Effectiveness and cost-effectiveness of interventions targeting harm reduction and chronic hepatitis C cascade of care in people who inject drugs; the case of France

Running title: Modelling hepatitis C among PWID in France

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ABSTRACT

Background: Direct-acting antivirals (DAAs) represent an opportunity to decrease HCV morbidity/mortality and transmission among people who inject drugs (PWID). Improvement in current harm reduction (needle and syringe programs, opioid substitution therapies) is still possible.

Objective: To estimate the effectiveness and cost-effectiveness of interventions targeting harm reduction and chronic hepatitis C (CHC) care cascade among PWID in France.

Design: Dynamic model of HCV transmission and CHC natural history.

Data Sources: Published literature.

Target Population: PWID active in Paris area in 2015 (mean age=36).

Time Horizon: Lifetime.

Interventions: Improved harm reduction interventions, faster diagnosis/linkage to care, earlier treatment initiation, combined scenarios.

Perspective: Societal.

Outcome Measures: Life-expectancy in discounted quality-adjusted life-years (QALYs); direct lifetime discounted costs; incremental cost-effectiveness ratio (ICER), number of infections/reinfections.

Results of Base-Case Analysis: Under the current practice scenario, life expectancy was 15.847 QALYs, for a mean lifetime cost of €24,058. Improved testing/linkage to care increased life expectancy to 16.085 QALYs, and was cost-effective (ICER=€6,900/QALY gained). These improvements and a treatment initiation at F0 fibrosis stage, increased life expectancy to 16.696 QALYs and was cost-effective (ICER=€8,400/QALY). Combining these interventions with harm reduction improvement was the most effective scenario, with a life expectancy of 16.704 QALYs (ICER= €76,400/QALY). It decreased by 37% new infections vs. current practice.

Results of Sensitivity Analysis: Results were sensitive to treatment cost and HCV incidence.

Limitations: Not all input data were from France. Harm reduction health benefits on other health issues in PWID were not assessed.

Conclusions: Improvements in HCV care cascade is critical to enhance DAAs individual and societal benefits in PWIDs. Combined with early treatment initiation and improvements in harm reduction, it would decrease future infections by a third.
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INTRODUCTION

Chronic hepatitis C is a viral disease responsible for over 500,000 deaths/year worldwide (1). Among people who inject drugs (PWID), hepatitis C virus (HCV) transmission risk is high, due to injecting equipment sharing (2). This, combined with other health issues related to injection practices, (HIV infection, bacterial and fungal infections, and overdoses), has led to the introduction of harm reduction interventions in many countries. In France, these interventions are mainly based on opioid substitution therapies (OST) using methadone or buprenorphine, and on providing access to sterile injection equipment in needles and syringes provision (NSP) programs. However, HCV seroprevalence in this population remains around 70% (3). Although 85% of active PWID report having been on OST during the last six months (ANRS-Coquelicot study (4), unpublished data) improvements are probably still needed in harm reduction area. Up to 33% of PWID report difficulties to access to sterile syringes (3). Moreover, PWID do not fall into NSP and OST programs right from the beginning of their drug-injecting habit.

Recently, with the availability of new direct-acting antiviral (DAA) regimens, a new approach has emerged to decrease the transmission of HCV. These new therapies are better tolerated and more effective than the previous treatments, with sustained virological response (SVR) rates of around 95% in clinical trials (5-14). Thus, HCV elimination using treatment as prevention (TasP) is now widely considered as an option. This means providing early treatment to PWID who have become infected, in order to prevent HCV transmission. A previous modeling study in a PWID population in France showed that low HCV prevalence rates (<10%) could be achieved through a TasP strategy including improvements in testing, linkage to care, and adherence to treatment, and a treatment initiation at F0/F1 fibrosis scores (15). Harm reduction strategies were, however, not considered in that analysis. Meanwhile, the cost of the new therapies (> €46,000 for a 12-week treatment in France) raises the question of the economic impact and feasibility of this strategy.

In this study, we use a dynamic individual-based model of HCV transmission in PWID to assess the effectiveness and cost-effectiveness of interventions designed to improve both harm reduction and the cascade of HCV care in PWID in France, in the context of the new DAAs.

METHODS

Model

We simulated HCV transmission, cascade of care, and health outcomes in a population of initially active (at the beginning of the study, they had injected in the last month) PWID in France, using an updated version of our previous dynamic model (15). In this model, each PWID has a HCV status: susceptible or infected. Each infected individual has a status in the cascade of care according to diagnosis, linkage to care and treatment (Figure 1.B.). The infection rate depends on the number of infectious injecting partners among the injectors, which is modeled using a random graph (supplementary material S1). The network of PWID is modeled with a household structure, i.e. small groups of strongly connected PWID in the population, which can themselves be connected together. The liver disease's progression related to chronic hepatitis was modeled taking into account fibrosis progression from F0 to F4, cirrhosis complications (decompensation and hepatocellular carcinoma(HCC)), and death related to HCV infection (Figure 1.C.). Compared to our previous model, we added hepatic transplants for HCV complications, which are associated with high costs (16). Finally, we added states describing the status of each PWID according to harm reduction, NSP and OST (Figure 1.A.). In this model, PWID start in a state of "difficult access to injecting equipment", corresponding to the period before they enter a NSP program. Individuals then progress to the 'NSP' state. After entering 'NSP', they can begin an OST and progress to the state of 'NSP+OST'. PWID can stop their OST and return to the 'NSP' state in the model.

Input Parameters

The key parameters of the model are presented in Table 1. The initial incidence of HCV in this PWID population was estimated at 12/100 person-years (p.y.) (17)., The infection rate/infected partner was adjusted to obtain this incidence during the first year using Approximate Bayesian Computation (18, 19). The average duration between first injection and recruitment in an NSP program was not available in literature. We assumed an average duration of two years between the PWID individual's first

injection and their entry into an NSP program. The high proportion of active PWID currently using OST, and experts' opinions suggesting OST is initiated quickly when on OST, led us to assume a short duration before individuals would accede to the 'NSP+OST' state (one year). About 37% of PWID individuals on OST remain under treatment for 10 months: year (20), corresponding, according to the survival function of the exponential distribution, to 2.32 years on average before cessation of OST. In addition, this data, and the high proportion of PWID on OST, suggest that the cessation of OST occurs for short periods: we assumed OST re-initiation after three months. Relative risks of HCV infection acquisition in each state were estimated in a meta-analysis (21). The transition parameters and the initial distribution in the HCV cascade of care were mainly derived from ANRS-Coquelicot study data, an HCV-seroprevalence cross-sectional survey conducted among drug users in France (4, 15).

Input parameters for the social-network model were estimated by Approximate Bayesian Computation, using data for a population of PWID in Melbourne, Australia, (22) due to the absence of local data in France (supplementary information S1). Based on these parameters, we simulated networks of a size equivalent to the PWID population in the Paris area (10,000 PWID) (15).

Cost & utilities

We derived the structural costs associated with harm reduction interventions from the budgets of French harm reduction facilities and treatment centers for PWID (23, 24). These included reception and harm reduction support centers for drug users (CAARUD), and medical centers for drug and alcohol dependence (CSAPA). To the latter, we added in the cost of opioid substitution therapies and needles (20, 23-25). Costs associated with HCV testing were included for susceptible PWID. For PWID in our model who had been both diagnosed and linked to care, costs associated with HCV were obtained from a study on healthcare consumption in chronic hepatitis C in France (16) (Table 2). Finally, the cost of the new DAAs was set at €46,000 (26).

We used health utilities estimated from a cross-sectional study HCV-infected individuals in France , but who were not necessarily drug users (27, 28).

The detailed costs and utilities included in the model are presented in supplementary material.

Strategies

In the main analysis, we simulated 6 interventions, each representing a scenario corresponding to different improvements in harm reduction interventions, in the chronic hepatitis C cascade of care, and in treatment-initiation criteria. Table 3 presents the detailed scenarios.

Outcomes

We simulated populations of 10,480 PWID, each divided into 20 clusters of 524 individuals, which is the estimated size of the PWID community for the Australian study (29). The outcomes were estimated for the initial cohort of PWID. PWID entering the population during simulations (incident PWID) were not taken into account. We performed 500 simulations for each scenario. For each simulation the average lifetime costs, life expectancy in life years (LYs), and life expectancy in quality-adjusted life years (QALYs) were estimated. We applied to these outcomes an annual discount rate of 4% for individuals younger than 30, which was linearly decreased to 2% between 30 and 50 years of age, and set at 2% after 50, as per French guidelines for cost-effectiveness analysis (30). The incremental cost-effectiveness ratio (ICER) was estimated in euros/QALY. According to World Health Organization guidelines (31), a scenario was considered as very cost-effective if the ICER was below French GDP/capita (around €30,000 (32)), and as cost-effective if the ICER was below three times the French GDP/capita. For each scenario, we also estimated the mean number of infections in the population, the mean number of reinfections after an SVR, and the ICER in euros/LY. Costs were in 2015 euros.

Sensitivity analysis

We performed sensitivity analyses for some key parameters, using values from other settings. We changed the initial HCV incidence from 12/100p.y. in the main analysis: first to 22/100p.y. (Montréal, Canada (33, 34), and then to 42/100p.y. (London, United-Kingdom (35)). Moreover, we changed the mean value for time to diagnosis from 1.25/1.45 years: first to 2.0 years (Montréal, Canada (33, 34), and then to 7.8 years (London, United-Kingdom (36)). Furthermore, we changed the rate of loss to follow-up from 14% /year, to assumptions: firstly of 20%/ year, and, then, of 30%/year. Due to the

uncertainty about harm reduction parameters, we also performed a sensitivity analysis by changing the transition rates to a worst-case scenario. We changed the transition time from "difficult access to injecting equipment" to "NSP" from two years to three years, and the transition time from NSP to NSP+OST from one year to two years. Furthermore, we set initial distribution at NSP=40%, vs. 30% in the main analysis, and at NSP+OST=45%, vs. 50% in the main analysis. We estimated the impact of a decreased risk of reinfection after an SVR, by dividing the risk of infection for PWID by three (37, 38). The risk of reinfection was equal to the level of infection in the main analysis. We assessed the impact of utilities on the analyses by using utilities estimated from an HCV-infected German population with dual therapy (39, 40)(Table S17). We also estimated the impact of a 25%, 50% and 75% decrease in the treatment cost.

Role of the Funding Source

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RESULTS

Main analysis

Results of the main analysis are presented Table 4. Figure 2 shows the efficiency curve, while Figure S5 (supplementary material S2) illustrates the evolution of the number of newly infected people in the population. We sorted results on a scale of increasing costs. S1 (the current practice) was the least expensive scenario, with an average lifetime cost/person of €24,058 (standard deviation (SD)=187). In this scenario, the adjusted average life expectancy of each person was 15.847 (SD=0.057) QALYs. For the overall cohort of 10,480 people, the total number of HCV infections was estimated at 3,465 (SD=83), among which there were 999 (SD=41) reinfections following a previous SVR. An improvement in harm reduction interventions in S2 led to a moderate increase in adjusted life expectancy, which was estimated at 15.865 (SD=0.054) QALYs. However, this scenario yielded a higher incremental cost-effectiveness ratio than the strategy of improving testing and linkage to care (S4), which is a more effective strategy and corresponds to extended dominance. Meanwhile, S4 increased the adjusted average life expectancy to 16.085 (SD=0.060) QALYs, and was also very cost-effective (€6,900/QALY). In S3, we initiated treatment from F0 instead of F2. The adjusted average life expectancy increased to 16.377 (SD=0.061) QALYs. However, we observed an extended dominance on the part of S5, in which we combined the improvements made in strategy S4 with a treatment initiation at F0, instead of from F2 in the current-practice scenario. S5 led to an adjusted life expectancy of 16.696 QALYs (SD=0.055), and decreased the number of new infections in the population to 2,178 (SD=99) for a lifetime cost of €30,834 (SD=325). This scenario was also very cost-effective, with an ICER of €8,400/QALY.

Finally, the S6 scenario, in which we combined improvements in harm reduction interventions, testing, and linkage to care, with a treatment initiation from F0, led to an increase of the adjusted life-expectancy efficacy (+0.009 QALYs) for an ICER of €76,400/QALYs. This scenario was also the one that yielded the lowest number of infections, which fell to 978 (60).

When we considered the incremental cost-effectiveness/life years saved, rather than QALY saved, we found S4 (improved cascade of care) to be the most cost-effective strategy (=0.238LY saved compared

with the current practice). S6 was the most effective scenario, but it was associated with a high cost-effectiveness ratio compared with S5 (€319,800/LY; >3 times France's GDP/capita).

Sensitivity analysis

The complete results of the sensitivity analysis are given in the supplementary material S3. We only mention here the most notable results.

In summary, S4, where we improved testing and linkage to care, became more cost-effective when we decreased the cost of treatment (Tables S5 to S7). When we applied a 75% decrease in the treatment cost (€11,500 vs. €46,000, Table S7) to our scenarios, S4 became the least expensive scenario, with a lifetime cost of €22,180 (SD=191) vs. €22,874 (SD=187) in S1. The most effective scenario, S6, which is S3 plus treatment from F0 and an improvement in harm reduction measures, remained cost-effective: ICER= €76,600.

When we increased the initial incidence in our scenarios from 12/100 p.y. to the values estimated in studies for Montréal (22/100 p.y.) and London (42/100 p.y.), strategies where the treatment is initiated from F0 (S3, S5 and S6) became costlier (see Figure 2 and Tables S8 to S9). S6, which combined improvements in harm reduction interventions and in the cascade of care with treatment as of F0 remained the most effective, and continued to be cost-effective.

When we changed the transition rate in the harm reduction model, and the initial distribution of the population in harm reduction measures, to a worst case, we observed a higher impact of improvements in harm reduction-interventions (S2) on the number of HCV infections (7.7% of infections avoided compared with S1 vs. 4.2% in the main analysis). Still, the impact on the adjusted life expectancy remained similar (+0.030 QALYs compared with S1 vs. +0.018 QALYs in the main analysis). However, the scenario remains dominated by S4 (improvement in the HCV cascade of care).

DISCUSSION

In this study, we used a dynamic, individual-based model including a social network and a model of natural history of chronic hepatitis C to assess the cost-effectiveness of improvements in harm reduction measures and in the cascade of care of hepatitis C in the population of PWID in France. Several important points emerged from this analysis.

Firstly, an improvement in existing harm reduction interventions, either with faster access to NSP and OST (S2) alone, or combining this faster access with improvements in the cascade of care and treatment-initiation criteria (S6), only slightly increased the adjusted average life expectancy (+0.018 QALYs and +0.09 QALYs respectively) compared to similar scenarios that did not feature such improvements (S1 and S5). Secondly, improvements in testing and linkage to care (S4) increased the adjusted average life expectancy (16.085 QALYs vs. 15.847 in the current practice) and were very cost-effective. Thirdly, an improvement in testing and linkage to care, together with a treatment initiation from F0 vs. F2 in the current-practice scenario, considerably increased the lifetime cost, but was very effective and cost-effective (adjusted life expectancy=16.696 QALY; ICER=€8,400/QALY, vs. S4). Moreover, this strategy dramatically decreased the number of new infections in the population: around 2,000 over the lifetime of the initial population of the model vs. 3,500 in the current practice. Notably, a strategy that relied simply on initiating treatment at F0 instead of F2 (S3) had a higher incremental cost-effectiveness ratio than a strategy that, in addition, also improved testing and linkage to care.

In our main analysis, improving existing harm reduction interventions merely by delivering faster access to NSP and OST had a limited effectiveness. This was mainly due to the fact that access to OST is already high in France, with 85% of PWID reporting having been on OST during the last 6 months in ANRS-Coquelicot study (unpusblished data (4)). In addition, data we used for HCV epidemiology in PWID corresponded to people recruited in harm reduction facilities, treatment centers, and accommodation facilities for drug users. Individuals who do not attend such facilities, who are more marginalized and with a higher HCV risk, were not included. Both the effectiveness and the coverage

rate used for these interventions in our analysis may be optimistic. However, improving existing harm reduction interventions, along with an improvement in the HCV cascade of care, and an initiation of treatment as of F0 was cost-effective. Moreover, in sensitivity analysis, when we used a high initial HCV incidence rates, corresponding to estimates from PWID populations in London, the scenario combining an improvement in harm reduction, an improvement in the HCV cascade of care, and an initiation of treatment as of F0, resulted in cost savings when compared to a situation that only included an improvement in HCV cascade of care and an initiation treatment at F0. Thus, there is a threshold of initial incidence in the interval of realistic values, above which an improvement in harm reduction-interventions would be cost-saving compared with improvements in access to antiviral treatments alone.

This study illustrated the high effectiveness, and cost-effectiveness, of improving both testing and linkage to care. This strategy should, in the future, play a central role both in improving the life expectancies of those living with HCV, and in reducing HCV transmission. In a previous study (15), we showed that improving testing and linkage to care would have an impact on the occurrence of complications (11% of cirrhosis complications avoided after 40 years with an improvement in testing, and 13% with an improvement in linkage to care). This decrease in the number of complications explains the increase in life expectancy in the present study. Combining these improvements with a treatment initiation at F0 instead of F2 made it possible, in addition, to avoid many new infections in the population. A decrease in the number of new infections could only be reached through this combined scenario. When the only intervention is to initiate treatment right from F0 instead of from F2 (S5), the number of new infections remains almost equal to that of the current-practice scenario, due to the high number of reinfections.

In this analysis, we found that a strategy of treatment as prevention, combining improvements in all stages of the cascade of care with a treatment initiation from F0 (S5), was cost-effective, despite the high HCV treatment costs. However, the budgetary impact of such a strategy would be high. The additional cost was estimated at €6,776/PWID compared with the current situation, corresponding to

an additional overall cost of €71 million. A decrease in HCV treatment cost would, therefore, be an important factor in making it possible to implement a strategy of TasP.

Data in the literature are scarce on the impact of combined interventions for treating an HCV epidemic in PWID that include harm reduction interventions, improvements in the cascade of care, and antiviral treatment. Martin *et al.* have studied the impact, among PWID in London, of combined interventions including NSP, OST, and treatment delivery (41). They found that combining antiviral treatment with OST and a high-coverage NSP is necessary in order to halve HCV prevalence over 10 years. The combined impact of testing and linkage to care on an HCV epidemic has seldom been evaluated in the past. In our analysis, it was shown to be critical.

Our study presents several limitations. First, uncertainties persist around the parameters we used in the model, for example, for the current status of harm reduction interventions and their effectiveness, or for quality-of-life data for PWIDs. However, the impact of these uncertainties was evaluated in the sensitivity analysis. Second, in the absence of data about PWID social networks in France, we used Australian data (22). Despite the possibility of network structures in France being different, the use of these data allowed us to build a realistic network model, with a restriction of HCV-transmission possibilities to a small subgroup of injecting partners. Third, we did not take into consideration any health benefits from the harm reduction interventions deployed in our scenarios on other health issues in PWID, such as HIV infection prevention (42), drug related morbidities (43), or drug related crimes (44). Finally, we only assessed the impact of a scaling-up of interventions that are currently implemented, namely NSP and OST. Supervised injection facilities, implemented on an experimental basis in France, were not considered. In a meta-analysis, supervised injection facilities have been proven to significantly decrease the frequency of needle/syringe sharing, lending, or borrowing (45), and they have a favorable impact in encouraging people to begin OST and to stop injecting drugs (46).

In conclusion, in this model, improvements in NSP and OST interventions only had a limited impact on the HCV epidemic in France. This limited result was mostly related to the very high coverage of

OST in France, and was sensitive to the initial HCV incidence in the population. Improvement in testing and linkage to care was, in our analyses, the critical intervention for increasing PWID life expectancy in France, and it would be cost-effective. Together with an access to treatment regardless of the stage of HCV disease, it would significantly decrease new HCV infections. Decreasing the cost of the new antiviral drugs would facilitate the implementation of these strategies by decreasing their budgetary impact.

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Table 1 Key parameters for the model: initial population, infection, and care.

Parameter	Value	References
Population size	20×524*	
Initial distribution infection and care		
Susceptible	57.2%	ANRS-Coquelicot (4), unpublished data
Acute hepatitis	0%*	
Non-diagnosed chronic hepatitis	9.2%	ANRS-Coquelicot, unpublished data
Diagnosed, non-linked to care chronic hepatitis C	11.3%	
Diagnosed and linked to care chronic hepatitis C	16.0%	
Under treatment	2.2%	
Non-responders after treatment	4.1%	
Initial distribution related to harm reduction interventions		
None	30%*	Derived from (3, 47-49)
NSP	20%*	
NSP+OST	50%*	
Infection rate by injecting partner in S'	0.184 y^{-1}partner^{-1}	Fitted by ABC to have a 12/100 p-y baseline incidence (17) – median value from western countries in absence of data in France
Relative risk of infection when under		
NSP	0.5	(21)
NSP+OST	0.21	For a high-coverage needle program (i.e. where a sterile syringe is available for 100% of the injections of the user)
Transition from "no harm reduction intervention" to NSP	2y*	(3, 47-49)
Transition from NSP to NSP+OST		
First time	1y*	
Next times	0.25y*	
Transition from NSP+OST to NSP	2.3y*	
Average time from chronic infection to diagnosis		
Current PWID	1.25 y	Derived from ANRS Coquelicot data (4, 15)
Former PWID	1.45 y	
Average time before linkage to care	2.6 y	Derived from ANRS Coquelicot data (4, 15)
Loss to follow-up rate	14%/y	(50)
Treatment: incoming DAAs regimens		
Duration	12 weeks	(6-8, 11-14, 51)
SVR rate – treatment naïve – all genotypes- clinical trials	95%	
Ratio of the effectiveness in real life to the efficacy in clinical trials	0.903	Derived from (52)

* Hypothesis
IBM: Individual-based model
SVR: Sustained virological response
PWID: People who inject drugs
y^{-1}: per year
HCC: Hepatocellular carcinoma
DAA: Direct-acting antiviral

HCV: Hepatitis C virus

Table 2 Annual mean costs (SD) attributable to chronic hepatitis C: ambulatory costs (never treated and after HCV treatment failure) and hospitalization costs (no death and in-hospital death)(16)

Liver disease stage	**Ambulatory costs (€)**		**Hospitalization costs (€)**	
	Never treated	**After treatment failure**	**No death**	**In-hospital death**
F0/F1	70 (10)	53 (12)	278 (1,087)	337 (1,377)
F2/F3	128 (22)	86 (15)		
F4	228 (20)	71 (18)	1,295 (3,732)	6,450 (11,422)
Decompensation	96 (21)		9,874 (12,246)	16,119 (17,778)
HCC	96 (21)		11,745 (11,634)	16,643 (14,137)
Liver transplant				
First year	96 (21)		56,021 (40,329)	90,712 (55,462)
Following years	96 (21)		5,445 (11,123)	15,911 (23,307)

Table 3 Description of the 6 scenarios simulated

Scenario	time before access to NSP after injection initiation (mean)	time before access to OST when in NSP (mean)	Time to diagnosis (active/inactive PWID) (mean)	Time to linkage to care (mean)	Lost to Follow-up (%/year)	Treatment eligibility	Remark
S1 – Reference (current practice)	2 years	1 year	1.25/1.45 years	2.6 years	14%/year	F2→F4	Comparator
S2 – Improved harm reduction interventions	1 year	0.5 year	1.25/1.45 years	2.6 years	14%/year	F2→F4	We improved access to NSP and OST in the population. Indeed, as the risk of HCV infection is particularly high during the first year of injection (53, 54), faster access to NSP or OST could help to reduce infections.
S3 – Treatment initiation: fibrosis ≥ F0	2 years	1 year	1.25/1.45 years	2.6 years	14%/year	F0→F4	All diagnosed individuals who have been linked to care, receive treatment (excluding those with a cirrhosis complication).
S4 – Improved cascade of care	2 years	1 year	0.5 year	0.5 year	5%/year	F2→F4	In order to accelerate access to care in this scenario, we improved testing, linkage to care, and LTFU rate.
S5 – Combined S3 and S4	2 years	1 year	0.5 year	0.5 year	5%/year	F0→F4	We improved testing and linkage to care for chronic hepatitis C, and treatment was initiated from F0 for an earlier antiviral treatment initiation.
S6 – Combined S2, S3 and S4	1 year	2 years	0.5 year	0.5 year	5%/year	F0→F4	We improved harm reduction interventions and the cascade of care for chronic hepatitis C, and treatment was initiated from F0.

NSP: needle and syringe program; OST: opioid substitution therapy; LTFU: loss to follow-up

Table 4 Results of the main analysis. Costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (y)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference (current practice)	24,058 (187)	18.407 (0.062)	15.847 (0.057)	3,465 (83)	999 (41)		
S2 – Improved harm reduction interventions	24,994 (203)	18.405 (0.056)	15.865 (0.054)	3,320 (84)	952 (43)	Dominated	Extended dominance
S4 – Improved cascade of care	25,698 (205)	18.499 (0.063)	16.085 (0.060)	3,497 (87)	1,198 (47)	17,800	6,900
S3 – Treatment initiation: fibrosis ≥F0	30,240 (312)	18.419 (0.062)	16.377 (0.061)	3,209 (111)	1,467 (65)	Dominated	Extended dominance
S5 – Combined S3 and S4	30,834 (325)	18.513 (0.056)	16.696 (0.055)	2,178 (99)	1,052 (63)	Extended dominance	8,400
S6 – Combined S2 and S3 and S4	31,445 (303)	18.517 (0.054)	16.704 (0.053)	2,036 (94)	978 (60)	319,800	76,400

sd: standard deviation ; y: year ; QALY: quality-adjusted life-year, SVR: sustained virological response, ICER: incremental cost-effectiveness ratio.
Cost, life expectancy and quality-adjusted life expectancy are discounted according to French guidelines (30): discount rate of 4% for individuals younger than 30, which was linearly decreased to 2% between 30 and 50 years of age, and set at 2% after 50. The scenarios were sorted by increasing costs.

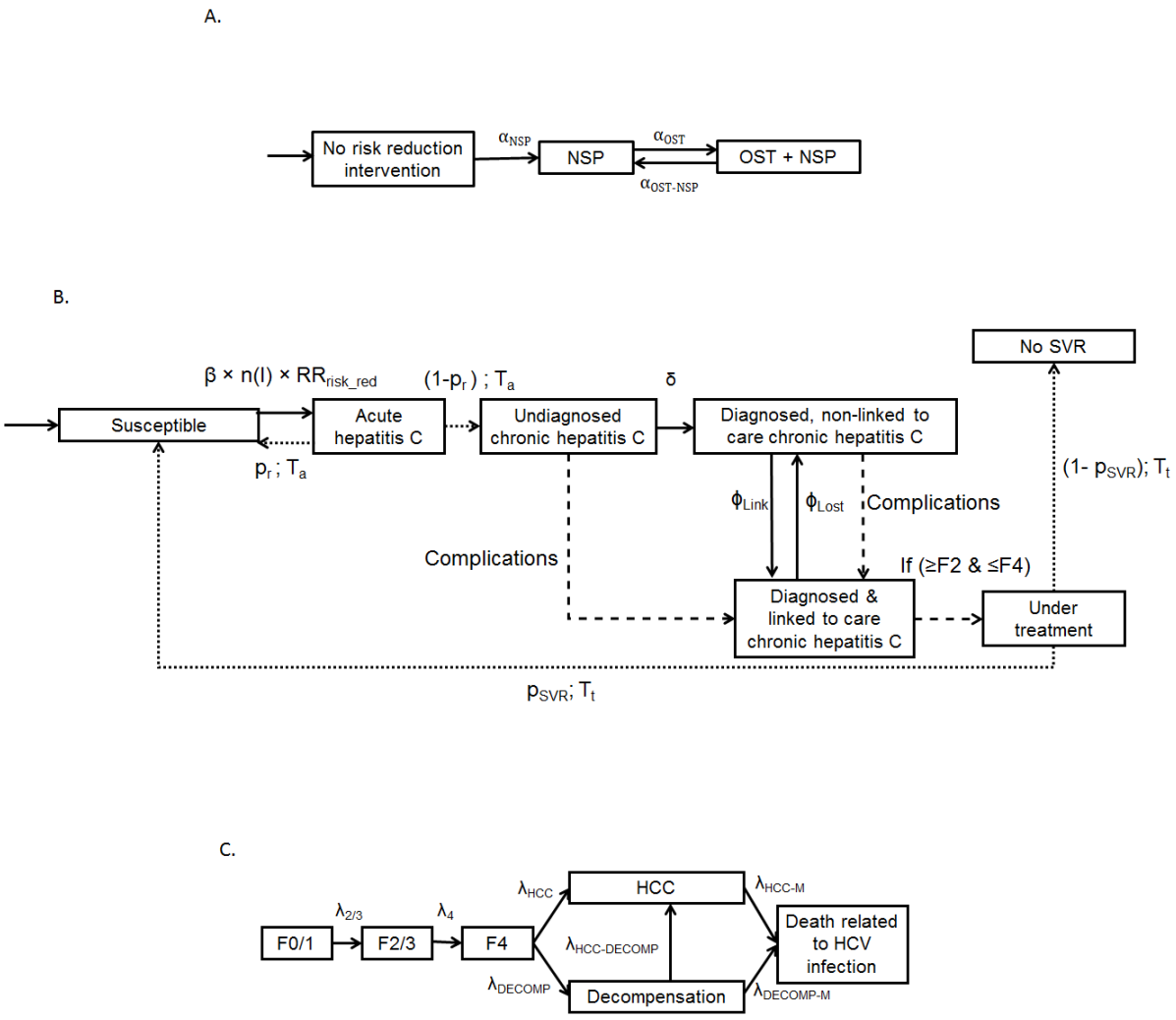
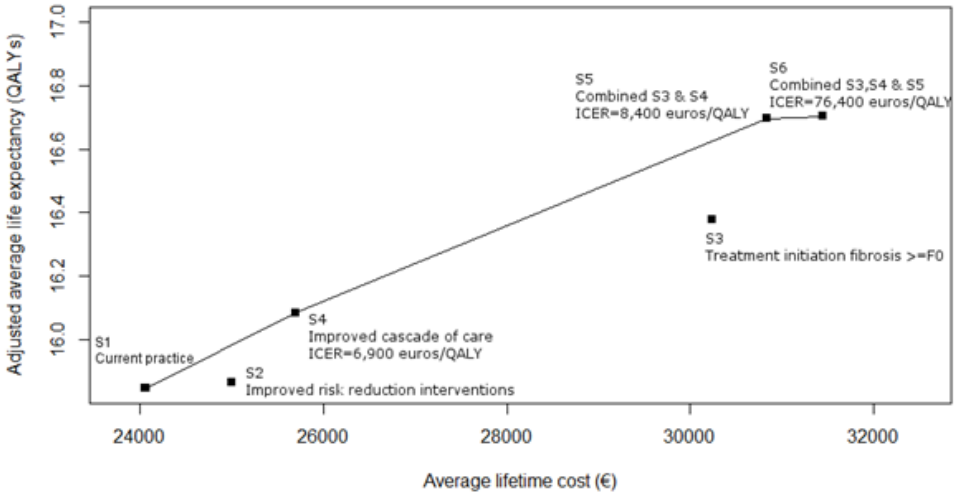


Figure 1. Dynamic model for harm reduction, HCV transmission and care, and chronic hepatitis C natural history. A. Harm reduction interventions. NSP=Needle and syringe program, OST=Opioid substitution therapy. New PWID enter the model in the "Difficult access to injecting equipment" compartment. Each transition occurs according to exponential law. $\alpha_{OST-NSP}$ depends on the existence of a previous OST among the PWID: patients tend to wait less time to return to OST than they did between starting to inject and trying OST for the first time. B. Model for HCV infection and care. A new PWID enters the model as susceptible. Plain arrows correspond to transitions occurring according to exponential probability distributions. Dashed lines correspond to transition occurring after a fixed time with a given probability. Dotted lines correspond to transitions related to a transition in the natural history model. n(i) refers to the number of infectious injecting partners of the PWID. RR_{risk_red} refers to the relative risk of infection related to the status of PWID in relation to harm reduction interventions. C. Natural history of chronic hepatitis C in the model. F0/F1 refers to an F0 or F1 Metavir score; and F2/F3 to an F2 or F3 Metavir score. Each transition occurs according to exponential law. λ_{TP-D} depends on the time since transplant: the mortality rate is higher during the first year.

A.



B.

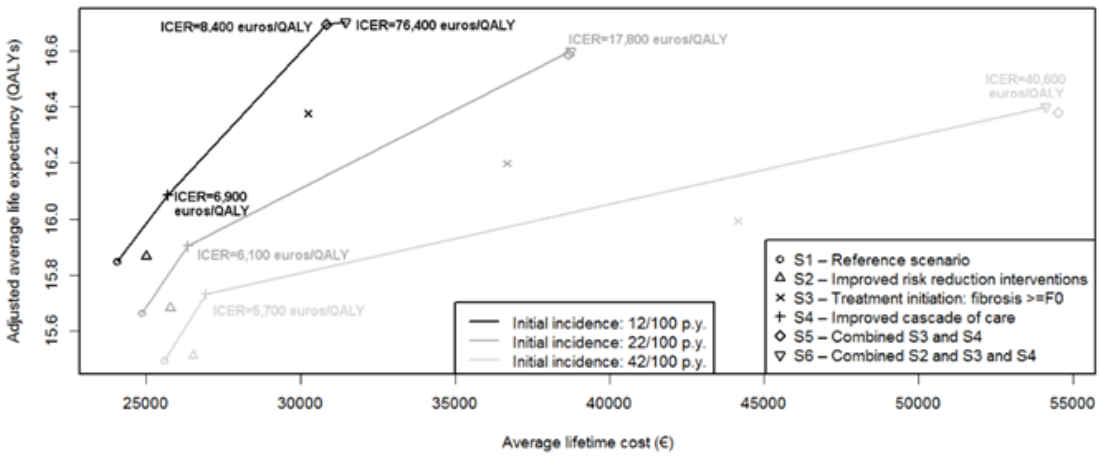


Figure 2. Efficiency curve representing the results of A. the main analysis and B. the sensitivity analysis, when varying the initial incidence. Each dot represents a scenario, and the dots are linked for non-dominated scenarios. The slope of the line gives a visual representation of the ICER: a steep slope corresponds to a highly cost-effective scenario. ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year.

SUPPLEMENTARY MATERIAL

S1: MODEL DETAILS AND PARAMETERS ESTIMATIONS

MODEL AND PARAMETERS

Population

The initial population of the model is a population of PWID in Paris area. As in a previous study, we supposed that the order of magnitude of this population is 10,000 (1, 2). The population is structured in 3 levels: each PWID is in a compartment in the transmission and healthcare model, a position in the network of injectors sharing drugs and a life expectancy (excluding HCV mortality).

The initial age distribution is described in Table S1.

Table S1 Age distribution according to the gender in active (i.e. injection in the last month) PWID in 2011 from ANRS-Coquelicot study.

Age	Women	Men
20	1.4	0.1
22	6.2	1.5
23	5.0	1.8
24	10.3	2.7
25	0.1	1.1
26	1.5	0.7
27	0.7	5.9
28	1.8	0.5
29	1.1	3.0
30	5.3	2.9
31	5.6	8.3
32	0.0	3.3
33	3.5	1.9
34	0.1	4.7
35	1.0	1.9
36	2.9	4.8
37	17.8	4.4
38	0.6	5.5
39	5.7	6.8
40	1.5	7.0
41	4.7	4.6
42	0.0	1.5
43	0.0	2.7

44	6.4	5.5
45	0.2	2.3
46	4.9	1.6
47	3.4	0.8
48	3.4	0.3
49	1.4	5.0
50	0.0	2.1
51	3.6	1.2
53	0.0	0.2
54	0.0	0.0
55	0.0	1.3
56	0.0	0.5
59	0.0	1.6

Each compartment in the model corresponds to:

- A state concerning the harm reduction intervention in which he/she participates
- A state related to HCV infection and care
- For chronically HCV-infected PWID, a state in the natural history model

The possible states for each of these characteristics are described below.

Social network

Model

HCV is mainly transmitted by needles/syringes sharing in the PWID population; however paraphernalia sharing (e.g. filter, spoon) seems also to play an important role (3). To take into account the global risk of infection for a PWID given that we consider only transmissions occurring during shared drug injections, we chose, as previously described by Rolls *et al.*, to model the network of the sharing partners: two PWID are linked together if they inject together even without sharing needles/syringes (4). In this network, two PWID are linked if they reported “intraveneous drug use at the same place and time” in the previous 3 months.

Compared with mixed models, taking into account the social network allows to take the neighborhood size of individuals into consideration and to propose more realistic estimations of infections parameters, for instance. Spread of the disease is also more constrained by the network on which it propagates.

One of our objectives was to simulate possible paths of HCV transmission in PWID and we need to model a random network to allow repeated generation of structures with similar topologies.

We chose a *household graph model* (5, 6). These models generate networks where individuals are clustered in subgroups ("households") in which pairs have a high probability to be linked. Individuals belonging to different subgroups have a low probability to be linked.

Our model is constructed as follows

1) In a population of *n* individual, we randomly assign each member to an household of size 1 (the individual is alone in his/her household), 2 or 5, with probabilities π_1 , π_2 or π_5 .
2) Each couple of individuals belonging to the same household is considered linked with an edge with a probability depending on the type of household they belong to $p_{ij}, (i,j) \in \{1,2,5\}^2$. Probabilities p_{22} and p_{55} are considered higher than p_{12} , p_{15} , and p_{25} .

The sizes 1,2 or 5 of the household is chosen by analysis of the Australian data (7)

Parameters

For simplicity, we assumed that $p_{11}=0$, because structure that would be formed if $p_{11}>0$ would be similar to household of size 2. Thus, we needed to estimate the following parameters: π_1 , π_2 , π_5 and p_{12} , p_{15} , p_{22} , p_{25} and p_{55} .

For this purpose, we used Approximate Bayesian Computation (ABC). ABC is a bayesian method used to infer some parameters of a model without likelihood estimation (8). Briefly, the main idea of ABC is to fit the (possibly set of) parameter(s) θ of a model thanks to simulations and computation of a (possibly set of) summary statistic(s) $s_i, i=1,\ldots,N$ that are compared to the observed values on the data s_{obs} . More precisely, we draw a sample $\theta_i, i=1,\ldots,N$ in a prior probability distribution. For each θ_i , the model is simulated with this parameter set and simulations are 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 θ $(¿¿i, W_i / \sum_{i=1}^{N} W_i), i=1,\ldots,N$ ¿ 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 to obtain a tighter posterior distribution. For more details about ABC, the reader can refer to (9).

Due to the lack of data about PWID social networks in France, we used the data collected in a survey in Melbourne (Australia) (7). The data available was a network of 305 PWID in Melbourne (Australia). These data were obtained using snowball sampling (RDS): starting from an initial set of 151 PWID, each of them were asked to report a maximum of five injecting partner in the population. The investigators then tried to find these partners to make them participate in the survey, and ask them to report in turn their injecting partners, etc. The final obtained network was constituted of 305 PWID, of which 47 without identified partners. The total population size was estimated at 524 from this sample. This network is partial, due to the limitation in the number of reported injected partners.

To calibrate our household model from Melbourne data, we used ABC with the following process:

Step 1: A sample of N=90,000 parameters values for the household graph model was drawn. The parameters $\theta = (p_{12}, p_{15}, p_{22}, p_{25}, p_{55})$ were drawn in uniform prior distributions in respectively [0, 0.2/250], [0, 0.05/250], [0, 0.2/250], [0, 0.05/250] and [0, 3/250]. The prior law distributions of π_1, π_2 or π_5 were uniform distributions renormalized so that the distribution summed to 1 with respective means of 0.25, 0.25 and 0.5 respectively. The parameters for the prior distributions were chosen according to an exploratory descriptive analysis of the sample.

Step 2: For each set of parameters in the sample, we simulated a corresponding household graph of size 524. This value was the estimated size of the initial PWID community in which the snowball sample was drawn according to Rolls *et al.* (7).

Step 3: A snowball sampling process was simulated on each of these networks in the following manner (implemented in C++):

A. An initial set of 151 nodes was randomly chosen in the graph

B. For each of these nodes

    1. If the node's degree (i.e. the number of edges linked to the node) is inferior or equal to 5, all the neighbors of the index node are included in the snowball sample

    2. If the node's degree is superior to 5, 5 nodes are randomly and uniformly drawn among the neighbors to be included in the snowball sample

C. The same process is applied from B to the nodes newly included in the sample, until the sample size reached 305

Step 4: A set of summary statistics are computed for each snowball sample. These statistics are: the number of isolated nodes, the number of edges, the number of triangles in the network, the number of isolated couples and the diameter of the network (i.e. the maximum number of edges between two nodes of the network). This generates a set of inputs for the ABC constituted of N=90,000 summary statistics.

Step 5: We applied ABC using the package "abc" (10) of the statistical software R (11). The observed statistics in the Melbourne's snowball sample were: 47 isolated nodes, 263 edges, 61 triangles, 23 isolated couples, and a diameter of 17. We used an Epanechnikov kernel with a tolerance threshold corresponding to 10% of the simulations. π_2 or π_5 values were logit-transformed to ensure final estimates between 0 and 1, and π_1 estimates was derived from π_2 or π_5 to sum to 1. p_{12}, p_{15}, p_{22}, p_{25} and p_{55} were log-transformed to ensure their positivity. We applied a correction on the parameters values using linear regression, as explained above.

Step 6: The mean value of each posterior distribution was used as the final estimate for the corresponding parameter.

The results obtained were: ($\widehat{\pi_1}$, $\widehat{\pi_2}, \widehat{\pi_5}¿ = (0.26, 0.237, 0.503)$ and ($\widehat{p_{12}}$,

$\widehat{p_{15}}, \widehat{p_{22}}, \widehat{p_{25}}, \widehat{p_{55}}¿ = (3.42\,e^{-4}, 7.52\,e^{-5}, 3.20\,e^{-4}, 1.56\,e^{-4}, 2.48\,e^{-4})$.

We can see that according to these results, around 50% of the PWID belong to a household of size 5. $\widehat{p_{12}}$ and $\widehat{p_{22}}$ are the highest values, implying the emergence of arborescent structures in the

simulated graphs. The probabilities for individuals belonging to households of 5 people to connect with people of other households $\widehat{p_{15}}$, $\widehat{p_{25}}$ and $\widehat{p_{55}}$ are lower, suggesting that such households are more isolated. However with 5 people in each household, there are 5 times more chances to connect with other households.

Example

An example of simulated household graph is given Figure S1.

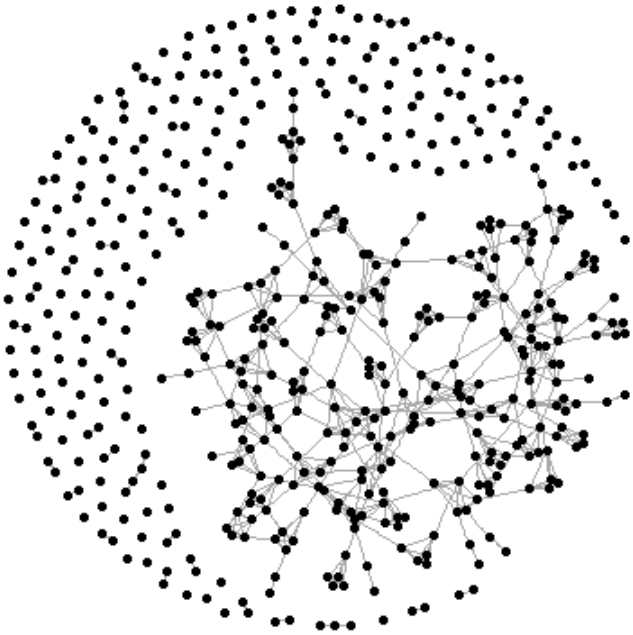


Figure S1 example of simulated household graph with N=524

Harm reduction interventions

We included the two main harm reduction interventions currently available in France at a national level: access to sterile injection equipment through harm reduction facilities, harm reduction kits in pharmacy or via automatic dispensers; and opioid substitution treatments (buprenorphine or methadone). The model is represented Figure S2, and the parameters values are given Table S2.

We assumed a mean time before access to NSP of 2 years, based on the high number of PWID reporting difficulties to access syringes (30%, see (12)). The high proportion of active PWID currently under OST, and experts' opinions suggesting that NSP and OST are initiated almost simultaneously lead us to consider a relatively short duration before entering in the NSP+OST compartment (1 year). About 37% of PWID under OST remain under treatment 10 months of the year (13) , given 2.3 years in average before cessation of OST according to the survival function of the exponential distribution (and assuming such distribution). In addition, this data and the high proportion of PWID under OST suggest that the cessation of OST is short: we assumed a come-back under OST after 3 months. Relative risk of HCV infection in each compartment was estimated in a meta-analysis (14). In this study NSP parameters were estimated considering a high-coverage needle program (i.e. where a sterile syringe is available for 100% of the injections of the user).

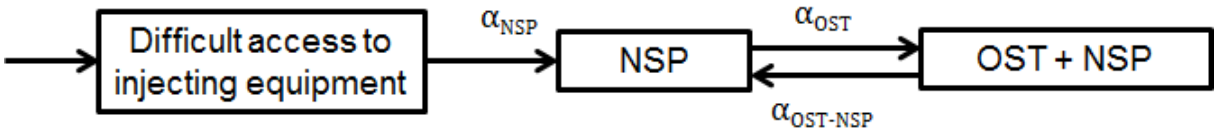


Figure S2 harm reduction interventions. NSP=Needle and syringe program, OST=Opioid substitution therapy. Each transition occurs according to exponential law. $\alpha_{OST-NSP}$ depends on the existence of a previous OST among the PWID: the return under OST is faster than the first OST initiation.

Natural history

The previously used model for chronic hepatitis C natural history included the fibrosis progression, the two cirrhosis complications (decompensated cirrhosis and HCC). We changed it to include hepatic transplant in cirrhosis complications, due to the high costs incurred. A representation of the model is given Figure S3. The corresponding parameters are described in Table S2.

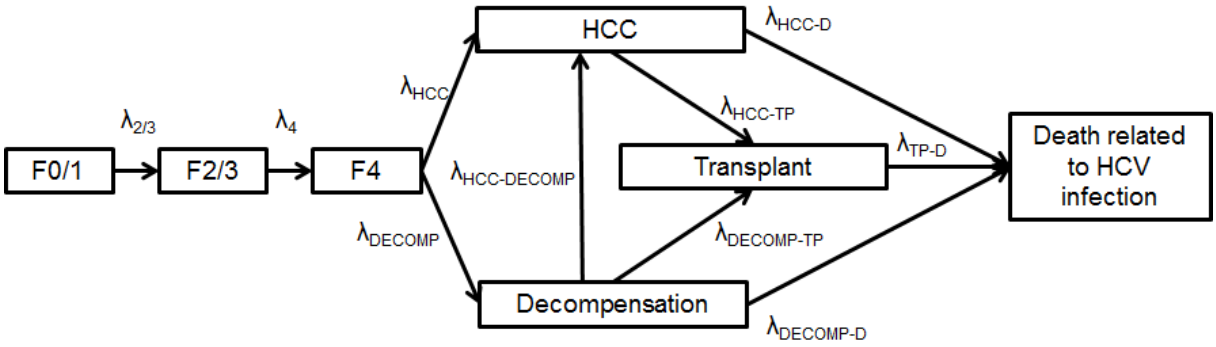


Figure S3 natural history of chronic hepatitis C in the model. F0/F1 refers to a F0 or F1 Metavir score; and F2/F3 to a F2 or F3 Metavir score. Each transition occurs according to exponential law. λ_{TP-D} depends on the time since transplant: the mortality rate is higher during the first year.

Infection and care

The model is represented in Figure S4. Briefly, starting from the susceptible state, an active (i.e. before cessation of injection) PWID can be infected with an infection rate depending on the number of his/her infectious injecting partners on the network and his/her status related to harm reduction interventions. After the acute phase of hepatitis C he/she can spontaneously recover with probability and become susceptible again or progress to chronic hepatitis C. Then, he/she can be diagnosed at a rate that depends on his/her status related to injection: active or inactive injector. Once diagnosed, he/she can be linked to healthcare, and he/she can be lost to follow-up, or be treated if his/her Metavir score is between F2 and F4 (in the current practice). Then he/she can have SVR and become susceptible again or otherwise progress to “Non SVR”, in which he/she can not be treated again. When a complication of cirrhosis occurs, a PWID is automatically linked to care.

Parameters values are given Table S2.

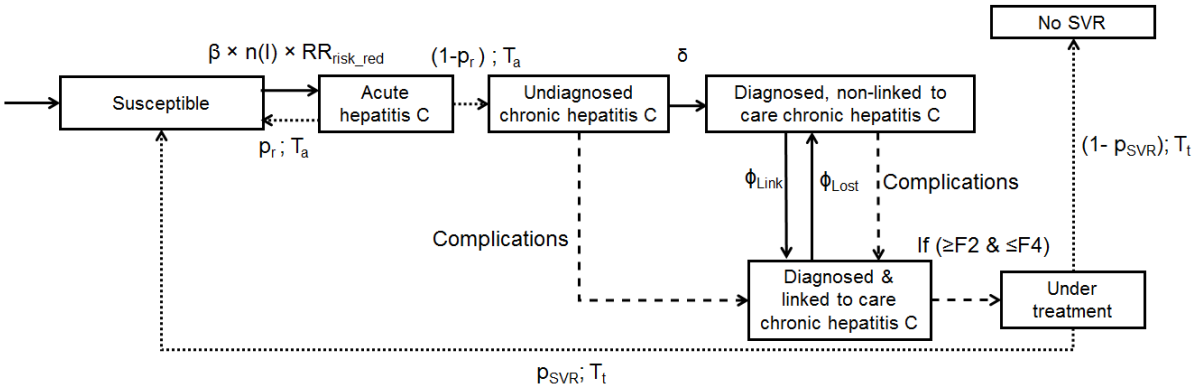


Figure S4 model for HCV infection and care. A new PWID enters the model as susceptible. Plain arrows correspond to transitions occurring according to exponential probability distributions. Dashed lines correspond to transition occurring after a fixed time with a given probability. Dotted lines correspond to transitions related to a transition in the natural history model. n(i) refers to the number of infectious injecting partners of the PWID. RR_{risk_red} refers to the relative risk of infection related to the PWID status regarding harm reduction interventions.

Cessation of drug injection and mortality non-related to HCV

The model takes also into account the cessation of injection: the duration of the injecting career is supposed to be 13.9 years (15, 16).

The mortality in the model depends on the gender, the age and the current injecting status (active injector or former injector). We assumed that the mortality for former injectors is similar to that of general French population, and we used the table of the mortality rates for the years 2012 in this case (17). For active injector, we applied a relative risk of 5.19 for men and 9.52 for women (18).

Table S2 Parameters for the model: initial population, infection, care and natural history

Parameter	Value	References
Population size	20×524*	
Initial distribution infection and care		
Susceptible	57.2%	ANRS-Coquelicot
Acute hepatitis	0%*	
Non-diagnosed chronic hepatitis	9.2%	ANRS-Coquelicot data (19)
Diagnosed, non-linked to care chronic hepatitis C	11.3%	
Diagnosed and linked to care chronic hepatitis C	16.0%	
Under treatment	2.2%	
Non-responders after treatment	4.1%	
Initial distribution in the natural history model		
F0/F1	35.0%	(20)
F2/F3	51.0%	
F4	14.0%	

Decompensated cirrhosis	0.0%*	
HCC	0.0%*	
Initial distribution related to harm reduction interventions		
Difficult access to injecting equipment	30.0%*	Derived from (12, 21-23)
NSP	20.0%*	
NSP+OST	50.0%*	
Men among current PWID	75.5%	ANRS-Coquelicot
Infection rate by injecting partner in S'	0.184 $y^{-1}$$partner^{-1}$	Fitted by ABC to have a 12/100 p-y baseline incidence (24) – median value from western countires in absence of data in France
Relative risk of infection when under		
NSP	0.5	(14)
NSP+OST	0.21	For a high-coverage needle program (i.e. where a sterile syringe is available for 100% of the injections of the user)
Transition from "Difficult access to injecting equipment" to NSP	2y*	Derived from (12, 21-23)
Transition from NSP to NSP+OST		
First time	0.5y*	
Next times	0.25y*	
Transition from NSP+OST to NSP	2.3y*	
Duration of acute hepatitis C	0.5 y	(25)
Probability of spontaneous recovery	26%	
Average time from chronic infection to diagnosis		
Current PWID	1.25 y	Derived from ANRS Coquelicot data (1, 19)
Former PWID	1.45 y	
Average time before linkage to care	2.6 y	Derived from ANRS Coquelicot data (1, 19)
Loss to follow-up rate	14%/y	(26)
Treatment: incoming DAAs regimens		
Duration	12 weeks	(27-37)
SVR rate – treatment naïve – all genotypes- clinical trials	95%	
Ratio of the effectiveness in real life to the efficacy in clinical trials	0.903	Derived from (20)
Duration of injecting career	13.9 y	(15, 16)
Transition rate F0/F1→ F2/F3	0.052 y^{-1}	(38)
Transition rate F2/F3→ F4 (λ_4)	0.054 y^{-1}	
Transition rate F4→Decompensated cirrhosis	0.04 y^{-1}	(39, 40)
Transition rate F4→HCC	0.021 y^{-1}	
Transition rate Decompensated cirrhosis→Death related to HCV	0.306 y^{-1}	
Transition rate HCC→Death related to HCV	0.433 y^{-1}	
Transition rate Decompensated cirrhosis→HCC	0.021 y^{-1}	

Transition rate Decompensated cirrhosis→Transplantation	0.128 y^{-1}	¿	
Transition rate HCC→Transplantation	0.186 y^{-1}	¿	
Transition rate Transplantation→Death related to HCV		¿	(41, 42)
First year	0.174 y^{-1}	¿	
Following years	0.033 y^{-1}	¿	
Relative risk in patients achieving SVR in F4			
Death related to HCV infection	0.13	¿	
Decompensated cirrhosis	0.08	¿	(43)
HCC	0.27	¿	

* Hypothesis
IBM: Individual-based model
SVR: Sustained virological response
PWID: People who inject drugs
y^{-1}: per year
HCC: Hepatocellular carcinoma
DAA: Direct-acting antiviral
HCV: Hepatitis C virus

COSTS AND UTILITIES

Costs

In the analysis, we included all the relevant costs related to harm reduction interventions and chronic hepatitis C testing, healthcare and treatment on an annual basis.

Harm reduction interventions

NSP: Budget by PWID of the active file of French harm reduction facilities (CAARUD) are estimated at 630€ annually (44), thus we used this estimate for PWID in NSP in our model.

OST: The average annual budget of French healthcare centers in addictology (CSAPA) is 746,472€ for an average active file of 574 PWID (45), thus we used an estimate at 1,300€ per PWID. In addition, based on the distribution of PWID on buprenorphine and methadone, the distribution between the princeps and generic form for buprenorphine delivery, the distribution between capsule and syrup for methadone, and the average posology for each of this treatment (from (13)) and the cost of each of product (from (46)) we estimated the annual cost on OST at 530€. The final estimate is thus 1,830€ for PWID in OST in the model.

Chronic hepatitis C related costs

Testing: the cost of a serology for PWID susceptible was set at 19.575€ (47). The annual cost depends on the testing rate delta assumed in the scenario.

Ressources consumption for HCV care: These costs were only taken into account for PWID linked to the healthcare system. We used estimates from French general population (48). These costs are summarized in Table S3.

Table S3 Annual mean costs (SD) attributable to chronic hepatitis C: ambulatory costs (never treated and after HCV treatment failure) and hospitalization costs (no death and in-hospital death) (48)

Liver disease stage	**Ambulatory costs (€)**		**Hospitalization costs (€)**	
	Never treated	**After treatment failure**	**No death**	**In-hospital death**
F0/F1	70 (10)	53 (12)	278 (1,087)	337 (1,377)

F2/F3	128 (22)	86 (15)		
F4	228 (20)	71 (18)	1,295 (3,732)	6,450 (11,422)
Decompensation	96 (21)		9,874 (12,246)	16,119 (17,778)
HCC	96 (21)		11,745 (11,634)	16,643 (14,137)
Liver transplant				
First year	96 (21)		56,021 (40,329)	90,712 (55,462)
Following years	96 (21)		5,445 (11,123)	15,911 (23,307)

Treatment: the cost of new antiviral therapies was assumed to be 46,000€ for a 12-weeks treatment, which is the current cost of the treatment by a combination ledipasvir+sofosbuvir at the time of the study (49). In addition, the healthcare cost for monitoring these treatments (physician consultations and laboratory tests) were estimated used French treatment guidelines to 740€.

Costs of implementation of the scenarios

Improvements in harm reduction interventions: as the annual cost we used for NSP and OST include the operating budget of the corresponding structures (CAARUD and CSAPA), we added no supplementary cost for the improvements of these interventions (corresponding to the opening of additional structures).

Treatment from F0: as we assumed in our analyses interferon free regimens with short treatment duration, we assumed that the treatment cost and healthcare monitoring costs would mainly be the cost of implementing this strategy.

Improvements in testing and, linkage to care to treatment: based on a previous cost-effectiveness analysis about HIV screening in France (50), we estimated that the start-up cost of improving testing would mainly be the cost of training physicians working in CSAPA. Among the 70 CSAPA in Paris metropolitan area, considering an average of 9.6 employees/CSAPA including 16% of physicians, we estimated their number to be 40 (45). Considering a two-days training with 20 participants per training receiving 330€/day and instructors 1,500€/course, and 80% of acceptance, the cost is 29,400€ for this strategy.

In a similar way, the cost related to improvements in linkage to care would concern more healthcare workers: general practitionners (20,235) and gastroenterologists-hepatologists (840) (51); and CSAPA physicians were estimated at 12M€. This estimation represents probably an overestimation of the cost of this strategy, because the amount of physician that would be trained would probably be lower. However, in a conservative way we included this cost in the corresponding scenarios.
We made the hypothesis that with interferon free regimens and such shorter durations, an improvement in the adherence to treatment could occur relatively easily and we neglected the costs related.

Utilities

The measure of the quality of life was adjusted to take into account the impact of drug injection, chronic HCV infection and treatment with new DAAs.

Drug injection

For PWID before injection cessation, we adjusted the number of life years gained by a factor 0.9 (52).

Chronic hepatitis C related utilities

Due to the lack of data about French PWID with new DAAs regimens in F0 to F0 fibrosis scores, we used utilities estimated from a cross sectional study in France in HCV infected patients under dual therapy peg-interferon/ribavirin (53). Utilities in cirrhosis complications where derived from (54).

Table S4 Utilities estimated in an HCV-infected French population according to disease stage (53, 54) and assumptions used in the model.

	HCV-RNA-positive	**HCV-RNA-negative***
F0/F1	0.82	0.95
F2/F3†	0.76	0.85
F4	0.60	0.85
Decompensated cirrhosis/HCC	0.60	0.60
Liver transplantation (first year)	0.55	0.55
Liver transplantation (following years)	0.82	0.82
Multiplied under IFN-free regimens	0.950	

*In case of SVR. †We conservatively assumed that the utilities in F2/F3 compartment correspond to that of F3 in Schwarzinger *et al.* study.

Treatment

We assumed that the future HCV treatment will be injection-free DAAs regimens with few adverse events. Thus, by hypothesis we adjusted the number of life years gained by a factor 0.95 (55).

S2 : EVOLUTION OF THE NUMBER OF NEWLY INFECTED PEOPLE IN THE POPULATION

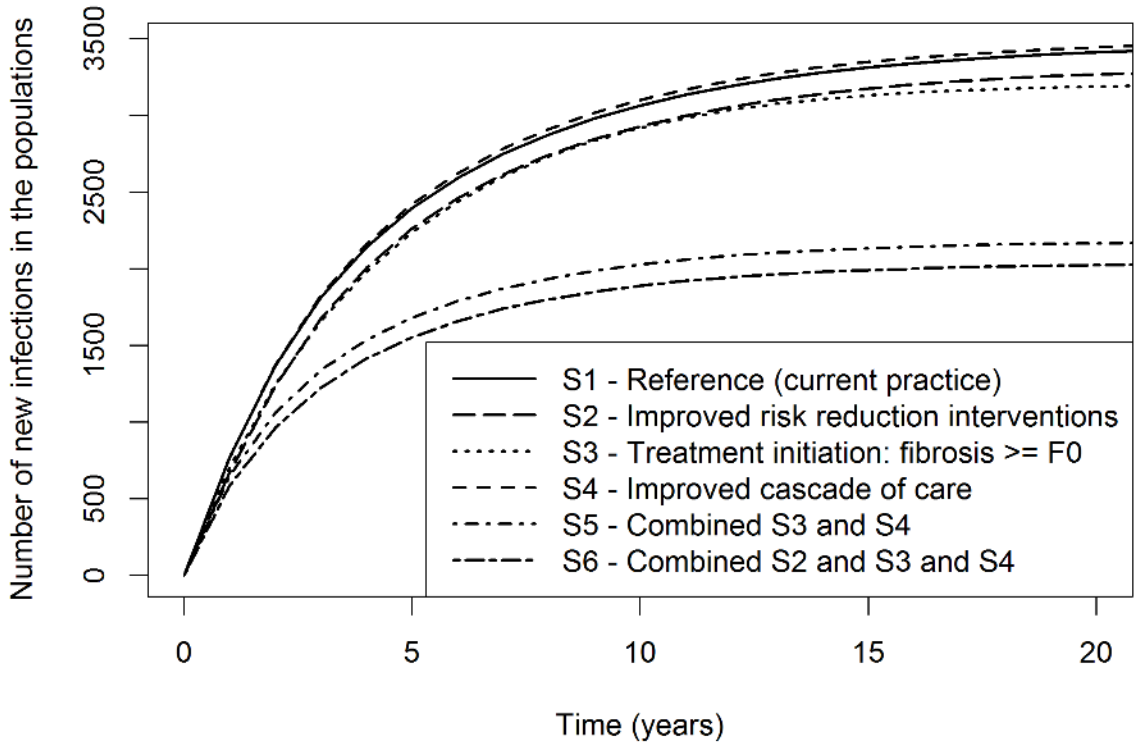


Figure S4 Evolution of the number of new infections in the population over the first 20 years.

S3: SENSITIVITY ANALYSIS

In this section, we present the results obtained by changing the key parameters in the simulations.

Treatment cost

Table S5 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. Compared with the main analysis, a 25% decrease was applied to the treatment cost.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	23,663 (185)	18.407 (0.062)	15.847 (0.057)	3,465 (83)	999 (41)		
S4 – Improved cascade of care	24,525 (197)	18.499 (0.063)	16.085 (0.060)	3,497 (87)	1,198 (47)	9,400	3,600
S2 – Improved harm reduction interventions	24,600 (199)	18.405 (0.056)	15.865 (0.054)	3,320 (84)	952 (43)	Dominated	Dominated
S5 – Combined S3 and S4	29,151 (325)	18.513 (0.056)	16.696 (0.055)	2,178 (99)	1,052 (63)	Extended dominance	7,600
S3 – Treatment initiation: fibrosis ≥F0	29,753 (314)	18.419 (0.062)	16.377 (0.061)	3,209 (111)	1,467 (65)	Dominated	Dominated
S6 – Combined S2 and S3 and S4	29,763 (304)	18.517 (0.054)	16.704 (0.053)	2,036 (94)	978 (60)	153,000	76,500

sd: standard deviation ; QALY: quality adjusted life-year

Table S6 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. Compared with the main analysis, a 50% decrease was applied to the treatment cost.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	23,269 (185)	18.407 (0.062)	15.847 (0.057)	3,465 (83)	999 (41)		
S4 – Improved cascade of care	23,352 (192)	18.499 (0.063)	16.085 (0.060)	3,497 (87)	1,198 (47)	900	300
S2 – Improved harm reduction interventions	24,207 (196)	18.405 (0.056)	15.865 (0.054)	3,320 (84)	952 (43)	Dominated	Dominated
S5 – Combined S3 and S4	27,469 (326)	18.513 (0.056)	16.696 (0.055)	2,178 (99)	1,052 (63)	Extended dominance	6,700
S6 – Combined S2 and S3 and S4	28,081 (307)	18.517 (0.054)	16.704 (0.053)	2,036 (94)	978 (60)	34,600	76,500
S3 – Treatment initiation: fibrosis ≥F0	29,266 (316)	18.419 (0.062)	16.377 (0.061)	3,209 (111)	1,467 (65)	Dominated	Dominated

sd: standard deviation ; QALY: quality adjusted life-year

Table S7 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. Compared with the main analysis, a 75% decrease was applied to the treatment cost.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S4 – Improved cascade of care	22,180 (191)	18.499 (0.063)	16.085 (0.060)	3,497 (87)	1,198 (47)		
S1 – Reference scenario	22,874 (187)	18.407 (0.062)	15.847 (0.057)	3,465 (83)	999 (41)	Dominated	Dominated
S2 – Improved harm reduction interventions	23,814 (195)	18.405 (0.056)	15.865 (0.054)	3,320 (84)	952 (43)	Dominated	Dominated
S5 – Combined S3 and S4	25,786 (328)	18.513 (0.056)	16.696 (0.055)	2,178 (99)	1,052 (63)	Extended dominance	5,900
S6 – Combined S2 and S3 and S4	26,399 (311)	18.517 (0.054)	16.704 (0.053)	2,036 (94)	978 (60)	153,300	76,600
S3 – Treatment initiation: fibrosis ≥F0	28,780 (320)	18.419 (0.062)	16.377 (0.061)	3,209 (111)	1,467 (65)	Dominated	Dominated

sd: standard deviation ; QALY: quality adjusted life-year

Initial incidence

Table S8 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The initial incidence used was 22/100 p.y. (vs. 12/100 p.y. in the main analysis), corresponding to a study among PWID in Montréal, Canada (derived from local data – SurvUDI network (56, 57)).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	24,870 (210)	18.380 (0.059)	15.661 (0.058)	4,968 (92)	1,644 (55)		
S2 – Improved harm reduction interventions	25,764 (215)	18.384 (0.063)	15.682 (0.062)	4,814 (99)	1,589 (53)	Extended dominance	Extended dominance
S4 – Improved cascade of care	26,340 (209)	18.482 (0.054)	15.902 (0.053)	5,266 (107)	2,061 (73)	14,400	6,100
S3 – Treatment initiation: fibrosis ≥F0	36,683 (446)	18.393 (0.057)	16.198 (0.055)	6,131 (166)	3,340 (122)	Dominated	Extended dominance
S5 – Combined S3 and S4	38,669 (594)	18.493 (0.060)	16.589 (0.060)	5,198 (214)	3,068 (157)	Extended dominance	Extended dominance
S6 – Combined S2 and S3 and S4	38,736 (548)	18.495 (0.052)	16.600 (0.051)	4,850 (203)	2,836 (151)	33,500	17,800

sd: standard deviation ; QALY: quality adjusted life-year

Table S9 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The initial incidence used was 42/100 p.y. (vs. 12/100 p.y. in the main analysis), corresponding to a study among PWID in London, United-Kingdom (58).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	25,583 (210)	18.351 (0.051)	15.493 (0.048)	6,280 (89)	2,307 (61)		
S2 – Improved harm reduction interventions	26,514 (224)	18.352 (0.054)	15.511 (0.052)	6,139 (109)	2,256 (68)	Extended dominance	Extended dominance
S4 – Improved cascade of care	26,924 (233)	18.457 (0.055)	15.730 (0.052)	6,866 (121)	2,963 (91)	12,700	5,700
S3 – Treatment initiation: fibrosis ≥F0	44,165 (444)	18.352 (0.056)	15.993 (0.058)	9,553 (176)	5,887 (146)	Dominated	Extended dominance
S6 – Combined S2 and S3 and S4	54,124 (826)	18.456 (0.057)	16.400 (0.057)	10,972 (313)	7,706 (267)	Dominated	40,600
S5 – Combined S3 and S4	54,524 (755)	18.451 (0.061)	16.381 (0.058)	11,497 (288)	8,129 (251)	Dominated	Dominated

sd: standard deviation ; QALY: quality adjusted life-year

Mean time to diagnosis

Table S10 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The mean time to diagnosis was set at 2.0 years (vs. 1.25/1.45 years for active/inactive PWID in the main analysis) corresponding to a study among PWID in Montréal, Canada (derived from local data – SurvUDI network (56, 57)).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	24,135 (211)	18.391 (0.058)	15.814 (0.055)	3,437 (84)	962 (45)		
S2 – Improved harm reduction interventions	25,049 (203)	18.392 (0.06)	15.831 (0.061)	3,308 (82)	923 (39)	Extended dominance	Extended dominance
S4 – Improved cascade of care	25,698 (205)	18.499 (0.063)	16.085 (0.060)	3,497 (87)	1,198 (47)	14,500	5,800
S3 – Treatment initiation: fibrosis ≥F0	29,985 (300)	18.413 (0.058)	16.33 (0.058)	3,278 (112)	1,478 (64)	Dominated	Extended dominance
S5 – Combined S3 and S4	30,834 (325)	18.513 (0.056)	16.696 (0.055)	2,178 (99)	1,052 (63)	Extended dominance	8,400
S6 – Combined S2 and S3 and S4	31,445 (303)	18.517 (0.054)	16.704 (0.053)	2,036 (94)	978 (60)	152,800	76,400

sd: standard deviation ; QALY: quality adjusted life-year

Table S11 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The mean time to diagnosis was set at 7.8 years (vs. 1.25/1.45 years for active/inactive PWID in the main analysis) corresponding to a study among PWID in London, United-Kingdom (59).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	24,128 (209)	18.300 (0.054)	15.600 (0.053)	3,316 (80)	807 (37)		
S2 – Improved harm reduction interventions	25,038 (211)	18.307 (0.06)	15.625 (0.06)	3,184 (70)	772 (35)	Extended dominance	Extended dominance
S4 – Improved cascade of care	25,698 (205)	18.499 (0.063)	16.085 (0.06)	3,497 (87)	1,198 (47)	7,900	3,200
S3 – Treatment initiation: fibrosis ≥F0	27,810 (250)	18.312 (0.053)	16.027 (0.052)	3,276 (97)	1,345 (55)	Dominated	Dominated
S5 – Combined S3 and S4	30,834 (325)	18.513 (0.056)	16.696 (0.055)	2,178 (99)	1,052 (63)	Extended dominance	8,400
S6 – Combined S2 and S3 and S4	31,445 (303)	18.517 (0.054)	16.704 (0.053)	2,036 (94)	978 (60)	152,800	76,400

sd: standard deviation ; QALY: quality adjusted life-year

Mean time to linkage to care

Table S12 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The mean time to linkage to care was set at 4.0 years (vs. 2.6 years in the main analysis).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	24,127 (186)	18.372 (0.053)	15.766 (0.053)	3,424 (81)	931 (39)		
S2 – Improved harm reduction interventions	25,036 (204)	18.373 (0.058)	15.782 (0.054)	3,283 (81)	891 (41)	Extended dominance	Extended dominance
S4 – Improved cascade of care	25,698 (205)	18.499 (0.063)	16.085 (0.060)	3,497 (87)	1,198 (47)	12,400	4,900
S3 – Treatment initiation: fibrosis ≥F0	29,854 (310)	18.393 (0.055)	16.288 (0.058)	3,311 (115)	1,483 (69)	Dominated	Extended dominance
S5 – Combined S3 and S4	30,834 (325)	18.513 (0.056)	16.696 (0.055)	2,178 (99)	1,052 (63)	Extended dominance	8,400
S6 – Combined S2 and S3 and S4	31,445 (303)	18.517 (0.054)	16.704 (0.053)	2,036 (94)	978 (60)	152,800	76,400

sd: standard deviation ; QALY: quality adjusted life-year

Loss to follow-up rate

Table S13 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The annual loss to follow-up rate was set at 20%/year (vs. 14%/year in the main analysis).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	23,696 (205)	18.400 (0.056)	15.836 (0.052)	3,456 (74)	985 (38)		
S2 – Improved harm reduction interventions	24,687 (222)	18.406 (0.056)	15.854 (0.053)	3,319 (84)	947 (43)	Extended dominance	Extended dominance
S4 – Improved cascade of care	25,698 (205)	18.499 (0.063)	16.085 (0.060)	3,497 (87)	1,198 (47)	20,200	8,000
S3 – Treatment initiation: fibrosis ≥F0	30,252 (294)	18.429 (0.057)	16.387 (0.056)	3,215 (105)	1,475 (67)	Dominated	Extended dominance
S5 – Combined S3 and S4	30,834 (325)	18.513 (0.056)	16.696 (0.055)	2,178 (99)	1,052 (63)	Extended dominance	8,400
S6 – Combined S2 and S3 and S4	31,445 (303)	18.517 (0.054)	16.704 (0.053)	2,036 (94)	978 (60)	152,800	76,400

sd: standard deviation ; QALY: quality adjusted life-year

Table S14 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The annual loss to follow-up rate was set at 30%/year (vs. 14%/year in the main analysis) by authors' choice.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	23,382 (202)	18.405 (0.058)	15.825 (0.058)	3,454 (80)	983 (41)		
S2 – Improved harm reduction interventions	24,300 (208)	18.399 (0.059)	15.837 (0.057)	3,309 (79)	936 (39)	Dominated	Extended dominance
S4 – Improved cascade of care	25,698 (205)	18.499 (0.063)	16.085 (0.060)	3,497 (87)	1,198 (47)	24,600	Extended dominance
S3 – Treatment initiation: fibrosis ≥F0	30,234 (340)	18.419 (0.063)	16.377 (0.062)	3,195 (115)	1,461 (71)	Dominated	Extended dominance
S5 – Combined S3 and S4	30,834 (325)	18.513 (0.056)	16.696 (0.055)	2,178 (99)	1,052 (63)	Extended dominance	8,600
S6 – Combined S2 and S3 and S4	31,445 (303)	18.517 (0.054)	16.704 (0.053)	2,036 (94)	978 (60)	152,800	76,400

sd: standard deviation ; QALY: quality adjusted life-year

Risk of reinfection following a SVR

Table S15 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The risk of reinfection per infected injecting partner β was divided by 3 after a previous infection successfully treated (60, 61).

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Base case	23,964 (216)	18.415 (0.06)	15.872 (0.058)	3,268 (76)	820 (37)		
S2 – Improved harm reduction interventions	24,902 (187)	18.409 (0.051)	15.880 (0.052)	3,143 (78)	793 (36)	Dominated	Extended dominance
S4 – Improved cascade of care	25,629 (195)	18.498 (0.052)	16.099 (0.052)	3,286 (86)	1,009 (45)	20,100	7,300
S3 – Treatment initiation: fibrosis ≥F0	29,824 (305)	18.430 (0.056)	16.400 (0.057)	2,988 (107)	1,270 (59)	Dominated	Extended dominance
S5 – Combined S3 and S4	30,454 (305)	18.517 (0.056)	16.705 (0.055)	2,016 (91)	909 (56)	253,900	8,000
S6 – Combined S2 and S3 and S4	31,095 (302)	18.509 (0.055)	16.701 (0.056)	1,883 (91)	850 (51)	Dominated	Dominated

sd: standard deviation ; QALY: quality adjusted life-year

Harm reduction

Table S16 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The initial distribution and transition rates in the harm reduction interventions model were changed for a worst case: initial distribution in NSP=40% and in NSP+OST=45% vs. 30% and 50% respectively in the main analysis.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Reference scenario	23,088 (202)	18.411 (0.052)	15.838 (0.052)	3,600 (85)	1,046 (44)		
S4 – Improved cascade of care	24,694 (194)	18.496 (0.059)	16.067 (0.056)	3,646 (94)	1,258 (51)	18,900	7,000
S2 – Improved harm reduction interventions	24,920 (210)	18.411 (0.055)	15.868 (0.053)	3,324 (78)	952 (41)	Dominated	Dominated
S3 – Treatment initiation: fibrosis ≥F0	29,662 (338)	18.423 (0.057)	16.372 (0.056)	3,389 (112)	1,566 (67)	Extended dominance	Extended dominance
S5 – Combined S3 and S4	30,156 (333)	18.512 (0.053)	16.693 (0.052)	2,318 (100)	1,129 (65)	70,000	8,700
S6 – Combined S2 and S3 and S4	31,450 (296)	18.519 (0.056)	16.704 (0.055)	2,052 (92)	983 (58)	184,900	117,600

sd: standard deviation ; QALY: quality adjusted life-year

Quality of life

Table S17 Quality of life data used for the sensitivity analysis from (62, 63)

	HCV-RNA-positive	**HCV-RNA-negative***
F0/F1	0.931	0.95
F2/F3†	0.902	0.95
F4	0.872	0.89
Decompensated cirrhosis/HCC	0.794	0.81
Liver transplantation	0.843	0.843
Multiplied under IFN-free regimens	0.950	

*In case of SVR. †We conservatively assumed that the utilities in F2/F3 compartment correspond to that of F3 in Siebert *et al.* study.

Table S18 Results of the sensitivity analysis. The costs, life expectancy and adjusted life expectancy are discounted according to French guidelines. The scenarios were sorted by increasing costs. The quality of life data we used for the impact of HCV infection were changed for those of a German study (62, 63), see Table S17.

Scenario	Average lifetime cost (sd) (€)	Average life expectancy (sd) (years)	Adjusted average life expectancy (sd) (QALYs)	Average number of new infections (sd)	Average number of reinfections after SVR (sd)	ICER (€/LY)	ICER (€/QALY)
S1 – Base case	24,058 (187)	18.407 (0.062)	16.572 (0.053)	3,465 (83)	999 (41)		
S2 – Improved harm reduction interventions	24,994 (203)	18.405 (0.056)	16.572 (0.054)	3,320 (84)	952 (43)	Dominated	Dominated
S4 – Improved cascade of care	25,698 (205)	18.499 (0.063)	16.728 (0.059)	3,497 (87)	1,198 (47)	17,800	10,500
S3 – Treatment initiation: fibrosis ≥F0	30,240 (312)	18.419 (0.062)	16.747 (0.057)	3,209 (111)	1,467 (65)	Dominated	Extended dominance
S5 – Combined S3 and S4	30,834 (325)	18.513 (0.056)	16.937 (0.054)	2,178 (99)	1,052 (63)	366,900	24,600
S6 – Combined S2 and S3 and S4	31,445 (303)	18.517 (0.054)	16.934 (0.055)	2,036 (94)	978 (60)	152,800	Dominated

sd: standard deviation ; QALY: quality adjusted life-year

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