID, and  $\phi_{Link}$  the rate of linkage to care. We have also nuisance parameters (i.e. parameters necessary for the model): the distribution in DCL, DCNL, T, and Non-SVR in 2004. These parameters are estimated from the following data of ANRS Coquelicot study:

- Prevalence among active PWID in 2011: 42.8%

- Distribution of inactive PWID in DCNL: 11.3%
- Distribution of inactive PWID in NDC: 16%
- Distribution of inactive PWID in T: 2.2%.

Since the Coquelicot study allowed us to have the prevalence in the model in 2004, we performed simulations over the 2004-2011 period. We used specific data available for this period about the mortality among former PWID, the testing rate, and the distribution in S, S', and NDC instead of the parameters we used in the base case (see Table S2).

Concerning the parameters of ABC, we performed 25,000 simulations, the tolerance threshold  $\delta$  was 0.1 and we used an Epanechnikov kernel, i.e. for all  $u$  in  $\mathbb{R}$ :

$$K_{\delta}(u) = \frac{3}{4\delta} \left( 1 - \frac{u^2}{\delta^2} \right) \mathbb{1}_{u \leq \delta}$$

To ensure positivity of  $\beta$  and  $\phi_{Link}$ , these parameters were log-transformed and the distribution in 2004 of infected and diagnosed individuals was logit-transformed to ensure it corresponded to a distribution and summed to 100%. The prior law distributions were:  $\log(\beta) \sim U[0.003; 0.3]$ ;  $\log(\phi_{Link}) \sim U[0.1; 15]$  where  $U[a; b]$  is a uniform law on  $[a; b]$ . The prior law distributions of DCL, DCNL, T, and Non-SVR were uniform distributions (renormalized so that the distribution in the model summed to 100% with respective means of 14%, 8.8%, 2.1% and 4.5% for the afore-mentioned states).

**Table S2** - parameters for ABC implementation

Parameter	Value	References
Distribution in 2004 in the IBM		
S	3%	ANRS-Coquelicot
S'	43%	
NDC	16.7%	
% Men (current PWID)	80.7%	
Duration of treatment (bithérapie)	36 weeks	(16)
%SVR bithérapie (naïve, all genotypes)	58%	(5)
Former PWID mortality (Men -Women)	11.3 - 9.6/1000 PY	(20, 21)

IBM: Individual-based model  
PWID: People who inject drugs  
SVR: sustained virological response  
PY: person-year



## Results

We found the following results (with 95% confidence intervals), depending on the average number of injecting partners:

**Table S3** Infection rate per partner  $\beta'$  and time to linkage to care estimates by Approximate Bayesian Computation, according to the average number of injecting partners (with 95% confidence intervals)

Average number of injecting partners	Infection rate per partner $\beta'$ ( $y^{-1}$ )	Time to linkage to care $1/\phi_{Link}$ (y)
3	0.019 (0.004-0.045)	2.6 (2.3-2.9)
6	0.01 (0.003-0.02)	2.6 (2.3-2.9)
15	0.004 (0.002-0.008)	2.6 (2.3-2.9)

### S3: ESTIMATING THE TIME BEFORE DIAGNOSIS BY MAXIMUM LIKELIHOOD FROM THE DATA OF THE ANRS COQUELICOT STUDY

We wanted to estimate the test rate  $\delta$  using the data available in the Coquelicot study. PWID undergo test until they are diagnosed with HCV. We assume that to each PWID without HCV diagnosis is associated a Poisson process of rate  $\delta$ , that is to say that intervals between successive tests follow exponential distribution with parameter  $\delta$ .

Let's assume that we observed  $n$  PWID without HCV diagnosis, i.e. people non-infected or unaware of their infection.

For each PWID  $i$ , we observed :

- $T$  the delay between the beginning of his/her injecting career (i.e. the first injection) and the time of the Coquelicot study
- $C$  indicator of the presence of a HCV test before the survey
- $S$  the time of the last test done before the survey

We denote by  $(t_i, c_i, s_i)_{1 \leq i \leq n}$  the observations of  $(T, C, S)$  for the  $n$  PWID, and  $N_c = \sum_{1 \leq i \leq n} c_i$  the number of PWID in the survey with a previous HCV test.

We define the likelihood of  $\delta, (c_i, s_i)_{1 \leq i \leq n}$  conditionnally to the  $(t_i)_{1 \leq i \leq n}$  as

$$L(\delta, (c_i, s_i)_{1 \leq i \leq n} | (t_i)_{1 \leq i \leq n}) \propto \prod_{i|c_i=0} P(N(t_i) = 0 | T = t_i) \prod_{i|c_i=1} f_{t_i}(s_i) P(C = 1 | T = t_i)$$

With  $N(t_i)$  be the number of tests done on the interval  $[0, t_i]$  for the individual  $i$ , and  $f_{t_i}$  the density of  $S$  knowing that and  $T = t_i$  and  $C = 1$

Proposition: The maximum-likelihood estimator of  $\delta$  is

$$\hat{\delta} = \frac{N_c}{\sum_{i|c_i=0} t_i + \sum_{i|c_i=1} s_i}$$

Proof:  $N(t)$  follows a Poisson distribution of parameter  $\delta t$ .

We have:

- 1)  $P(N(t) = 0 | T = t) = e^{-\delta t}$
- 2)  $P(C = 1 | T = t) = 1 - P(N(t) = 0) = 1 - e^{-\delta t}$
- 3) Knowing  $T = t$  and  $C = 1$ , the survival function of  $S$  is,  $\forall s < t$

$$P(S > s|T = t, C = 1) = \sum_{k>0} P(X_k < t - s|T = t, N(t) = k)P(N(t) = k|T = t, N(t) \geq 1)$$

With  $X_k$  the elapsed time between the first injection and the  $k^{\text{th}}$  test of the PWID. Knowing that he/she had had  $k$  tests, the tests repartition on  $[0, t]$  follows a uniform distribution on the injecting period, as the PWID are tested following a Poisson process. Thus, if for  $1 \leq l \leq k$ ,  $U_l$  follows an uniform distribution on  $[0, t]$  we have :

$$P(X_l < t - s|T = t, N(t) = k) = P\left(\max_{1 \leq l \leq k} U_l < t - s\right) = \prod_{1 \leq l \leq k} P(U_l < t - s) = \left(\frac{t - s}{t}\right)^k$$

Moreover,

$$P(N(t) = k|T = t, N(t) \geq 1) = \frac{P(N(t) = k|T = t)}{P(N(t) \geq 1|T = t)} = \frac{e^{-\delta t} (\delta t)^k}{k! (1 - e^{-\delta t})}$$

Thus,

$$\begin{aligned} P(S > s|T = t, C = 1) &= \sum_{k>0} \left(\frac{t - s}{t}\right)^k \frac{e^{-\delta t} (\delta t)^k}{k! (1 - e^{-\delta t})} \\ &= \frac{e^{-\delta t}}{(1 - e^{-\delta t})} \sum_{k>0} \frac{\delta^k (t - s)^k}{k!} = \frac{e^{\delta(t-s)} - 1}{e^{\delta t} - 1} \end{aligned}$$

Then,

$$P(S > s|T = t, C = 1) = \frac{e^{-\delta s} - e^{-\delta t}}{1 - e^{-\delta t}}$$

Therefore,  $\forall s < t_i$

$$f_t(s) = \frac{e^{-\delta s}}{1 - e^{-\delta t}}$$

And the likelihood for a sampling:

$$L(\delta, (c_i, s_i)_{1 \leq i \leq n} | (t_i)_{1 \leq i \leq n}) \propto \prod_{i|c_i=0} e^{-\delta t_i} \prod_{i|c_i=1} \delta e^{-\delta s_i} = \lambda^{N_c} e^{-\delta(\sum_{i|c_i=0} t_i + \sum_{i|c_i=1} s_i)}$$

Therefore,

$$\ln(L(\delta, (c_i, s_i)_{1 \leq i \leq n} | (t_i)_{1 \leq i \leq n})) = N_c \ln(\delta) - \delta \left( \sum_{i|c_i=0} t_i + \sum_{i|c_i=1} s_i \right) + A$$

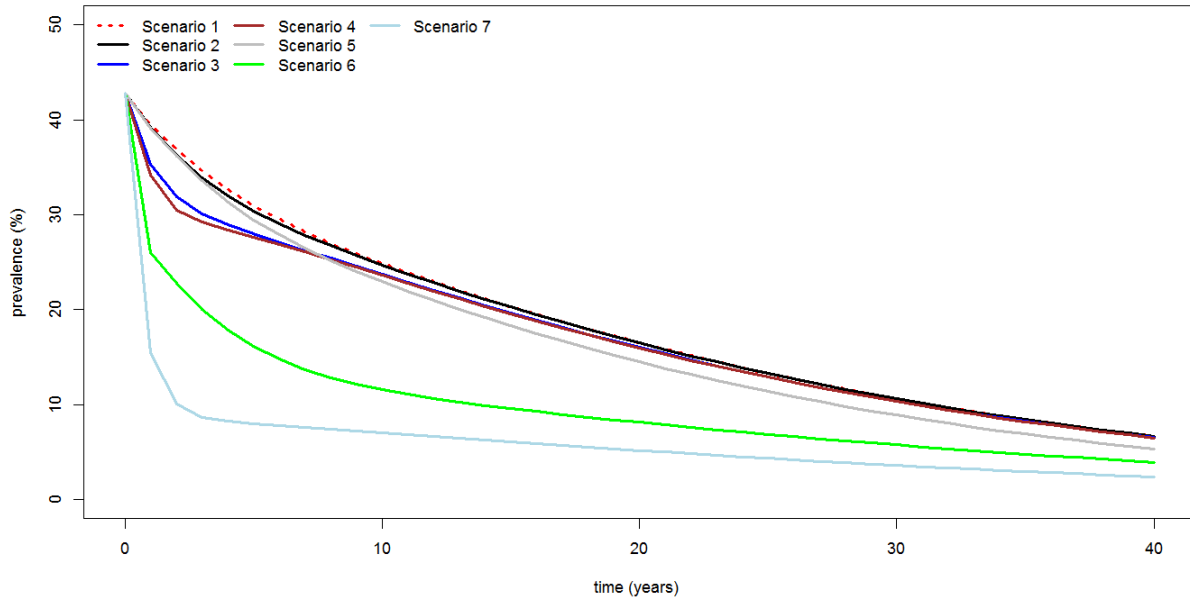
Where  $A$  is a constant. It follows that the maximum-likelihood estimator of  $\delta$  be that proposed above.

## **Results**

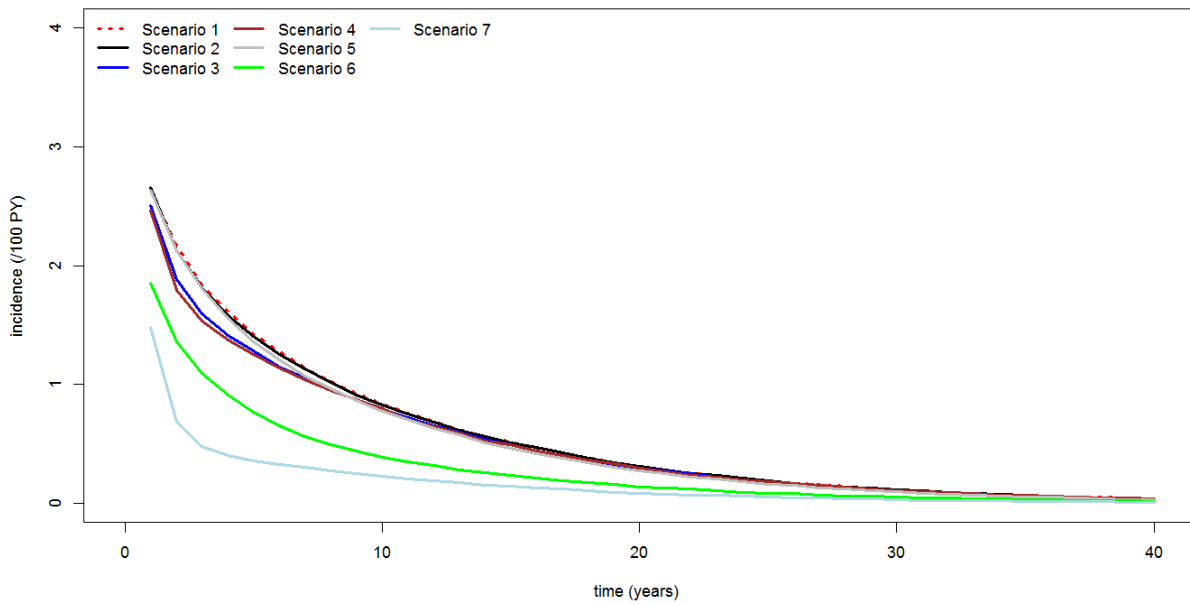
Using the data of the ANRS Coquelicot survey, we found an estimate of  $0.80 \text{ years}^{-1}$  for active PWID and  $0.69 \text{ years}^{-1}$  for inactive PWID (PWID after cessation of drug use), corresponding to an average duration of 1.25 and 1.45 years before diagnosis.

### S4: EVOLUTION OF THE PREVALENCE, INCIDENCE, AND THE NUMBER OF CIRRHOSIS COMPLICATIONS OVER THE FIRST 40 YEARS

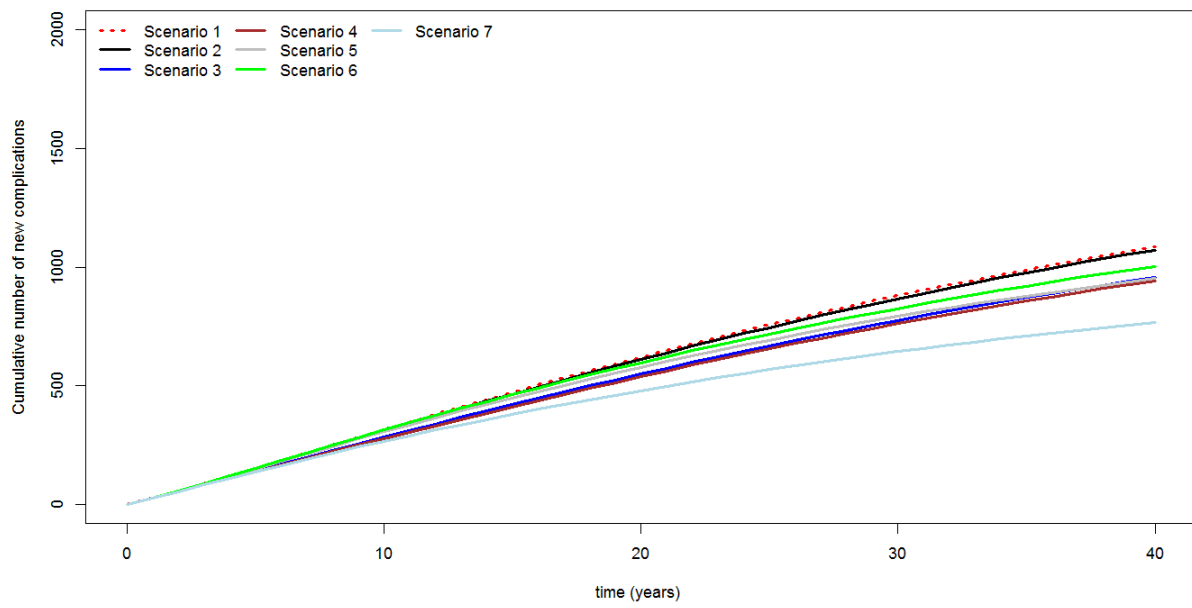
A.



B.



C.



**Figure S1** evolution of A) the prevalence of HCV in the population, B) the incidence of HCV infection and C) the number of new cirrhosis complications over the first 40 years.

## S5: SENSITIVITY ANALYSES

We present the results of some sensitivity analyses. First, the parameters' values used in the deterministic sensitivity analysis are summarized in Table S3. The results are represented in a tornado diagram (Figure S2), giving the most sensitive parameters according to each outcome. Briefly, the prevalence at 10 years is mainly sensitive to the infection rate per partner and the parameters determining the access to treatment (transition rate from F0/F1 to F2/F3, linkage to care and loss to follow-up rates). The incidence at 10 years is mainly impacted by parameters related to the infection risk: infection rate, average time before cessation of drug use, relative risk of infection during the first year. The cumulative number of cirrhosis complication over 10 years is mainly impacted by the transition rate to cirrhosis, the initial fibrosis distribution and the linkage to care and loss to follow-up rates; meanwhile over 40 years, the average time to diagnosis has also an impact on it.

Table S4 gives the results for settings with an average of 3, 6 (base case), and 15 injecting partners. The results show similar incidence and prevalence at 10 years, and number of new complications in the population at 40 years.

Figures S3 and S4 presents the results when we increased  $\beta$  to 5 and 10 times the base case. Base case analysis results also presented for comparison. These three settings correspond respectively to a stable, increasing and decreasing prevalence at 10 years in the reference scenario. The conclusion of the base case remains valid in these other two settings. The clinical benefits are even better in setting with higher infection rates.

**Table S3** Description of the sensitivity analysis

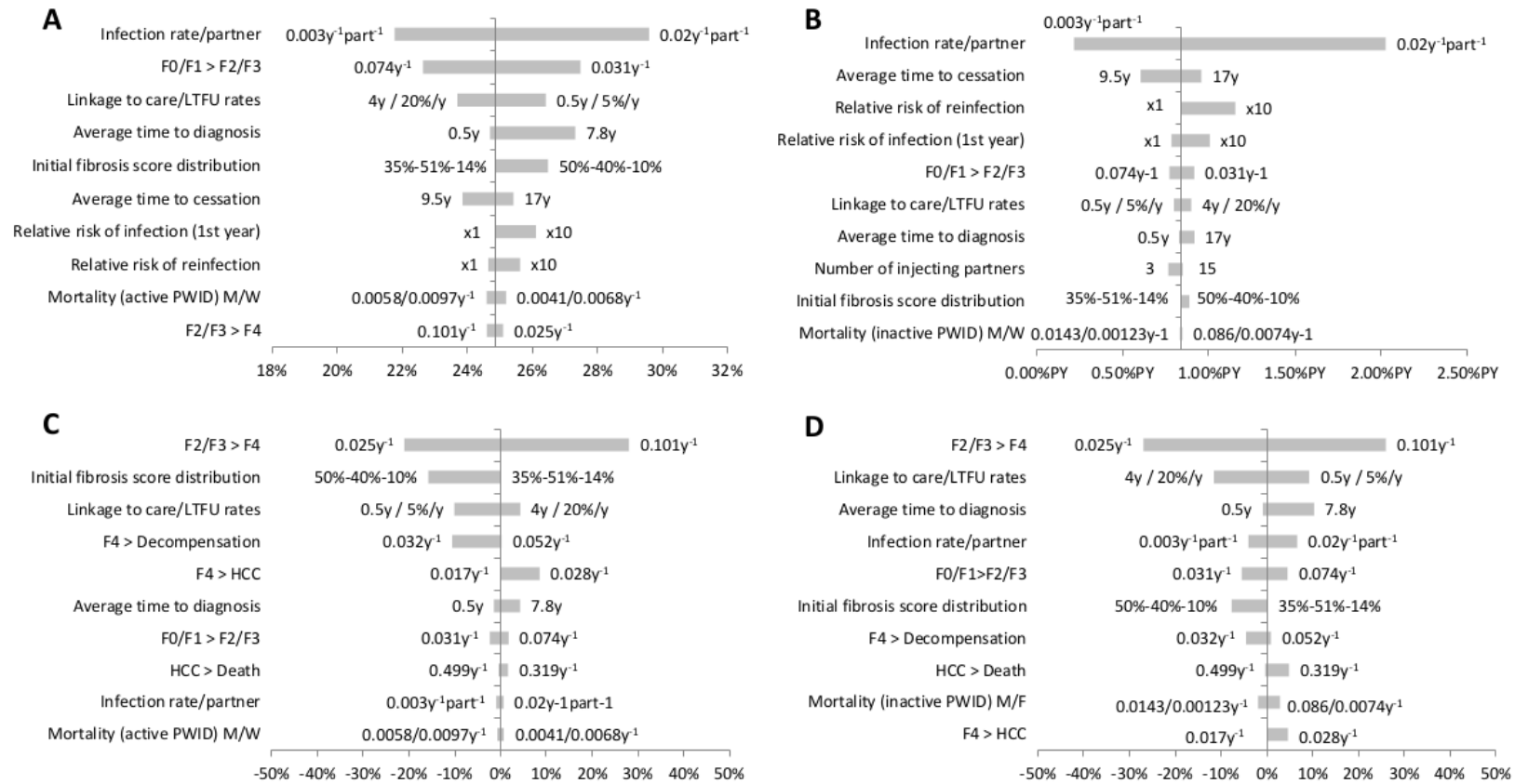
Parameters	Base case value	Sensitivity analysis	References
Initial distribution in the natural history model			
$F0/F1$	35%	50%	} Assumption
$F2/F3$	51%	40%	
$F4$	14%	10%	
Number of injecting partners/PWID ( $\bar{d}$ )	6	3 – 15	Assumption
Infection rate in S' per infected injecting partner ( $\beta'$ )	0.01 y <sup>-1</sup> partner <sup>-1</sup>	0.003 – 0.02	See Supplementary Information S2
Relative risk of infection in S ( $\beta/\beta'$ )	3	1 – 10	Assumption

Relative risk of reinfection after SVR per infected partner	1	1-10	Assumption
Time between chronic infection and diagnosis (current PWID/former PWID) ( $1/\delta$ )	1.25/1.45 years	0.5 – 7.8	Scenario 2 -Value in UK (32)
Average time before linkage to care ( $1/\phi_{Link}$ )/ Loss to follow-up rate ( $\phi_{Lost}$ )	2.6 y / 14%/year	0.5 - 4 / 5 – 20	Scenario 3 – Assumption
Current PWID mortality (Men/Women) ( $\mu$ )	0.0077 $y^{-1}$ / 0.0054 $y^{-1}$	0.0058 - 0.0097 / 0.0041 - 0.0068	Assumption
Former PWID mortality (Men/Women) ( $\mu$ )	0.0114 $y^{-1}$ / 0.0098 $y^{-1}$	0.0086 - 0.0143 / 0.0074 - 0.0123	Assumption
Average duration of injecting career ( $1/\theta$ )	13.9 years	9.5 – 17	(17, 18)
Transition rate F0/F1 → F2/F3 ( $\lambda_{2/3}$ )	0.052 $y^{-1}$	0.031 - 0.074	} (22)
Transition rate F2/F3 → F4 ( $\lambda_4$ )	0.054 $y^{-1}$	0.025 – 0.101	
Transition rate F4 → Decompensated cirrhosis ( $\lambda_{Decomp}$ )	0.04 $y^{-1}$	0.032 – 0.052	} (23, 24)
Transition rate F4 → HCC ( $\lambda_{HCC}$ )	0.021 $y^{-1}$	0.017 – 0.028	
Transition rate Decompensated cirrhosis → Death related to HCV ( $\lambda_{Decomp-M}$ )	0.306 $y^{-1}$	0.129 – 0.395	
Transition rate HCC → Death related to HCV ( $\lambda_{HCC-M}$ )	0.433 $y^{-1}$	0.319 – 0.499	
Transition rate Decompensated cirrhosis → HCC ( $\lambda_{Decomp-HCC}$ )	0.021 $y^{-1}$	0.017 – 0.028	

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PWID: People who inject drugs  
 $y^{-1}$ : per year  
 HCC: Hepatocellular carcinoma  
 HCV: Hepatitis C virus  
 SVR: Sustained Virological Response





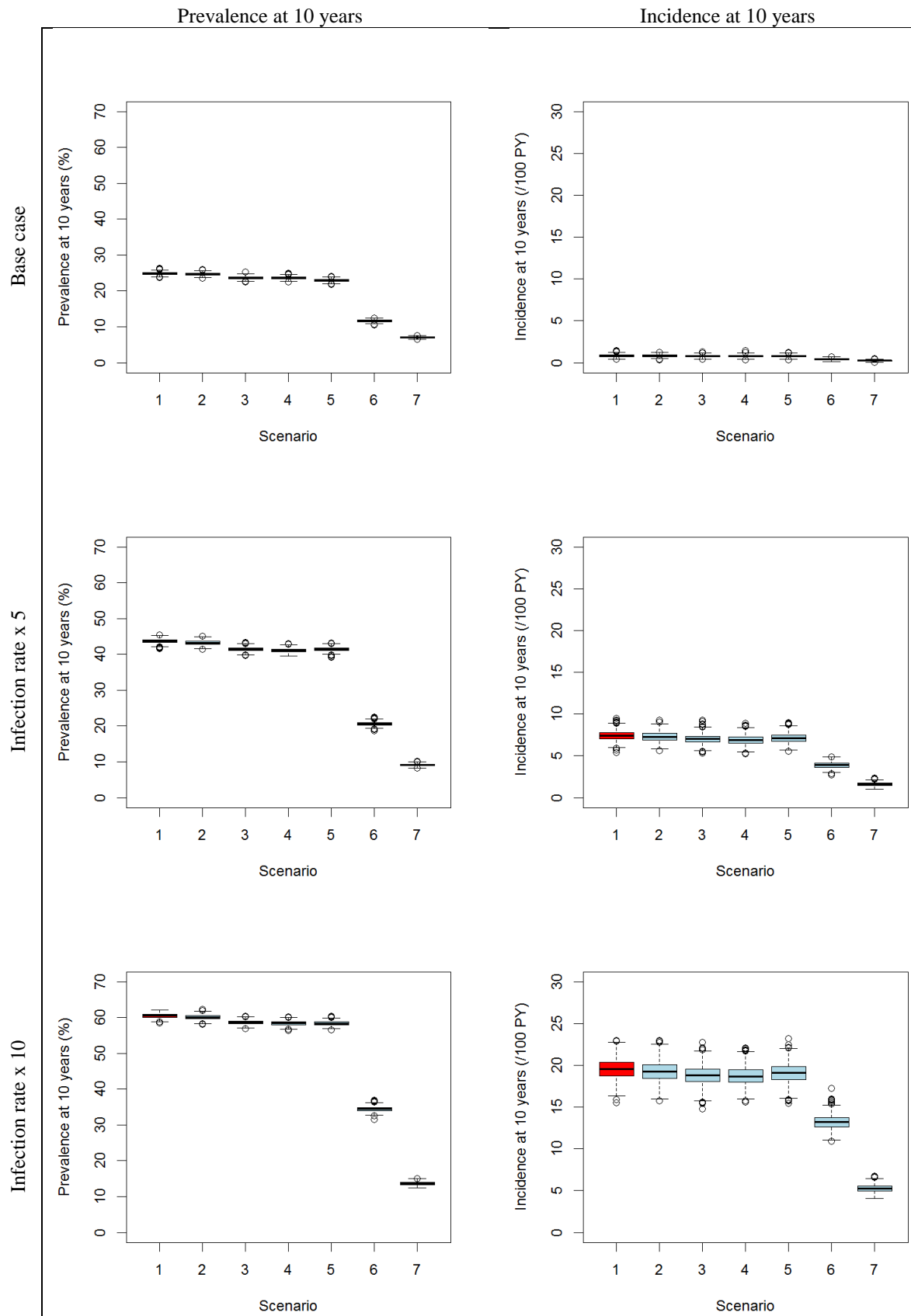
**Figure S2** Tornado diagrams for the sensitivity analysis of A. prevalence at 10 years; B. incidence at 10 years; C. cirrhosis complications avoided over 10 years; D. change in the number of cirrhosis complications occurring over 40 years. The diagrams represent the change in the outcomes for each parameter varied. Parameters are sorted according to the magnitude of variation of the outcome. Only the 10 most sensitive parameters were plotted. The values on the graph indicate the parameters' values used.

**Table S4** Results per scenario for an average number of 3, 6 and 15 injecting partners.

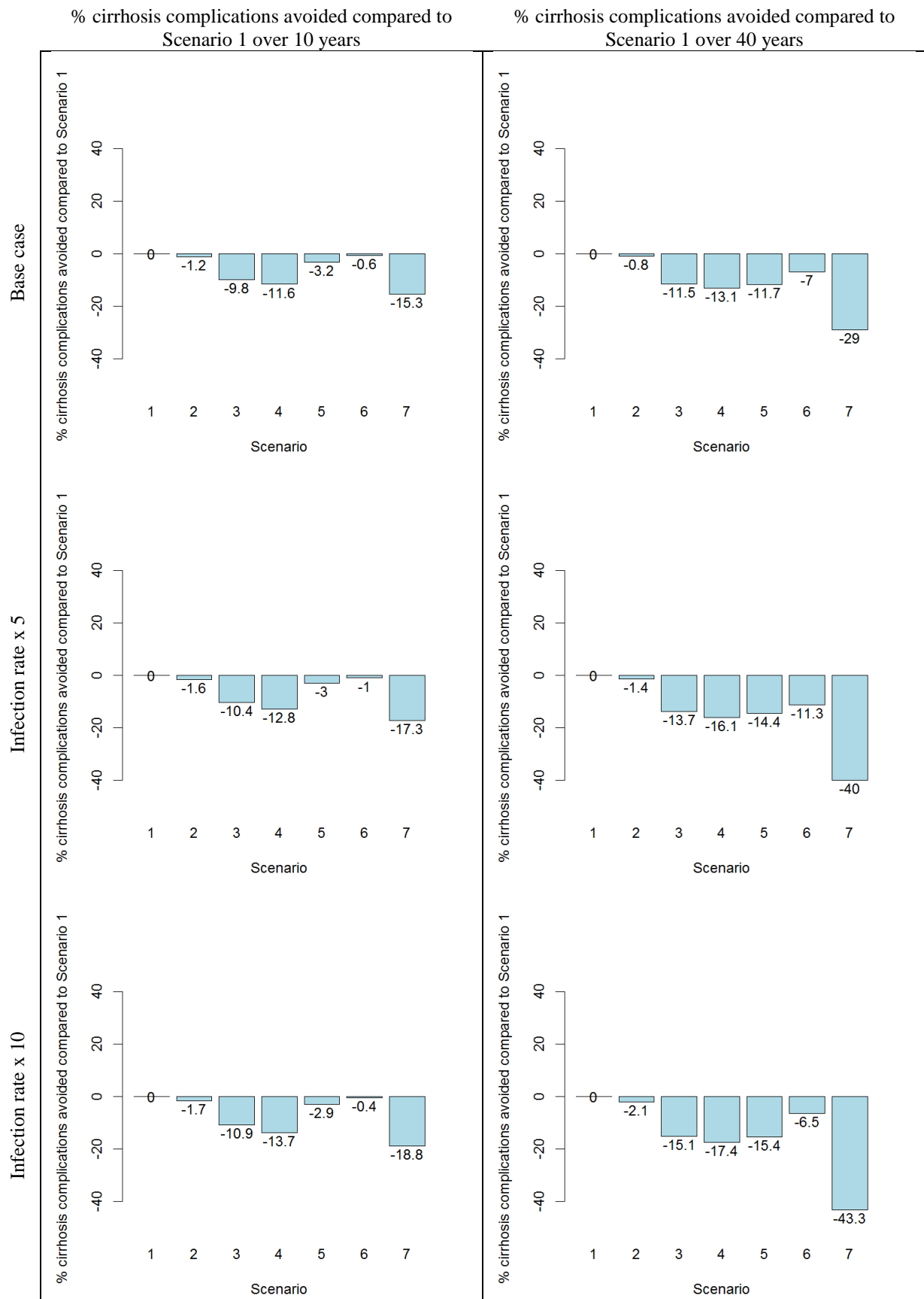
Scenario	Average number of injecting partners	Prevalence at 10 years (%)	Incidence at 10 years (/100 PY)	% cirrhosis complications avoided compared to Scenario 1 over 10 years	% cirrhosis complications avoided compared to Scenario 1 over 40 years
		mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)
<b>Scenario 1</b>	3	<b>24.6 (24.5;24.7)</b>	<b>0.77 (0.74;0.79)</b>	/	/
	6	<b>24.9 (24.8;24.9)</b>	<b>0.84 (0.81;0.87)</b>	/	/
	15	<b>24.9 (24.9;25)</b>	<b>0.85 (0.82;0.88)</b>	/	/
Scenario 2	3	24.4 (24.3;24.5)	0.75 (0.73;0.78)	-1.2 (-2.6;0.3)	-0.9 (-2.7;0.9)
	6	24.7 (24.6;24.8)	0.83 (0.8;0.86)	-1.2 (-2.6;0.2)	-0.8 (-2.6;0.9)
	15	24.8 (24.7;24.8)	0.86 (0.83;0.89)	-1.2 (-2.6;0.1)	-1.7 (-3.4;0.1)
Scenario 3	3	23.4 (23.4;23.5)	0.72 (0.69;0.74)	-9.6 (-10.9;-8.2)	-11.5 (-13.1;-10)
	6	23.7 (23.6;23.8)	0.8 (0.77;0.83)	-9.8 (-11.1;-8.5)	-11.5 (-13.1;-10)
	15	23.8 (23.7;23.8)	0.81 (0.79;0.84)	-9.6 (-10.9;-8.3)	-11.9 (-13.4;-10.3)
Scenario 4	3	23.3 (23.2;23.4)	0.72 (0.69;0.74)	-11.7 (-13;-10.4)	-13.1 (-14.6;-11.6)
	6	23.6 (23.5;23.7)	0.78 (0.76;0.81)	-11.6 (-12.9;-10.3)	-13.1 (-14.6;-11.6)
	15	23.7 (23.6;23.7)	0.81 (0.78;0.84)	-11.6 (-12.9;-10.4)	-13.2 (-14.7;-11.6)
Scenario 5	3	22.7 (22.6;22.7)	0.71 (0.69;0.74)	-2.9 (-4.2;-1.5)	-12.2 (-13.8;-10.7)
	6	22.9 (22.9;23)	0.78 (0.75;0.81)	-3.2 (-4.6;-1.8)	-11.7 (-13.3;-10)
	15	23 (22.9;23.1)	0.79 (0.77;0.82)	-3.1 (-4.4;-1.7)	-12.4 (-14;-10.9)
Scenario 6	3	11.5 (11.5;11.6)	0.36 (0.34;0.38)	-0.2 (-1.6;1.3)	-7.5 (-9;-5.9)
	6	11.6 (11.6;11.7)	0.39 (0.37;0.41)	-0.6 (-2;0.9)	-7 (-8.6;-5.4)
	15	11.6 (11.6;11.7)	0.4 (0.38;0.42)	-0.5 (-1.9;1)	-7.4 (-9;-5.8)
Scenario 7	3	7 (7;7.1)	0.21 (0.2;0.23)	-15.1 (-16.4;-13.7)	-29 (-30.1;-27.8)
	6	7 (7;7.1)	0.23 (0.22;0.25)	-15.3 (-16.6;-14)	-29 (-30.1;-27.9)
	15	7 (7;7.1)	0.23 (0.22;0.25)	-15.3 (-16.6;-14.1)	-29.6 (-30.7;-28.4)

CI: Confidence interval

PY: person-year



**Figure S3** Boxplots of the prevalence and incidence at 10 years according to the scenario in three settings: base case rate, infection rate/infected partners x 5 and infection rate/infected partners x 10



**Figure S4** Average percentage of cirrhosis complications avoided over 10 and 40 years according to the scenario in three settings: base case, infection rate/infected partners x 5 and infection rate/infected partners x 10

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