

Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility

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Background & Aims: Hepatitis C virus antiviral treatment is effective for individual patients but few active injecting drug users are treated. We considered the utility of antiviral treatment for primary prevention of hepatitis C.

Methods: A hepatitis C transmission model among injecting drug users was developed, incorporating treatment (62.5% average sustained viral response) with no retreatment after initial treatment failure, potential re-infection for those cured, equal genotype setting (genotype 1:genotype 2/3), and no immunity. In addition, we examined scenarios with varied treatment response rates, immunity, or retreatment of treatment failures.

Results: In the baseline scenario, annually treating 10 infections per 1000 injecting drug users results in a relative decrease in hepatitis C prevalence over 10 years of 31%, 13%, or 7% for baseline (untreated endemic chronic infection) prevalences of 20%, 40%, or 60%, respectively. Sensitivity analyses show that including the potential for immunity has minimal effect on the predictions; prevalence reductions remain even if SVR is assumed to be 25% lower among active IDU than current evidence suggests; retreatment of treatment failures does not alter the short-term (<5 years) projections, but does increase treatment gains within 20 years; hepatitis C free life years gained from treating active injecting drug users are projected to be higher than from treating non-injecting drug users for prevalences below 60%.

Conclusions: Despite the possibility of re-infection, modest rates of hepatitis C treatment among active injecting drug users could effectively reduce transmission. Evaluating and extending strategies to treat hepatitis C among active injectors are warranted.

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Introduction

Hepatitis C virus (HCV) is a blood-borne disease which causes significant morbidity and mortality worldwide [1]. Injecting drug use is the primary mode of transmission in developed countries [2], with 15–90% of injecting drug users (IDU) testing positive for HCV antibodies [3].

Current interventions for reducing HCV transmission focus on reducing the frequency of injecting and syringe sharing/unsafe injection [2,4]. These may have reduced HCV transmission in some settings [5–7], but there is no evidence for substantial reductions in HCV prevalence.

HCV antiviral treatment with peginterferon alfa and ribavirin is the standard care for chronic HCV, with a 50–85% cure rate (sustained viral response, SVR) depending on genotype [8]. In many countries, including the US and UK, treatment is recommended for all patient groups (including IDU) and is considered cost effective [8–11]. However, few current IDU have ever been treated (<3–4%) [12,13] because physicians are reluctant to treat due to concerns about treatment compliance and re-infection [14–16]. However, the limited information available from studies suggests that current IDU exhibit similar response rates to treatment [17–19] and compliance [18,20,21] when compared to non- or ex-IDU. Furthermore, there are little data on re-infection after successful treatment, except from small scale studies which report low rates in the first year [22].

In this paper, we used a mathematical model to project the potential impact HCV treatment could have on HCV prevalence among active IDU while allowing for re-infection.

Materials and methods

Mathematical model

The model shown in Fig. 1 describes the transitions between five groups of IDU: susceptible (including those who clear acute infection but are not immune), chronically infected who are naïve to treatment or re-infected (including those in the acute stage who progress to chronic infection), chronically infected who have failed treatment (non-SVR), currently in treatment, and immune. We are

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Abbreviations: HCV, hepatitis C virus; IDU, injecting drug users; SVR, sustained viral response; US, United States; UK, United Kingdom; LYG, life years gained.



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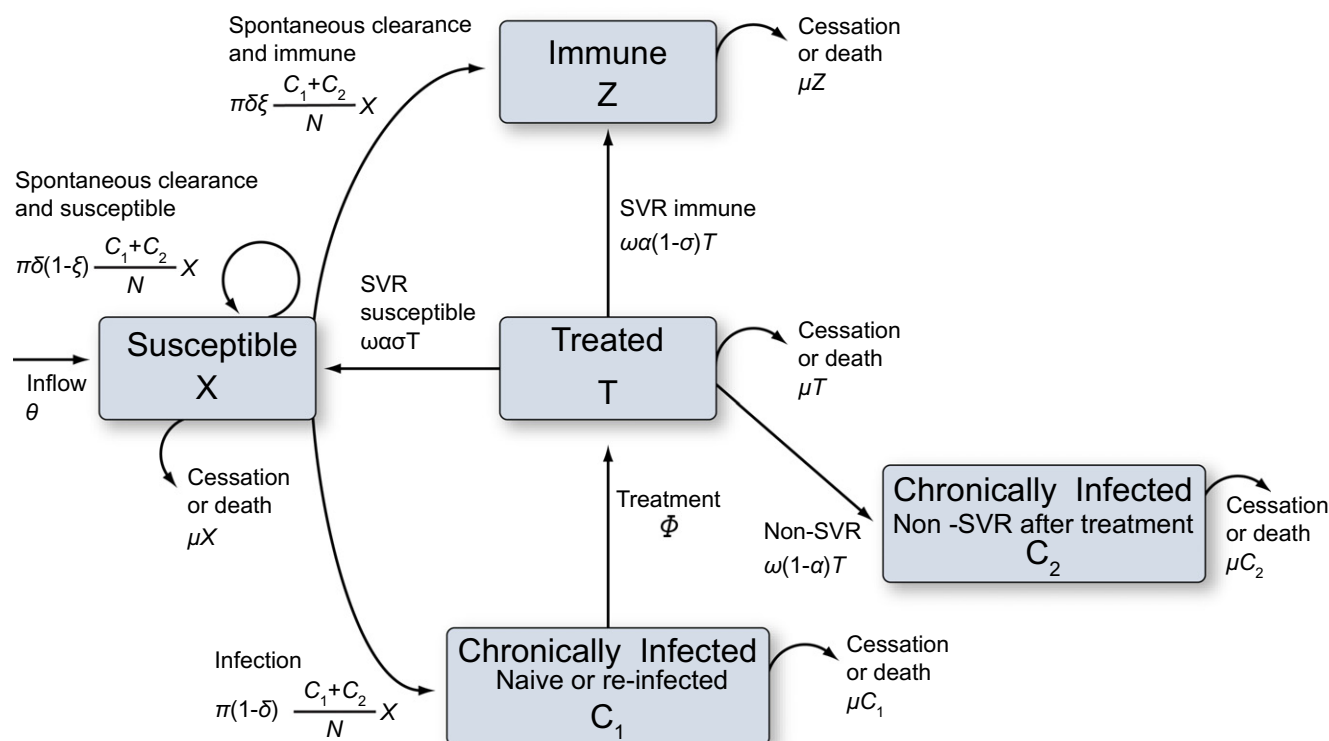


Fig. 1. Schematic for the mathematical model. The parameters used are: θ (new injector inflow rate), π (infection rate per year), δ (proportion of acute infections that spontaneously clear), ξ (proportion of spontaneously cleared infections resulting in immunity), Φ (treatment number), ω (1/treatment duration), α (proportion of treated infections cured), σ (1-proportion treated infections resulting in immunity), and μ (rate of leaving IDU population due to cessation of injections or death).

aware that the concept of sterilizing immunity following HCV infection is controversial and so assume no immunity in our baseline scenarios. All parameters specified are average rates or proportions (as noted in Table 1).

New IDU enter the susceptible pool at a fixed rate ' θ ', and leave all compartments (due to death or ceasing injection) at a per capita rate ' μ '. The rate of infection of susceptible IDU is proportional to the number of susceptibles, the fraction of the population chronically infected, and the infection rate ' π '. Acute infection spontaneously clear in a proportion ' δ ', a fraction of which becomes immune ' ξ ' ($\xi = 0$ in baseline scenario). The remaining infected (proportion ' $1 - \delta$ ') progress to chronic infection. Due to the relatively short duration of the acute stage [23] and the small proportion that spontaneously clear infection, the number of infections caused by IDU with acute HCV who spontaneously clear is likely to be small, and is neglected in this model.

Chronic infected IDU who are naïve to treatment or re-infected are recruited into the treatment at a fixed rate (Φ chronically infected IDU per 1000 IDU annually) unless the number of those infected is driven below Φ , whereupon all chronically infected IDU are treated. This fixed treatment number aims to provide a realistic scenario of potential treatment capacity and recruitment. IDU remain in treatment for an average $1/\omega$ and during this short period are assumed to be non-infectious (due to significantly reduced viral load [24,25]) and access to opiate substitution therapy and sterile equipment while on treatment). A proportion ' α ' of those treated are cured (achieve SVR) and in the baseline scenario become susceptible again. Those who are not cured (fraction ' $1 - \alpha$ ') move to the chronically infected non-SVR after treatment compartment. These IDU cannot be retreated. We explored the possibility of retreatment in an alternative scenario.

As most current HCV epidemics are not in the epidemic phase, we allowed the model to reach a stable endemic state prior to initiating treatment. Parameter values were obtained from treatment guidelines and recent published data (Table 1). We assumed no change in the infection rate or clearance/treatment success rates for those who cleared infection (spontaneously or through treatment).

We projected the relative decrease in chronic infection prevalence after different time periods with varying treatment rates, in settings with a range of untreated endemic chronic infection prevalences (referred to as 'baseline chronic prevalence').

Additionally, the relative impact of treating ex- or non-IDU compared to active IDU (who are at risk of re-infection but may prevent future transmissions) was evaluated by estimating the incremental number of life years free of HCV generated per treatment initiated (details in Supplementary data). A multivariate regression analysis identified which parameters were responsible for most uncertainty in the impact projections for a specific treatment scenario – 20 treated per 1000 IDU annually for 20 years at 40% baseline prevalence.

Model scenarios

Baseline scenario

In our general projections we assumed no immunity after spontaneous clearance or treatment. We did not allow retreatment for those who do not attain SVR, but allowed it for those that are successfully cured. To best represent the current genotype distribution in the UK, we assumed a 'mixed' genotype population, weighted half genotype 1 and half genotype 2/3. The US has a higher proportion of genotype 1 [9,26].

Alternative scenarios and uncertainty analysis

Different treatment efficacies

We investigated the effect of increasing or decreasing the average SVR by ~25% from the baseline estimate (from 62.5% to 45% or 80%), detailed in Table 2. This could either simulate different genotype distributions (from the 'mixed' baseline scenario to mainly genotype 1 (45% SVR) or genotype 2/3 (80% SVR)). Additionally, the 45% SVR simulation could describe a scenario where SVR is lowered in active IDU due to reduced completion or compliance.

Unrestricted treatment

We investigated the potential effect of retreatment while assuming a similar SVR in treatment naïve infections and first line treatment failures. This assumption was based on recent phase 3 trial findings showing Telaprevir with peginterferon

Table 1. Model parameters.

Model parameter definition	Symbol	Scenario	Value [Uncertainty Range]	Units	Source
Average leaving rate (cessation or death)	μ	All	0.085 ^a [0.05-0.2]	Per year	[37-40]
Average proportion of infections with SVR ^b	α_1	Genotype 1	0.45 [0.3-0.45]	-	[9, 26]
	$\alpha_{2/3}$	Genotype 2/3	0.8 [0.65-0.8]	-	
	α_m	Baseline ^c	0.625 ^d	-	
Average treatment duration	$1/\omega_1$	Genotype 1	0.5423 ^e	Per year	[9, 26]
	$1/\omega_{2/3}$	Genotype 2/3	0.4615		
	$1/\omega_m$	Baseline ^c	0.5019 ^f		
Average proportion of infections that spontaneously clear	δ	All	0.26 [0.22-0.29]	-	[41]
Average proportion of spontaneously cleared infections resulting in immunity	ξ	All	0 [0-0.25]	-	Little data, conservative assumption [42]
Average proportion of cured infections resulting in immunity	$1-\sigma$	All	0 [0-0.25]	-	Little data
Average new injector rate	θ	All	85	Per 1000 IDU annually	Given value to retain total population of 1000 IDU
Average infection rate per year	π	All	[0-0.95]	Per year	Varied to produce a range of baseline prevalences
Average treatment rate	ϕ	All	5-40	Per 1000 IDU annually	

^aBased on a cessation rate of 7.75% per year, and an IDU death rate of 0.75%. For the non-IDU models, the leaving rate is comprised only of the non-IDU death rate, about 1/8 that of the IDU (0.09%).

^bSVR: sustained viral response.

^cWeighted 50% genotype 1 and 50% genotype 2/3.

^dAverage of SVR proportions for genotypes 1 and 2/3: $0.5 \times \alpha_1 + 0.5 \times \alpha_{2/3}$. In the uncertainty analysis, baseline is calculated from the sampled LHS values of α_1 and $\alpha_{2/3}$.

^eWeighted average of treatment duration (48 weeks SVR, 12 weeks non-SVR) by SVR proportion: $(\alpha_1 \times 48 + [1 - \alpha_1] \times 12)/52$.

^fAverage of treatment duration for genotypes 1 and 2/3: $0.5 \times (1/\omega_1) + 0.5 \times (1/\omega_{2/3})$.

alfa and ribavirin has a high success rate (51%) among genotype 1 patients previously treated with peginterferon alfa and ribavirin who did not obtain SVR [27], and the anticipation that other future drugs will have similar effects. More details of this model are in the [Supplementary data](#) and [28].

Uncertainty analysis

Latin hypercube sampling of the parameter uncertainty ranges in [Table 1](#) was used to ascertain the uncertainty in the impact projections for the baseline scenario. Each parameter was sampled 500 times over a uniform distribution including the probability (0–25%) of immunity after spontaneous clearance or successful treatment. Some parameters were not sampled because their values were determined by the other sampled parameters. These include the new injector rate which was fitted to ensure a population of 1000 IDU. Likewise, the treatment duration was fitted from the sampled genotype success rates.

Results

Reduction in chronic prevalence

For an IDU population with 20% baseline chronic prevalence and treatment rates of 5, 10, 20, or 40 per 1000 IDU annually, the model predicts a 15%, 30%, 62%, and 72% reduction in chronic prevalence after 10 years, respectively ([Fig. 2](#)). These reductions in prevalence are at most halved for 40% baseline prevalence, and quartered for 60% prevalence.

[Fig. 3](#) shows how the impact projections could vary over time. For a 20% baseline chronic prevalence, annually treating 10 cases per 1000 IDU results in a 16% reduction in prevalence within 5 years, doubling to 30% after 10 years, and 57% after 20 years ([Fig. 3B](#)). In contrast, if the baseline prevalence was 40%, then the same treatment rate reduces prevalence by 8% after 5 years

Table 2. Model scenarios.

Model scenario	Immunity	Average SVR, α_m	Retreatment
Baseline scenario	None	62.5% ^a ($\alpha_1 = 45\%$ genotype 1, $\alpha_{2/3} = 80\%$ genotype 2/3)	None
Uncertainty analysis	Some: ($\xi = 1-\sigma = 0-25\%$)	At most reduced by 30% for each genotype: ($\alpha_1 = 31.5\%-45\%$, $\alpha_{2/3} = 56-80\%$)	None
SVR variation scenario	None	Varied by $\pm 28\%$: 45% ^b , 62.5% ^c , 80% ^d	None
Retreatment scenario	None	62.5% ^a ($\alpha_1 = 45\%$, $\alpha_{2/3} = 80\%$)	Allowed ^e

^{a,c}Weighted average of SVR proportions, 50% genotype 1 and 50% genotype 2/3, $\alpha_m = 0.5 \times \alpha_1 + 0.5 \times \alpha_{2/3}$.

^bIn this scenario, all are considered genotype 1, so $\alpha_m = \alpha_1 = 45\%$ and treatment duration is $\omega_m = \omega_1 = (\alpha_1 \times 48 + [1 - \alpha_1] \times 12)/52$.

^cIn this 'mixed' scenario, half are considered genotype 1 and half genotype 2/3. $\alpha_m = 0.5 \times \alpha_1 + 0.5 \times \alpha_{2/3}$ where $\alpha_1 = 45\%$ and $\alpha_{2/3} = 80\%$. Treatment duration is averaged at $\omega_m = 0.5 \times (1/\omega_1) + 0.5 \times (1/\omega_{2/3})$.

^dIn this scenario, all are considered genotype 2/3 so $\alpha_m = \alpha_{2/3} = 80\%$ and treatment duration is $\omega_m = \omega_{2/3} = 24/52$.

^eIn this scenario, there is no C_2 compartment, and all those who fail to attain SVR return to C_1 where they can be retreated.

and only 22% after 20 years. With a high 60% baseline prevalence, annually treating 10 cases per 1000 IDU may only achieve a 9% reduction in prevalence after 20 years.

If the treatment rate was 5 per 1000 IDU annually ([Fig. 3A](#)) then substantial prevalence reductions ($>20\%$) within 20 years only occur in populations with low baseline prevalences

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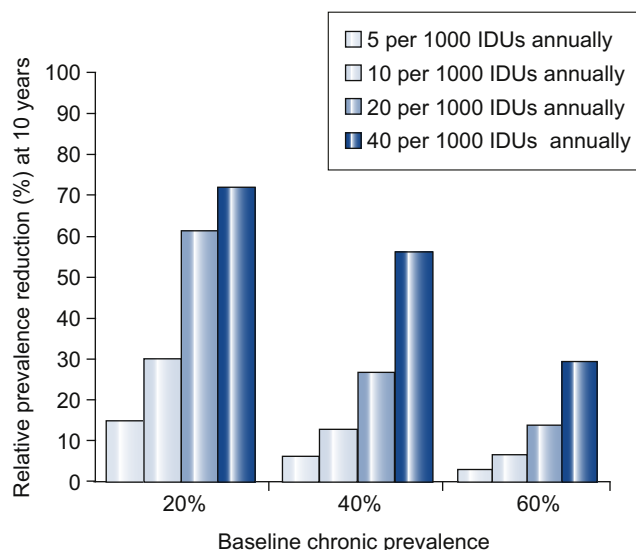


Fig. 2. Projected relative reduction in prevalence at 10 years for the baseline scenario (no immunity, mixed genotype) at different baseline prevalences and treatment rates. The figure shows the relative prevalence reduction from baseline chronic prevalence at 10 years. Baseline chronic prevalence is defined as untreated endemic chronic infection prevalence and is roughly equivalent to HCV antibody prevalence of 27%, 53%, and 80%, respectively.

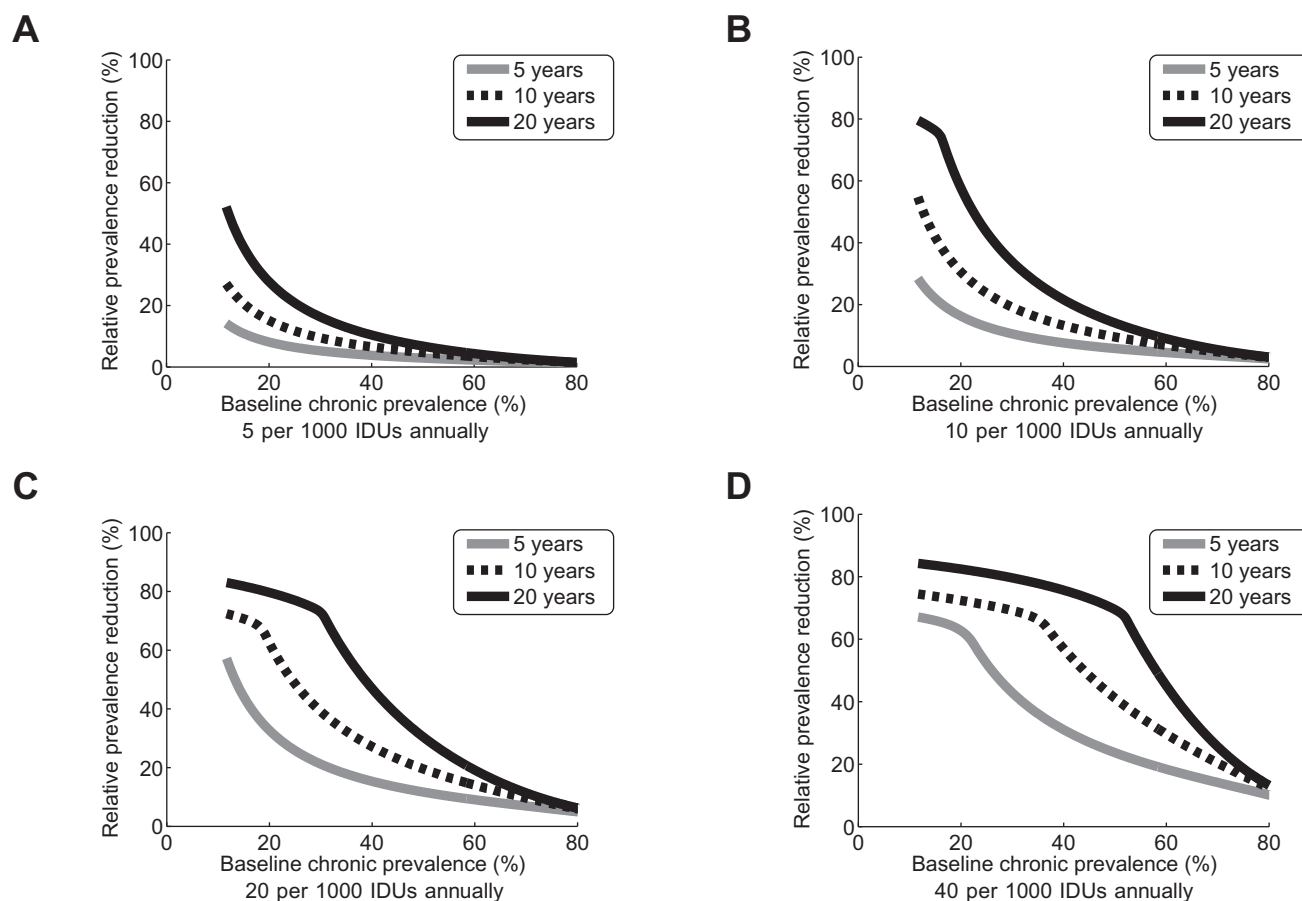


Fig. 3. Projected relative reduction in prevalence at 5, 10, and 20 years for the baseline scenario (no immunity, mixed genotype) at different baseline prevalences and treatment rates. The relative prevalence reduction from baseline chronic prevalence (vertical axis) is shown at 5 years (grey line), 10 years (black dashes), and 20 years (black line) for varying baseline untreated chronic prevalences (horizontal axis) and different treatment levels. Baseline chronic prevalence is defined as untreated endemic chronic infection prevalence.

($\leq 25\%$). In contrast, higher treatment rates (>20 per 1000 IDU annually) would be required to result in similar prevalence reductions in high prevalence settings ($>60\%$). Reductions in HCV incidence mirror the decrease in prevalence because fewer chronically infected IDU results in fewer new infections.

The prevalence reductions flatten off in the long-term (20 years) or for higher treatment rates (20–40 per 1000 IDU annually) due to the persistence of a non-responder population (Fig. 3C and D).

Comparing impact with treating non-IDU

Fig. 4 suggests that for baseline prevalences under 60%, the IDU intervention results in more HCV free life years gained (LYG) per person treated than for the ex/non-IDU intervention scenario, given equal SVR rates. Only at very high prevalences ($>60\%$) does the ex/non-IDU treatment intervention result in greater impact per treatment initiated, due to the high risk of re-infection in the IDU scenario at these prevalences. However, if treatment is 80% as effective in active IDU, greater impact is only seen with baseline prevalences less than 30% (Supplementary Fig. 1). Varying the treatment rate has minimal effect (data not shown).

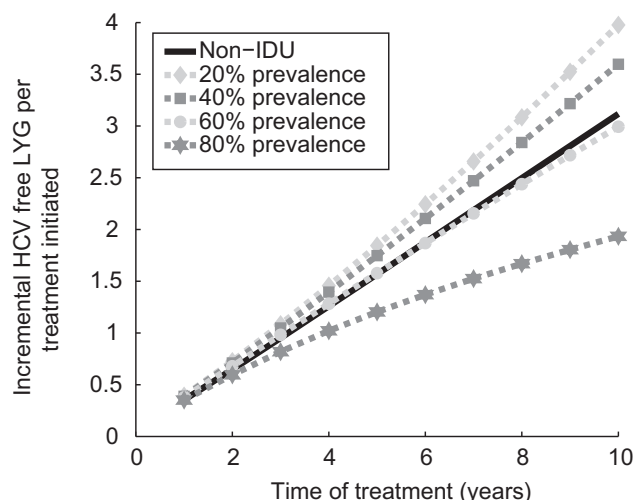


Fig. 4. Comparison of the incremental HCV free life years gained (LYG) per treatment initiated among a non-IDU (solid black line) or IDU population with different baseline chronic prevalences. Projections are given over 10 years and assume an annual treatment rate of 20 people per 1000 IDU. All projections assume baseline scenarios (restricted treatment, mixed genotype). Baseline chronic prevalence is defined as untreated endemic chronic infection prevalence.

Sensitivity and uncertainty analysis

Fig. 5 shows the results of the uncertainty analysis (based on an annual treatment rate of 20 per 1000 IDU) on the predicted reduction in prevalence, including the possibility of re-infection and lower SVR rates (parameter ranges from Table 1). Introduction of immunity has little impact on the projections (Fig. 5B). Overall, uncertainty increases as time progresses ($\pm 50\%$ after 20 years) and for higher treatment rates (not shown). The infection rate (π) and exit rate (μ) are collinear and along with treatment SVR rate (α) account for the majority of this variability (Fig. 5B). For most scenarios, greater impact is achieved in populations with lower incidence paired with long injecting durations. In certain circumstances (low prevalence and long time scales or

high treatment rates), longer injecting duration is associated with decreased treatment impact due to the persistence of the treatment failure population. In all scenarios, greater impact is seen for higher SVR rates.

Uncertainty around the SVR resulting from treatment (due to different genotype distributions or lower compliance to treatment) can increase or decrease projections by up to 27% over 20 years with an annual treatment rate of 10–20 per 1000 IDU (Fig. 6). The greater the treatment magnitude or intervention timescale, the more pronounced the difference between the impact projections for each genotype.

Adapting the model such that treatment failures are eligible for retreatment (Fig. 7) results in no change to the short-term impact projections, and only changes the long term projections at either low baseline prevalence ($<20\%$), or moderate prevalence ($<30\%$) with high levels of treatment (≥ 20 per 1000 IDU per year).

Lastly, there is little difference in the HCV free LYG predictions in relation to varying SVR (provided SVR rates are equal in non- or ex-IDU) or if retreatment is introduced (data not shown).

Discussion

Main findings

Our simplified HCV transmission model provides evidence that antiviral treatment at achievable rates may be an effective primary prevention tool for substantially reducing the prevalence of HCV infection, despite the persistent risk of re-infection. Even more substantial reductions in prevalence are possible if effective treatments become available for those who do not attain SVR with the current regimen. Reductions in average SVR (through more genotype 1 in the population, or lowered completion and compliance) reduces the expected reduction in HCV prevalence, whereas higher SVR (e.g. through more individuals with genotype 2/3 or improved treatment regimens) increases the impact of treatment. Re-infection will reduce the HCV free life years gained (HCV free LYG) from successfully treating an individual. However,

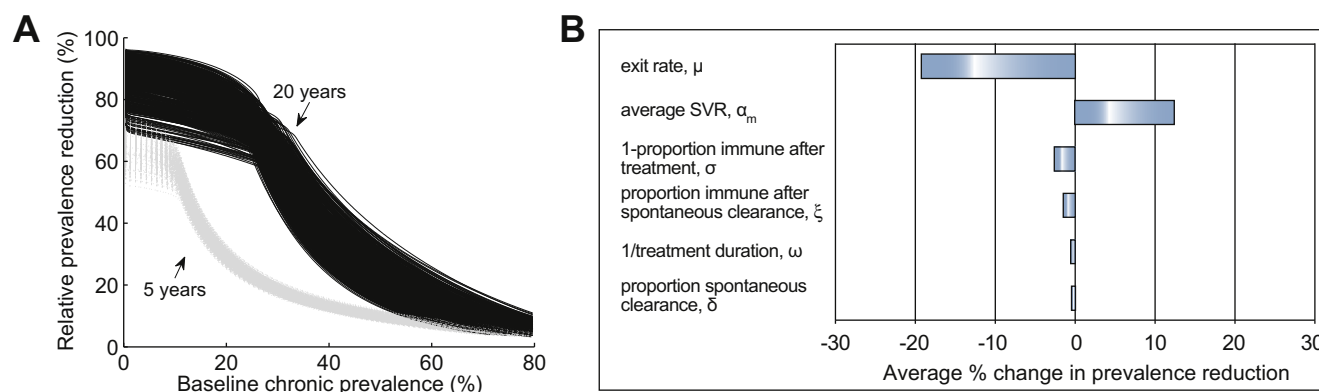


Fig. 5. Results of the uncertainty analysis. (A) Uncertainty analysis of the relative decrease in prevalence at 5 and 20 years (gray line and black lines, respectively). The percent relative prevalence reduction (vertical axis) is shown for varying baseline chronic prevalences (horizontal axis) and treatment level of 20 per 1000 IDU annually for the baseline model with parameters varied as in Table 1. (B) The average change in prevalence reduction as each parameter is varied over its full uncertainty range, calculated by multiplying the regression coefficient by each parameter range. Note that the general SVR rate and treatment durations are calculated from the sample values of each genotype SVR sample (α_1 and $\alpha_{2/3}$) as detailed in Table 1, and that infection rate is neglected as it is multicollinear with exit rate. Baseline chronic prevalence is defined as untreated endemic chronic infection prevalence.

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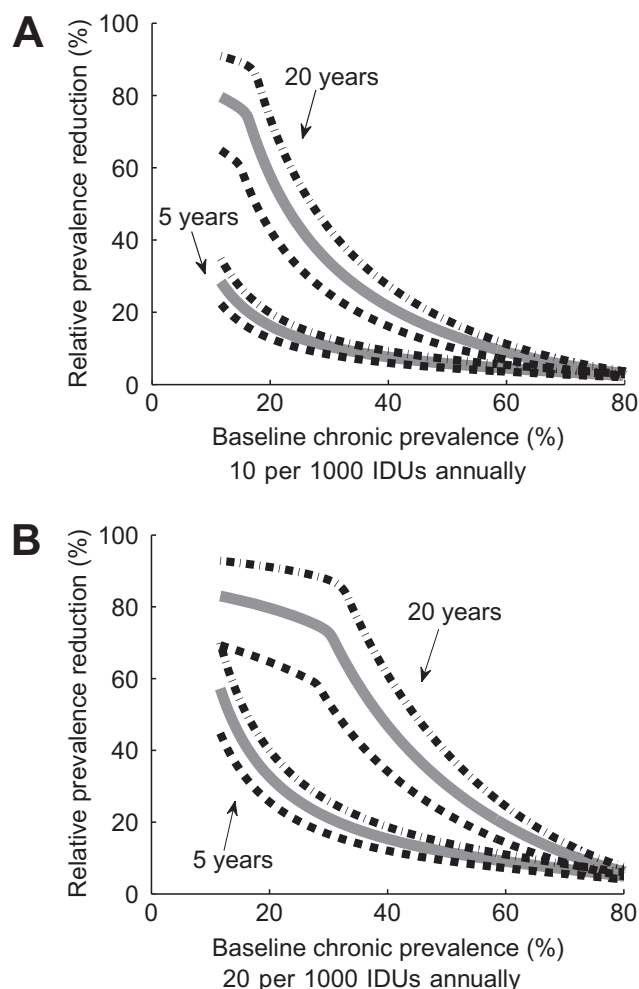


Fig. 6. Projected relative reduction in prevalence at 5, 10, and 20 years for the SVR variation scenarios compared to the baseline scenario at different baseline prevalences and treatment rates. The relative prevalence reduction from baseline chronic prevalence (vertical axis) predictions are shown at 5 and 20 years (see arrows) for varying baseline untreated chronic prevalences (horizontal axis). The prevalence reductions are shown for the baseline 62.5% SVR scenario (gray line), reduced 45% SVR scenario (black dashes) and increased 80% SVR scenario (black dot-dash) with treatment levels of (A) 10 per 1000 IDU annually and (B) 20 per 1000 IDU annually. Baseline chronic prevalence is defined as untreated endemic chronic infection prevalence.

because successful treatment also prevents a potential chain of HCV transmissions, our projections suggest more HCV free LYG are achieved from treating current IDU in populations with less than 60% chronic infection prevalence than from treating non- or ex-IDU.

Strengths and limitations

There are several limitations. First, the findings are based on model projections of the treatment effect instead of experimental evidence. Second, the use of a fixed treatment rate annually assumed that treatment could be sustained at the same rate despite a reduction in prevalence. This means that as prevalence decreases, a larger proportion of infected IDU will be treated each year although the number treated remains constant. In the short

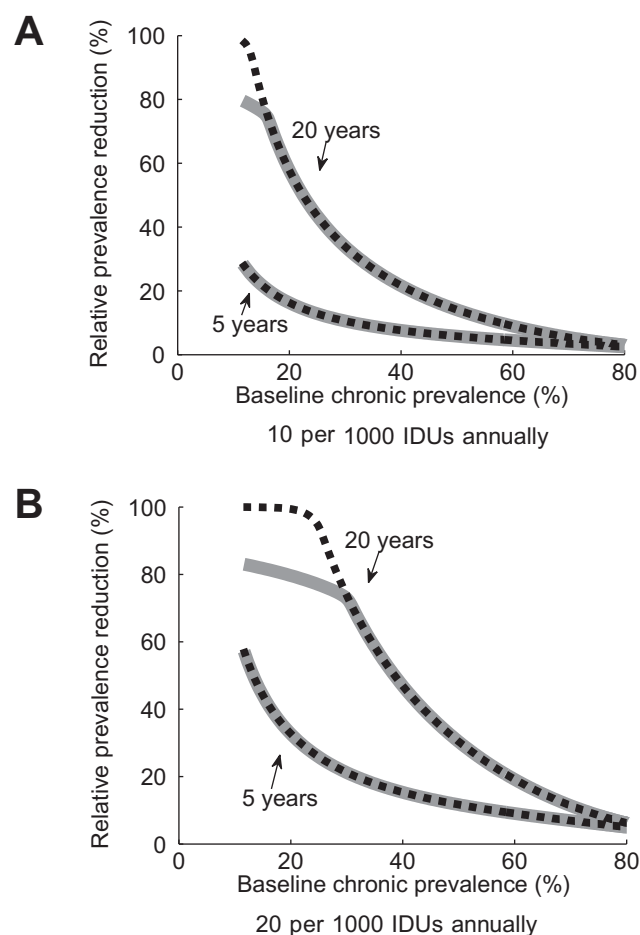


Fig. 7. Projected relative reduction in prevalence at 5, 10, and 20 years for the retreatment scenario compared to the baseline scenario at different baseline prevalences and treatment rates. The relative prevalence reduction from baseline chronic prevalence (vertical axis) predictions are shown at 5 and 20 years (see arrows) for varying baseline untreated chronic prevalences (horizontal axis). The prevalence reductions are shown for the baseline scenario (gray line) and retreatment scenario (black dashes). Baseline chronic prevalence is defined as untreated.

term, this may be a reasonable assumption, but would require increased efficiency in efficient and effective HCV testing and case finding to find those fewer infected IDU [29].

Third, the model assumed that all infected IDU have an equal probability of being treated, completing treatment and cure. In practice, barriers exist related to accessing IDU and ensuring they are referred to and remain in specialist care. Additionally, we assumed no difference in infection risk among non-immune IDU following spontaneous clearance or successful treatment. In reality, it is highly likely that there are heterogeneities in treatment presentation and completion (as well as in behavior and risk following treatment) both between different IDU and at different times during a person's injecting career. However, in the UK and many other developed countries, a high proportion of IDU are in opiate substitution treatment (~40%), and during this time IDU may continue to inject but at a lower injecting frequency or temporarily cease injecting. As most IDU will have periods of opiate substitution treatment, there will be multiple opportunities for HCV treatment among IDU in contact with

treatment services, who may achieve similar SVRs to published findings (used in our projections). Equally, biological and behavioral heterogeneity in infection risk may reduce the impact of treatment for a specific baseline prevalence. For example, there may be an elevated transmission risk in the acute stage of infection [30,31], injectors in their first year of injecting may be at a greater risk of becoming infected than at other times, and there may be a high risk group that is resistant to interventions that could promote HCV treatment (such as opiate substitution treatment). In addition, we have assumed average cessation and drug related death rates – whereas these may vary in the first year or at other times during an injectors' career [32]. Furthermore, it is possible, though not well documented, that those undergoing or exiting treatment may exhibit increased cessation rates. This increased cessation during or after treatment could decrease the potential impact of treatment, although it would still reduce prevalence and HCV transmission due to infected IDU being removed from the pool of active injectors. Unfortunately, there is insufficient evidence to parameterize any of these consequences or changes, which can only be incorporated once additional clinical evidence has been collected.

Fourth, although we explored SVR rates corresponding to scenarios with all genotype 1, all genotype 2/3, and mixed genotypes, we did not explicitly stratify the populations by genotype. Stratifying the population by genotype could refine our model predictions because we could incorporate the dynamic effect of treatment on the proportion of each genotype in a given population.

Fifth, the model used a deterministic approximation of the infection dynamics, and as such may not be reliable for very low prevalences where stochastic effects can have substantial effect. However, as HCV prevalence is currently extremely high, the use of a deterministic model is appropriate in the current circumstance.

Evidence from other studies

Only one other modeling study has considered the impact of HCV treatment on prevalence [33]. Although a similar model structure was used, our analysis produced more optimistic projections because our fixed number treatment term is a more realistic model of antiviral treatment capacity and delivery, in contrast to a treatment term which diminishes as the prevalence decreases. In addition, our analyses present a wider range of prevalence scenarios that have been observed in different sites and countries (over a wider range of follow-up times) rather than considering a single prevalence (>60%) scenario over a limited time period. A preliminary economic evaluation also suggests that HCV treatment may be a cost effective strategy [34].

Implications

To date, uptake of therapy remains low among active IDU, and is rarely encouraged. Many factors contribute to the low treatment rates in IDU including concerns about re-infection, the low priority of injectors for scarce treatment resources and the lack of evidence showing unequivocal benefits. Nonetheless, the available evidence suggests that IDU can be treated successfully [17–21,35], especially when innovative approaches to delivering therapy are used [36]. Our model suggests, for the first time, that therapy could play a valuable role in controlling the HCV

epidemic in IDU. However, the experimental or clinical data are limited and probably subject to considerable selection biases. The models outlined here require validation in clinical trials of the impact of therapy on disease prevalence among IDU. Such studies are complex as treatment only indirectly affects incidence through reductions in prevalence. This analysis emphasizes the importance of mathematical models for setting intermediate targets of changes in HCV prevalence for considering the effectiveness of treatment. Further modeling work is needed to examine the cost effectiveness of different treatment strategies; the benefits of combining HCV treatment with opiate substitution therapy or needle and syringe programmes; and to incorporate transitions between periods of injecting and drug treatment and extend the model to ex-IDU.

Disclosures

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Supplementary data

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