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

Anthony Cousien[1], Viet Chi Tran[3], Sylvie Deuffic-Burban[1,3], Marie Jauffret-Roustide[4,5], Guillaume Mabileau[1], Jean-Stéphane Dhersin[6], Yazdan Yazdanpanah[1,7]

[1] IAME, UMR 1137, INSERM, Univ Paris Diderot, Sorbonne Paris Cité, Paris, France

[2] Laboratoire Paul Painlevé UMR CNRS 8524, UFR de Mathématiques, Université des Sciences et Technologies Lille 1, Cité Scientifique, F-59655 Villeneuve d'Ascq Cedex, France

[3] Inserm, LIRIC-UMR995, F-59000 Lille, France; Univ Lille, F-59000 Lille, France

[4] CERMES3: Centre de Recherche Médecine, Sciences, Santé, Santé Mentale et Société, (INSERM U988/UMR CNRS8211/Université Paris Descartes, Ecole des Hautes Etudes en Sciences Sociales), Paris, France

[5] Institut de Veille Sanitaire, Saint-Maurice, France

[6] Université Paris 13, Sorbonne Paris Cité, LAGA, CNRS, UMR 7539, F-93430, Villetaneuse, France

[7] Service des Maladies Infectieuses et Tropicales, Hôpital Bichat Claude Bernard, Paris, France

Corresponding author

Anthony Cousien

Equipe 5, IAME, UMR 1137, INSERM

Université Paris 7, UFR de médecine – Site Bichat

16 rue Henri Huchard – 75018 Paris

Tel: +33 1 57 27 77 36

Fax: +33 1 57 27 75 21

Email: anthony.cousien@inserm.fr

Abbreviations

CHC: Chronic hepatitis C

DAA: Direct-acting antiviral

GDP: Gross domestic product

ICER: Incremental cost-effectiveness ratio

HCC: Hepatocellular carcinoma

HCV: Hepatitis C virus

LY: Life year

NSP: Needles and syringes provision programs

OST: Opioid substitution therapies

PWID: People who inject drugs

p.y.: Person-year

QALY: Quality-adjusted life year

sd: Standard deviation

TasP: Treatment as Prevention

Keywords: Hepatitis C; People who inject drugs; modelling; cost-effectiveness; direct-acting antiviral

ABSTRACT

Background and aims: Direct-acting antivirals (DAAs) represent an opportunity to improve Hepatitis C virus (HCV) care cascade. This, combined with improved harm reduction interventions may lead to HCV elimination especially in people who inject drugs (PWID). We assessed the effectiveness/cost-effectiveness of improvements in harm reduction and chronic hepatitis C (CHC) care cascade in PWID in France.

Methods: We used a dynamic model of HCV transmission and CHC natural history and evaluated: improved needle/syringe programs-opioid substitution therapies, faster diagnosis/linkage to care, earlier treatment initiation, alone and in combination among active PWID (mean age=36). Outcomes were: life expectancy (LE) in discounted quality-adjusted life-years (QALYs); direct lifetime discounted costs; incremental cost-effectiveness ratio (ICER); number of infections/reinfections.

Results: Under the current practice, LE was 15.846 QALYs, for a mean lifetime cost of €20,762. Treatment initiation at F0 fibrosis stage alone was less effective and more costly than faster diagnosis/linkage to care combined with treatment initiation at F0, that increased LE to 16.696 QALYs, decreased new infections by 37%, with a ICER=€5,300/QALY. Combining these interventions with harm reduction improvements was the most effective scenario (LE=16.701 QALYs, 41% decrease in new infections) but was not cost-effective (ICER= €105,600/QALY); it became cost-effective with higher initial HCV incidence rates and lower harm reduction coverage than in our base-case scenario.

Conclusion: This study illustrated the high effectiveness, and cost-effectiveness, of a faster diagnosis/linkage to care together with treatment from F0 with DAAs. This scenario, corresponding to a "Test and treat" strategy, should play a central role both in improving the LEs of HCV-infected patients, and in reducing HCV transmission.

INTRODUCTION

Chronic hepatitis C (CHC) 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 programs (NSP). However, HCV seroprevalence in this population remains around 70% [3]. Although 86% of active PWID report having been on OST during the last six months [4] improvements are still needed in harm reduction area, concerning access to injection equipment and safer environments for injecting practices. Up to 33% of PWID report difficulties to access to sterile syringes [3] and 54% of active PWID declared having done their last injection in public spaces [4]. 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 [5-12]. 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 [13]. Harm reduction strategies were, however, not considered in that analysis. Moreover cost and cost-effectiveness of these strategies were not considered. The cost of the new therapies (€28,730 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 with the idea of achieving HCV elimination in the future.

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 previously developed stochastic dynamic model [13]. In this model, each PWID has an 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. The latter is modeled using a random graph with a household structure, i.e. small groups of strongly connected PWID in the population, which can themselves be connected together (supplementary material S1). The liver disease's progression related to CHC was modeled taking into account fibrosis progression from F0 to F4, cirrhosis complications (decompensation and hepatocellular carcinoma (HCC)), death related to HCV infection (Figure 1.C.) and hepatic transplants for HCV complications, which are associated with high costs [14]. Finally, the model includes the status of each PWID according to harm reduction (Figure 1.A.).

We assumed the population with constant size but not closed: each PWID leaving the population during the simulation is replaced by a new, susceptible one.

Input Parameters

Parameters values were provided by a literature review, or fitted when no information was available. The key input parameters are presented in Table 1, and the complete table for the transition parameters and the initial population distribution are presented in Supplementary Material S1. The initial incidence of HCV in this PWID population was estimated at 12/100 person-years (p.y.) [15, 16], and we

fitted the infection rate to this initial value using Approximate Bayesian Computation [17, 18]. We assumed an average duration of two years between the PWID individual's first injection and their entry into an NSP program, as this duration was not available in literature. 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 per year [19], 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 [20]. The transition parameters and the initial distribution of the population in the model were mainly derived from ANRS-Coquelicot study data, an HCV-seroprevalence cross-sectional survey conducted among drug users in France [3, 4, 13, 21].

Input parameters for the social-network model were estimated by Approximate Bayesian Computation [17, 18], using data for a population of PWID in Melbourne, Australia [22], due to the absence of local data in France (supplementary information S1). 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 [23].

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 [24, 25]. To the latter, we added the cost of opioid substitution therapies and needles [19, 24-26]. Costs associated with HCV testing were also included. Costs associated with HCV were obtained from a study on healthcare consumption in CHC in France (Table 2) [14]. Finally, the cost of the new DAAs was set at €28,730, which is the cost of a treatment course for several DAAs in France [27].

We used health utilities estimated from a cross-sectional study HCV-infected individuals in France, but who were not necessarily PWID [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 CHC cascade of care, and in treatment-initiation criteria. Table 3 presents the detailed scenarios.

Outcomes

The outcomes were estimated for the initial cohort of PWID. Incident PWID were not taken into account. We performed 500 simulations for each scenario. For each simulation, the average lifetime costs (in 2015 euros), 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 accordingly to French guidelines for cost-effectiveness analysis [29]. The incremental cost-effectiveness ratio (ICER) was estimated in euros/QALY. In absence of a cost-effectiveness threshold in French guidelines[29], we used the World Health Organization guidelines [30], a scenario was considered as very cost-effective if the ICER was below French GDP/capita (around €33,000)[31], 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.

Sensitivity analysis

The model parameters were fixed to a single value for the main analysis, and the standard deviations given in the results only reflect the uncertainty due to the stochasticity of the model. To assess the impact of the uncertainty relying on the parameters values on the results, we performed sensitivity analyses for some key parameters. We changed the initial HCV incidence from 12/100 p.y. in the main analysis: first to 22/100 p.y. (Montréal, Canada [32, 33], and then to 42/100 p.y. (London, United-Kingdom)[34]. Moreover, we changed the mean value for time to diagnosis from 1.25/1.45 years: first to 2.0 years (Montréal, Canada [32, 33], and then to 7.8 years (London, United-Kingdom)[35]. 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 assessed the impact of utilities on the analyses by using utilities estimated from an HCV-infected German population with dual therapy (Table S17) [36, 37]. We also estimated the impact of a 25%, 50% and 75% decrease in the treatment cost. Finally, we assessed the sensitivity of the results to the connectivity of the social-network model using a "low connectivity" scenario and a "high connectivity" scenario: in these scenarios, the probabilities of linking 2 individuals in the random graph model were set respectively to the lower bounds and upper bounds of their confidence intervals (see Supplementary Material S1).

Manuscript approval

All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Main analysis

Results of the main analysis are presented Table 4. Figure 2 shows the efficiency curve. 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 €20,762 and an adjusted average life expectancy of each person was 15.846 QALYs. For the overall cohort of 10,480 people, the total number of HCV infections was estimated at 3,461, among which there were 992 reinfections following a previous SVR. An improvement in harm reduction interventions in S2 (improved harm reduction interventions) led to a moderate increase in adjusted life expectancy, which was estimated at 15.864 QALYs. Meanwhile, S4 (improved testing and linkage to care) increased the adjusted average life expectancy to 16.083 QALYs. In S3, we initiated treatment from F0 instead of F2. The adjusted average life expectancy increased to 16.382 QALYs, and costs increased (€24,566). However, all the previous scenarios yielded a higher incremental cost-effectiveness ratio than S5, in which we combined the improvements made in strategy S4 with a treatment initiation at F0. This situation corresponds to extended dominance. S5 led to an adjusted life expectancy of 16.694 QALYs, and decreased the number of new infections in the population to 2,176 for a lifetime cost of €25,223. This scenario was also very cost-effective, with an ICER of €5,300/QALY compared with S1.

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 (+0.007 QALYs) for an ICER of €105,600/QALY. This scenario was also the one that yielded the lowest number of infections, which fell to 2,025.

When we considered the incremental cost-effectiveness/life years saved, rather than QALY saved, we found S4 (improved testing/linkage to care) to be the most cost-effective strategy (=0.092LY 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 (€198,000/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, S3, where we improved testing and linkage to care, became an efficient scenario when we applied a 75% decrease in the treatment cost (€7,180 vs. €28,730, Table S7) to our scenarios; S3 became the second least expensive scenario (after S1), with a lifetime cost of €17,490 vs. €16,690 in S1. The most effective scenario, S6, which is S3 plus treatment from F0 and an improvement in harm reduction measures, remained not cost-effective under this scenario: ICER= €133,400/QALY.

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 relatively to other strategies (see Figure 2 and Tables S8 to S9). However, the efficiency of S6, which combined improvements in harm reduction interventions and improvements in testing/linkage to care with treatment as of F0 increased with the initial incidence. For an initial incidence of 22/100 p.y. (vs. 12/100 p.y in the main analysis), the ICER vs. S5 was €45,500/QALY (vs. €105,600/QALY in the main analysis). For an initial incidence of 42/100 p.y., there was an extended dominance of S5 by S6.

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: time from "difficult access to injecting equipment" to "NSP" from two years to three years, the transition time from NSP to NSP+OST from one year to two years, initial distribution at NSP=40%, vs. 30% in the main analysis, and at NSP+OST=45%, vs. 50% in the main analysis. Under these conditions, we observed a higher impact of improvements in harm reduction-interventions (S2) on the number of HCV infections (8.4% of infections avoided compared with S1 vs. 4.3% in the main analysis). Still, the impact on the adjusted life expectancy remained low (+0.031 QALYs compared with S1 vs. +0.018 QALYs in the main analysis). However, the scenario is dominated (i.e. more expensive, but less effective) by S4 (improvement in the HCV testing/linkage to care). Regarding the social network, the results remained similar when we increased or decreased the connectivity in the random graph model. The only remarkable change is that the improvement of testing and linkage to care (S4) was no more extended

dominated by S5 (combination of improvement in testing, linkage to care and treatment from F0) with an ICER=€5,900/S1.

DISCUSSION

In this study, we used a dynamic, individual-based model including a social network and a model of natural history of CHC to assess the cost-effectiveness of improvements in harm reduction measures and in the CHC cascade of care, using new DAAs, in the population of PWID in France with the idea of evaluating different strategies to achieve HCV elimination. 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 testing/linkage to care and treatment-initiation criteria (S6), only slightly increased the adjusted average life expectancy (+0.018 QALYs and +0.07 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 (16.083 QALYs vs. 15.846 in the current practice). Thirdly, treating from F0 considerably increased the lifetime cost, but was very effective (adjusted life expectancy=16.382 QALY). However, S5, combining the treatment from F0 with an improvement in testing and linkage to care, was very cost-effective and dominated (extended dominance) all the previous scenario (ICER=€5,300/QALY, vs. S1). Moreover, this strategy dramatically decreased the number of new infections in the population: around 2,200 over the lifetime of the initial population of the model vs. 3,500 in the current practice. Adding harm reduction improvements in this scenario was slightly effective, but not cost-effective (ICER=€105,600/QALY, vs. S5). However, it minimized the number of infections occurring during the simulations, which reached 2,000.

In our main analysis, improving access to NSP and OST had a limited effectiveness. This was mainly due to the already high access to OST in France, with 86% of PWID reporting having been on OST during the last 6 months in ANRS-Coquelicot study [4]. In addition, data we used for HCV epidemiology in PWID corresponded to people recruited in harm reduction facilities, treatment centers, and accommodation facilities. Thus, both the effectiveness and the coverage rate used for these interventions in our analysis may be optimistic. However, in the sensitivity analysis, when we used a higher initial HCV incidence rates, corresponding to estimates from PWID populations in

Montréal or London, the scenario combining an improvement in harm reduction, an improvement in the HCV testing/linkage to care, and an initiation of treatment as of F0, was cost-effective when compared to a situation that only included an improvement in HCV testing/linkage to 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 an efficient and cost-effective way to complete a TasP strategy.

This study illustrated the high effectiveness, and cost-effectiveness, of improving both testing and linkage to care together with a treatment from F0. This scenario, which corresponds to a "Test and treat" 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 [13], 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. 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. With the availability of new DAAs, in addition to treating early HCV-infected patients, we should increase testing to diagnose HCV-infected PWIDs earlier and link these patients to care.

In this analysis, we found that a strategy of treatment as prevention, combining improvements in testing and linkage to 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 €47 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 [38]. 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, 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 [39], drug related morbidities [40], or drug related crimes [41]. This could have make harm reduction strategies more cost-effective.

In conclusion, improvement in testing and linkage to care together with an access to treatment regardless of the stage of HCV disease, namely "Test and treat" strategy, was, in our analyses, the critical intervention for increasing PWID life expectancy in France, and it would be cost-effective. It would also dramatically decrease new HCV infections. Depending on the HCV incidence in PWID, completing this strategy by an improvement in harm reductions that may have an impact on safer environments for injecting practices could be efficient and critical. Decreasing the cost of the new antiviral drugs would facilitate the implementation of these strategies by decreasing their budgetary impact.

CONFLICT OF INTEREST

SDB has received grants from Roche, Janssen-Cilag and Schering-Plough, and received consultancy honoraria from Abbvie, Bristol-Myers Squibb, Gilead, HEVA, Janssen, Merck, Public Health Expertise and GlaxoSmithKline. YY received travel grants, honoraria for presentations at workshops and consultancy honoraria from Abbott, Bristol-Myers Squibb, Gilead, Merck, Roche, Tibotec and ViiV Healthcare. None of the other authors report any association that might pose a conflict of interest.

ACKNOWLEDGMENTS

This work was supported by the French Agence Nationale de Recherche sur le Sida et les Hépatites virales (ANRS, http://www.anrs.fr), grant number 95146. Viet Chi Tran was supported in part by the Labex CEMPI (ANR-11-LABX-0007-01). Anthony Cousien was supported in part by PoC-HCV, a European research project supported by the European Commission, grant number 601851. Jean-Stéphane Dhersin and Viet Chi Tran were supported by the ANR project CADENCE (ANR-16-CE32-0007).

We would like to thank the scientific advisory board of this study for their helpful advice: Elisabeth Avril, Patrizia Carrieri, Elisabeth Delarocque-Astagneau, Véronique Doré, Albert Herszkowicz, Christine Larsen, Gilles Pialoux, Philippe Sogni, Elisabeta Vergu. We thank Michael Schwarzinger for providing the estimates of healthcare cost in decompensated cirrhosis. We also thank Margaret E. Hellard for her helpful advice and David A. Rolls for sending us the data of the adjacency matrix of the graph used for the construction of the social network model [22]. Finally, we thank Caroline Lions for providing us information about harm reduction in France.

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

ReferencesUncategorized References

1. WHO. Hepatitis C fact sheet n°164, 2013.
2. Mathei C, Shkedy Z, Denis B, et al. Evidence for a substantial role of sharing of injecting paraphernalia other than syringes/needles to the spread of hepatitis C among injecting drug users. J Viral Hepat 2006;13:560-70.
3. Weill-Barillet L, Pillonel J, Semaille C, et al. Hepatitis C virus and HIV seroprevalences, sociodemographic characteristics, behaviors and access to syringes among drug users, a comparison of geographical areas in France, ANRS-Coquelicot 2011 survey. Revue d'epidemiologie et de sante publique 2016.
4. Jauffret-Roustide M, Chollet A, Santos A, et al. Theory versus practice, bacteriological efficiency versus personal habits: A bacteriological and user acceptability evaluation of filtering tools for people who inject drugs. Drug Alcohol Rev 2017.
5. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483-93.
6. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370:1879-88.
7. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet 2015;385:1075-86.
8. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878-87.
9. Naggie S, Cooper C, Saag M, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. The New England journal of medicine 2015;373:705-13.
10. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015;61:1127-35.
11. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973-82.
12. Reddy KR, Zeuzem S, Zoulim F, et al. Simeprevir versus telaprevir with peginterferon and ribavirin in previous null or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): a randomised, double-blind, non-inferiority phase 3 trial. The Lancet. Infectious diseases 2015;15:27-35.
13. Cousien A, Tran VC, Deuffic-Burban S, et al. Hepatitis c treatment as prevention of viral transmission and liver-related morbidity in persons who inject drugs. Hepatology 2015.
14. Schwarzinger M, Deuffic-Burban S, Mallet V, et al. Lifetime costs attributable to chronic hepatitis C from the French healthcare perspective (Anrs N°12188). Journal of Hepatology 2013;58:S21-22.
15. Brouard C, Le Strat Y, Larsen C, et al. The undiagnosed chronically-infected HCV population in France. Implications for expanded testing recommendations in 2014. PloS one 2015;10:e0126920.
16. Leon L, Kasereka S, Barin F, et al. Age- and time-dependent prevalence and incidence of hepatitis C virus infection in drug users in France, 2004-2011: model-based estimation from two national cross-sectional serosurveys. Epidemiol Infect 2017;145:895-907.
17. Blum MG, Tran VC. HIV with contact tracing: a case study in approximate Bayesian computation. Biostatistics 2010;11:644-60.
18. Marin J-M, Pudlo P, Robert CP, et al. Approximate Bayesian computational methods. Statistics and Computing 2012;22:1167-1180.
19. Brisacier A, Collin C. Données récentes relatives aux traitements de substitution aux opiacés - Analyse des données de remboursement concernant l'échantillon généraliste des bénéficiaires en 2011. In: OFDT, ed, 2013.

20. Turner KM, Hutchinson S, Vickerman P, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. Addiction 2011;106:1978-88.
21. Jauffret-Roustide M, Le Strat Y, Couturier E, et al. A national cross-sectional study among drug-users in France: epidemiology of HCV and highlight on practical and statistical aspects of the design. BMC Infect Dis 2009;9:113.
22. Rolls DA, Daraganova G, Sacks-Davis R, et al. Modelling hepatitis C transmission over a social network of injecting drug users. J Theor Biol 2011;297C:73-87.
23. Rolls DA, Wang P, Jenkinson R, et al. Modelling a disease-relevant contact network of people who inject drugs. Social Networks 2013;35:699-710.
24. Cadet-Taïrou A, Dambélé S. Les CAARUD en 2010 - Analyse des rapports d'activité annuels standardisés ASA-CAARUD. In: OFDT, ed, 2014.
25. Palle C, Rattanatray M. Les centres de soins, d'accompagnement de de prévention en addictologie en 2010 - situation en 2010 et évolutions sur la période 2005-2010. In: OFDT, ed, 2013.
26. Comité économique des produits de santé. Medicprix (Prix des médicaments).
27. AFEF. Recommandations AFEF sur la prise en charge de l'hépatite virale C. . In: d'Hépatologie SF, ed, 2017.
28. Schwarzinger M, Cossais S, Deuffic-Burban S, et al. EQ-5D utility index in french patients with chronic hepatitis C (CHC) infection: severe comorbidities and perceived progression of CHC infection matter more than actual liver disease stage. J Hepatol 2015 2015;62:S605.
29. Haute Autorité de Santé. Choix méthodologiques pour l'évaluation économique à la HAS. 2011.
30. World Health Organization. WHO guide to cost-effectiveness analysis. 2003.
31. World Bank. GDP per capita.
32. Leclerc P, Morissette C, Tremblay C, et al. Le volet montréalais du Réseau SurvUDI: Direction de la santé publique, Agence de la santé et des services sociaux de Montréal, 2011.
33. Cousien A, Leclerc P, Morissette C, et al. The necessity of a treatment scale-up to impact HCV transmission in people who inject drugs in Montréal, Canada: a modelling study. Submitted 2016.
34. Judd A, Hickman M, Jones S, et al. Incidence of hepatitis C virus and HIV among new injecting drug users in London: prospective cohort study. BMJ 2005;330:24-5.
35. Martin NK, Hickman M, Miners A, et al. Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons. BMJ Open 2013;3.
36. Torrance GW, Feeny DH, Furlong WJ, et al. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996;34:702-22.
37. Siebert U, Sroczynski G, Wasem J, et al. Using competence network collaboration and decision-analytic modeling to assess the cost-effectiveness of interferon alpha-2b plus ribavirin as initial treatment of chronic hepatitis C in Germany. Eur J Health Econ 2005;6:112-123.
38. Martin NK, Hickman M, Hutchinson SJ, et al. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57 Suppl 2:S39-45.
39. MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. The International journal on drug policy 2014;25:34-52.
40. Cornish R, Macleod J, Strang J, et al. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ 2010;341:c5475.
41. Bukten A, Skurtveit S, Gossop M, et al. Engagement with opioid maintenance treatment and reductions in crime: a longitudinal national cohort study. Addiction 2012;107:393-9.

42. Cadet-Taïrou A. Résultats ENa-CAARUD 2010, profils et pratiques des usagers: OFDT, 2012.
43. Dupouy J, Bez J, Barsony J, et al. [Opiate substitution treatment's cycles in a five-year followed-up cohort in ambulatory practice]. Therapie 2013;68:155-61.
44. Dupouy J, Dassieu L, Bourrel R, et al. Effectiveness of drug tests in outpatients starting opioid substitution therapy. Journal of substance abuse treatment 2013;44:515-21.
45. Ndiaye B. Facteurs de risque de l'accès tardif aux soins et de la perte de vue chez les patients infectés par le VIH suivis à Bruxelles et dans la région Nord Pas-de-Calais. Volume Thèse de doctorat en Épidémiologie: Université de Lille 2, 2009.
46. Foster GR, Pianko S, Brown A, et al. Efficacy of Sofosbuvir Plus Ribavirin With or Without Peginterferon-alfa in Patients With HCV Genotype 3 Infection and Treatment-Experienced Patients with Cirrhosis and HCV Genotype 2 Infection. Gastroenterology 2015.
47. Sutton AJ, Gay NJ, Edmunds WJ, et al. Modelling the force of infection for hepatitis B and hepatitis C in injecting drug users in England and Wales. BMC Infect Dis 2006;6:93.
48. Hagan H, Pouget ER, Des Jarlais DC, et al. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. Am J Epidemiol 2008;168:1099-109.

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, see [13]
Acute hepatitis	0%*	
Non-diagnosed chronic hepatitis	9.2%	ANRS-Coquelicot, see [13]
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, 42-44]
NSP	20%*	
NSP+OST	50%*	
Infection rate by injecting partner	0.184 y^{-1}partner^{-1}	Fitted by ABC to have a 12/100 p-y baseline incidence [15, 16] – see Supplementary Material S1
Relative risk of infection when under		
NSP	0.5	[20] For a high-coverage needle program (i.e. where a sterile syringe is available for 100% of the injections of the user)
NSP+OST	0.21	
Transition from "no harm reduction intervention" to NSP	2y*	[3, 42-44]
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	Previously estimated from ANRS Coquelicot data, see [13, 21]
Former PWID	1.45 y	
Average time before linkage to care	2.6 y	Previously fitted from ANRS Coquelicot data using ABC, see [13, 21]
Loss to follow-up rate	14%/y	[45]
Treatment: incoming DAAs regimens		
Duration	12 weeks	[5-7, 10-12, 46]
SVR rate – treatment naïve – all genotypes- clinical trials	95%	

* Hypothesis
ABC: Approximate Bayesian Computation
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)[14]

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	Mean time before access to NSP after injection initiation (years)	Mean time before access to OST when in NSP (years)	Mean time to diagnosis (active/inactive PWID) (years)	Mean time to linkage to care (years)	Lost to Follow-up (%/year)	Treatment eligibility	Remark
S1 – Reference (current practice)	2	1	1.25/1.45	2.6	14	F2→F4	Comparator
S2 – Improved harm reduction interventions	1	0.5	1.25/1.45	2.6	14	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 [47, 48], faster access to NSP or OST could help to reduce infections.
S3 – Treatment initiation: fibrosis ≥ F0	2	1	1.25/1.45	2.6	14	F0→F4	All diagnosed individuals who have been linked to care, receive treatment (excluding those with a cirrhosis complication).
S4 – Improved testing/linkage to care	2	1	0.5	0.5	5	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	1	0.5	0.5	5	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	2	0.5	0.5	5	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)	20,762 (184)	18.402 (0.055)	15.846 (0.055)	3,461 (85)	992 (45)		
S2 – Improved risk reduction interventions	21,731 (184)	18.405 (0.056)	15.864 (0.055)	3,319 (83)	949 (42)	Extended dominance	Extended dominance
S4 – Improved testing/linkage to care	22,200 (155)	18.494 (0.057)	16.083 (0.057)	3,491 (87)	1,191 (49)	15,600	Extended dominance
S3 – Treatment initiation: fibrosis ≥F0	24,566 (242)	18.424 (0.054)	16.382 (0.054)	3,216 (112)	1,470 (70)	Dominated	Extended dominance
S5 – Combined S3 and S4	25,223 (227)	18.509 (0.055)	16.694 (0.054)	2,176 (100)	1,050 (65)	Extended dominance	5,300
S6 – Combined S2 and S3 and S4	25,962 (234)	18.513 (0.055)	16.701 (0.054)	2,025 (99)	971 (62)	198,000	105,600

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 [29]: 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. Dominated=more expensive and less effective. Extended dominance=at least one more expensive scenario is more cost-effective.

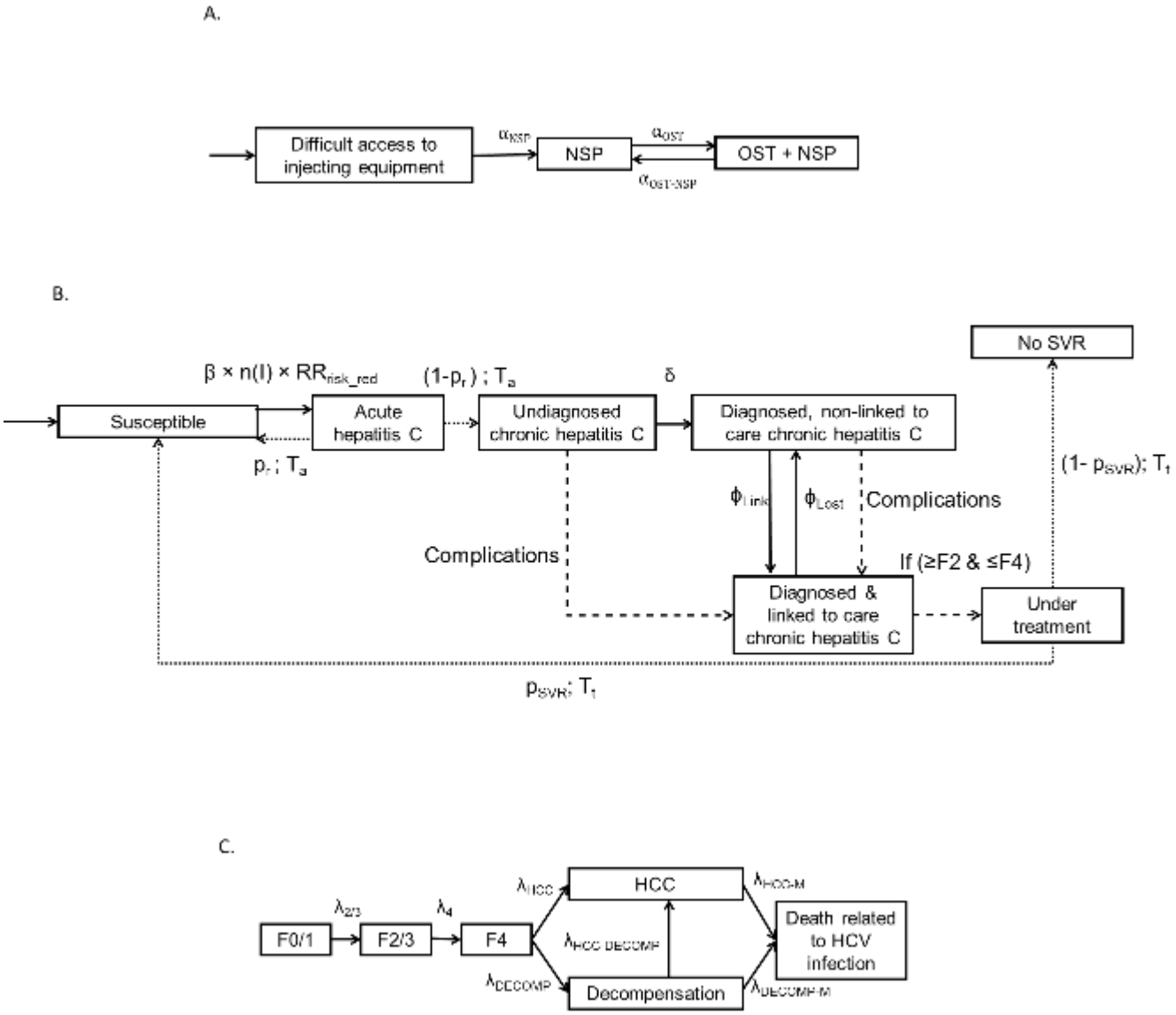

Figure 1. Dynamic model for harm reduction, HCV transmission and care, and chronic hepatitis C natural history. A. Harm reduction interventions. NSP=Needle and syringe program, OST=Opioid substitution therapy. New PWID enter the model in the "Difficult access to injecting equipment" compartment. Each transition occurs according to exponential law. $\alpha_{OST\text{-}NSP}$ 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. $\lambda_{TP\text{-}D}$ depends on the time since transplant: the mortality rate is higher during the first year.

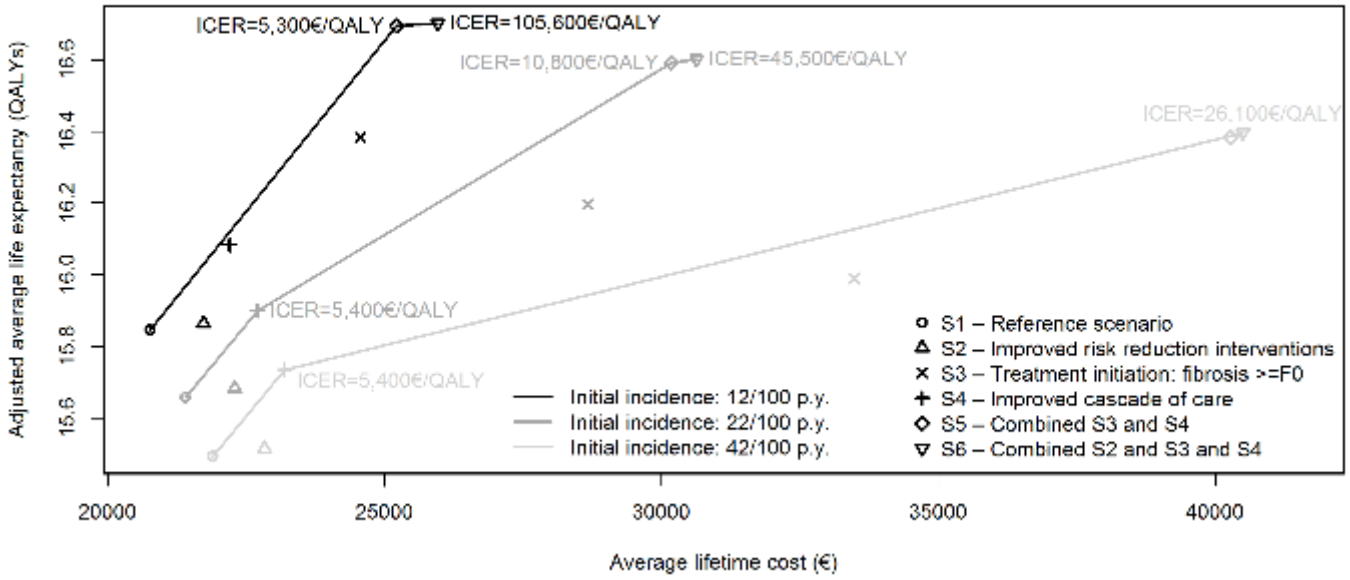

Figure 2. Efficiency curve representing the results of the main analysis (in black) and the sensitivity analysis, when varying the initial incidence to 22/100 person-years (in dark grey) and 42/100 person-years (in light grey). Each dot represents a scenario, and the dots are linked for non-dominated 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.