Supporting Information

**Title:** Are interferon-free direct-acting antivirals for the treatment of HCV enough to control the epidemic among people who inject drugs?

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Differential Equations

The full model has 105 differential equations (i.e. seven primary health states with five fibrosis stage sub-compartments, and further divided into three injection risk categories), and for simplicity in writing these equations, we used a vector notation in which each vector, one for each compartment, encompasses its five sub-components, one for each fibrosis stage (e.g., $\vec{S} = [S_0, S_1, S_2, S_3, S_4]^T$).

The explanation and assumptions for all parameters can be found in Supporting Information Table 1. The differential equations for each of the three risk categories (with $i = 0, 1, 2$ corresponding to zero, low and high injection risk, respectively) are given by:

**Susceptible compartments**

$$\frac{d\vec{S}}{dt} = n_2 \Pi + \rho (1 - \kappa) \Omega \vec{T}_2 + \gamma \vec{R}_2 + \theta \delta \vec{I}_2 + \psi \vec{S}_2 + c_1 \vec{S}_0 + c_3 \vec{S}_1 - \left( \lambda_{S_2} + \mu + c_0 + c_2 \right) \vec{S}_2$$

$$\frac{d\vec{S}_1}{dt} = n_1 \Pi + \rho (1 - \kappa) \Omega \vec{T}_1 + \gamma \vec{R}_1 + \theta \delta \vec{I}_1 + \psi \vec{S}_1 + c_1 \vec{S}_0 + c_2 \vec{S}_2 - \left( \lambda_{S_1} + \mu + c_0 + c_3 \right) \vec{S}_1$$

$$\frac{d\vec{S}_0}{dt} = \theta \delta \vec{I}_0 + \psi \vec{S}_0 + c_0 \left( \vec{S}_1 + \vec{S}_2 \right) - \left( \mu + 2c_1 \right) \vec{S}_0$$

**Acutely infected compartments**

$$\frac{d\vec{I}}{dt} = \lambda_{S_2} \vec{S}_2 + \lambda_{R_2} \vec{R}_2 + c_1 \vec{I}_0 + c_3 \vec{I}_1 - \left( \delta + F + \mu + c_0 + c_2 \right) \vec{I}_2$$

$$\frac{d\vec{I}_1}{dt} = \lambda_{S_1} \vec{S}_1 + \lambda_{R_1} \vec{R}_1 + c_1 \vec{I}_0 + c_2 \vec{I}_2 - \left( \delta + F + \mu + c_0 + c_3 \right) \vec{I}_2$$

$$\frac{d\vec{I}_0}{dt} = c_0 \left( \vec{I}_1 + \vec{I}_2 \right) - \left( \delta + F + \mu + 2c_1 \right) \vec{I}_0$$
Chronic unaware compartments

\[
\frac{d\tilde{C}_u^{a2}}{dt} = (1 - \theta)\delta\tilde{I}_2 + c_1\tilde{C}_u^{a0} + c_3\tilde{C}_u^{a1} - (\tau + F + \mu + c_0 + c_2)\tilde{C}_u^{a2}
\]

\[
\frac{d\tilde{C}_u^{a1}}{dt} = (1 - \theta)\delta\tilde{I}_1 + c_1\tilde{C}_u^{a0} + c_2\tilde{C}_u^{a2} - (\tau + F + \mu + c_0 + c_3)\tilde{C}_u^{a1}
\]

\[
\frac{d\tilde{C}_u^{a0}}{dt} = (1 - \theta)\delta\tilde{I}_0 + c_0(\tilde{C}_u^{a1} + \tilde{C}_u^{a2}) - (\tau + F + \mu + 2c_1)\tilde{C}_u^{a0}
\]

Chronic aware and eligible for treatment compartments

\[
\frac{d\tilde{C}_a^{a2}}{dt} = \tau\tilde{C}_a^{a2} + (1 - \rho)\omega\tilde{T}_2 + c_1\tilde{C}_a^{a0} + c_3\tilde{C}_a^{a1} - (\sigma_{c_a} + F + \mu + c_0 + c_2)\tilde{C}_a^{a2}
\]

\[
\frac{d\tilde{C}_a^{a1}}{dt} = \tau\tilde{C}_a^{a1} + (1 - \rho)\omega\tilde{T}_1 + c_1\tilde{C}_a^{a0} + c_2\tilde{C}_a^{a2} - (\sigma_{c_a} + F + \mu + c_0 + c_3)\tilde{C}_a^{a1}
\]

\[
\frac{d\tilde{C}_a^{a0}}{dt} = \tau\tilde{C}_a^{a0} + (1 - \rho)\omega\tilde{T}_0 + c_0(\tilde{C}_a^{a1} + \tilde{C}_a^{a2}) - (\sigma_{c_a} + F + \mu + 2c_1)\tilde{C}_a^{a0}
\]

Chronic aware and not eligible for treatment compartments

\[
\frac{d\tilde{C}_n^{a2}}{dt} = \zeta\sigma_{c_n}\tilde{C}_n^{a2} + c_1\tilde{C}_n^{n0} + c_3\tilde{C}_n^{n1} - (\sigma_{c_n} + F + \mu + c_0 + c_2)\tilde{C}_n^{a2}
\]

\[
\frac{d\tilde{C}_n^{a1}}{dt} = \zeta\sigma_{c_n}\tilde{C}_n^{a1} + c_1\tilde{C}_n^{n0} + c_2\tilde{C}_n^{n2} - (\sigma_{c_n} + F + \mu + c_0 + c_3)\tilde{C}_n^{a1}
\]

\[
\frac{d\tilde{C}_n^{a0}}{dt} = \zeta\sigma_{c_n}\tilde{C}_n^{a0} + c_0(\tilde{C}_n^{n1} + \tilde{C}_n^{n2}) - (\sigma_{c_n} + F + \mu + 2c_1)\tilde{C}_n^{a0}
\]
On treatment compartments

\[
\frac{dT_0}{dt} = (1 - \zeta) \sigma_{c_a} \ddot{C}_{a_0} + \sigma_{c_\omega} \ddot{C}_{\omega} + c_0 \ddot{T}_0 + c_3 \ddot{T}_1 - (\omega + \mu + c_1 + c_2) \ddot{T}_2
\]

\[
\frac{dT_1}{dt} = (1 - \zeta) \sigma_{c_a} \ddot{C}_{a_1} + \sigma_{c_\omega} \ddot{C}_{\omega_1} + c_1 \ddot{T}_0 + c_2 \ddot{T}_2 - (\omega + \mu + c_1 + c_3) \ddot{T}_1
\]

\[
\frac{dT_2}{dt} = (1 - \zeta) \sigma_{c_a} \ddot{C}_{a_2} + \sigma_{c_\omega} \ddot{C}_{\omega_2} + c_1 \ddot{T}_0 + (\ddot{T}_1 + \ddot{T}_2) - (\omega + \mu + 2c_1) \ddot{T}_0
\]

Risk reduction compartments

\[
\frac{d\bar{R}_0}{dt} = \rho \kappa \Omega \bar{T}_2 + \Psi \bar{R}_2 + c_0 \bar{R}_0 + c_3 \bar{R}_1 - (\gamma + \lambda_{R_2} + \mu + c_0 + c_2) \bar{R}_2
\]

\[
\frac{d\bar{R}_1}{dt} = \rho \kappa \Omega \bar{T}_1 + \bar{R}_1 + c_1 \bar{R}_0 + c_2 \bar{R}_2 - (\gamma + \lambda_{R_1} + \mu + c_0 + c_3) \bar{R}_1
\]

\[
\frac{d\bar{R}_2}{dt} = \rho \Omega \bar{T}_i + \bar{R}_0 + c_0 \bar{R}_1 + c_1 \bar{R}_2 - (\mu + 2c_1) \bar{R}_i
\]
Table 1. Model Parameters and Initial Conditions

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<tr>
<th>Parameter</th>
<th>Explanation and Values</th>
<th>References</th>
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<tr>
<td>$\tilde{S} = [S_0, S_1, S_2, S_3, S_4]^T$</td>
<td>Vector for Susceptible individuals: its components correspond to the five fibrosis levels. Initial values are for stable endemic equilibrium. The definition of this can be done in terms of the Control Reproduction Number ($R_c$). A $R_c &lt; 1$ means that, over time, the model will reach the disease-free equilibrium - meaning that on average an infected individual produces less than one new infection over the course of his/her infectious period, and thus, the epidemic cannot grow. A $R_c &gt; 1$ means that, over time, the model will reach a stable endemic equilibrium - meaning that each infected individual produces, on average, more than one new infection, and the disease continues to spread in the population.</td>
<td></td>
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<tr>
<td>$\tilde{I} = [I_0, I_1, I_2, I_3, I_4]^T$</td>
<td>Vector for Acutely Infected individuals: its components correspond to the five fibrosis levels. Initial values are for stable endemic equilibrium.</td>
<td></td>
</tr>
<tr>
<td>$\tilde{C}<em>u = [C</em>{u_0}, C_{u_1}, C_{u_2}, C_{u_3}, C_{u_4}]^T$</td>
<td>Vector for Chronic unaware individuals: its components correspond to the five fibrosis levels.</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Description</td>
<td></td>
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<tr>
<td>$\mathbf{C}<em>a = \begin{bmatrix} C_a, C</em>{a_1}, C_{a_2}, C_{a_3}, C_{a_4} \end{bmatrix}^T$</td>
<td>Initial values are for stable endemic equilibrium. Vector for Chronic aware individuals: its components correspond to the five fibrosis levels. Initial values are for stable endemic equilibrium.</td>
<td></td>
</tr>
<tr>
<td>$\mathbf{C}<em>n = \begin{bmatrix} C_n, C</em>{n_1}, C_{n_2}, C_{n_3}, C_{n_4} \end{bmatrix}^T$</td>
<td>Initial values are for stable endemic equilibrium. Vector for individuals Chronic aware and not eligible for treatment: its components correspond to the five fibrosis levels. Initial values are for stable endemic equilibrium.</td>
<td></td>
</tr>
<tr>
<td>$\mathbf{T} = \begin{bmatrix} T_0, T_1, T_2, T_3, T_4 \end{bmatrix}^T$</td>
<td>Initial values are for stable endemic equilibrium. Vector for individuals on Treatment: its components correspond to the five fibrosis levels.</td>
<td></td>
</tr>
<tr>
<td>$\mathbf{R} = \begin{bmatrix} R_0, R_1, R_2, R_3, R_4 \end{bmatrix}^T$</td>
<td>Initial values are for stable endemic equilibrium. Vector for individuals on risk reduction: its components correspond to the five fibrosis levels.</td>
<td></td>
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<tr>
<td>$\rho$</td>
<td>Proportion on Peg-IFN + RBV achieving SVR: 55%; Proportion on Peg-IFN + RBV plus (BOC or TPV) achieving SVR: 70%; Proportion on IFN-free DAA achieving SVR: 90%; Proportion on the Best Case Scenario achieving SVR: 100%.</td>
<td></td>
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<tr>
<td>$\kappa$</td>
<td>Rate of PWID moving into risk reduction after achieving SVR: Baseline scenario: 0 per 1000 PWID per year;</td>
<td></td>
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<tr>
<td>$\Omega$</td>
<td>Intervention scenarios: 100, 200, 400, 500, 600 and 800 per 1000 PWID per year.</td>
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<tr>
<td>Transition matrix across fibrosis stages after achieving SVR given by:</td>
<td></td>
<td></td>
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</table>
| $\Omega = \begin{pmatrix}
1 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 & 0
\end{pmatrix}$ |
| We assume that PWID who achieve SVR improve their fibrosis by one level. Thus, based on this matrix, PWID in $T_4$ can transition to either $R_3$ or $S_3$; PWID in $T_3$ can transition to either $R_2$ or $S_2$; PWID in $T_2$ can transition to either $R_1$ or $S_1$; and PWID in $T_0$ and $T_0$ can transition to either $R_0$ or $S_0$ after achieving SVR. |

| $\gamma$ | Loss of individuals from the risk reduction compartment: 60 per 1000 PWID per year | [8] |
| $\theta$ | Spontaneous clearance proportion: 25% | [9] |
| $1/\delta$ | Duration of acute phase: 0.5 years | [7, 10] |
| $\Psi$ | Fibrosis regression rate matrix: |
PWID who achieved SVR gradually improve their liver condition, which translates into decreases in their fibrosis level. In the model, PWID exit compartments $S_i$ and $R_i$ at a yearly rate of $\psi$, and arrive at compartments $S_{i-1}$ and $R_{i-1}$ with the same rate $\psi$, respectively, for $i=1$ to 4.

<table>
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<tr>
<th>$\psi$</th>
<th>Fibrosis regression rate from $F_j$ to $F_{j+1}$ for $j=1,2,3,4$:</th>
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<td></td>
<td>0.2 per year</td>
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Fibrosis progression rate matrix:

$$F = \begin{pmatrix}
 f_{01} & 0 & 0 & 0 & 0 \\
 -f_{01} & f_{12} & 0 & 0 & 0 \\
 0 & -f_{12} & f_{23} & 0 & 0 \\
 0 & 0 & -f_{23} & f_{34} & 0 \\
 0 & 0 & 0 & -f_{34} & 0
\end{pmatrix}$$

HCV infected individuals gradually deteriorate their liver condition, which translates into increases in their fibrosis level. In the model, individuals exit compartments $I_i$, $C_{u_i}$, $C_{a_i}$, $C_{n_i}$ at a yearly rate of $f_{i,i+1}$, and arrive at compartment $I_{i+1}$, $C_{u_{i+1}}$, $C_{a_{i+1}}$, $C_{n_{i+1}}$ with
the same rate $f_{i,i+1}$, respectively, for $i = 0$ to 3.

Baseline transition rates: $f_{01} = 0.067$ per year; $f_{12} = 0.049$ per year; $f_{23} = 0.069$ per year; $f_{34} = 0.051$ per year. These parameters were determined from a weighted average of sex and age-specific transition rates based on the paper by Razavi et al. [13]. The choice of age group was based on the top seven age groups in which the HCV incidence was the highest in the Remis report, i.e., 15-49 years [14]. A sensitivity analysis was performed using data from a meta-analysis by Thein et al. [15], which has faster transition rates $f_{01} = 0.109$ per year; $f_{12} = 0.068$ per year; $f_{23} = 0.113$ per year; $f_{34} = 0.125$ per year.

Another sensitivity analysis was performed using data from Razavi et al. [13], which also had values for slower transition rates $f_{01} = 0.054$ per year; $f_{12} = 0.039$ per year; $f_{23} = 0.051$ per year; $f_{34} = 0.041$ per year.

Status Quo testing rate: 140 per 1000 PWID per year;

The only intervention for this parameter was to assume immediate testing at the end of the acute
| $1/\omega$ | Duration of Peg-IFN + RBV treatment: 48 weeks depending on the genotype; Duration of Peg-IFN + RBV plus (BOC or TPV) treatment: 24 to 48 weeks depending on the genotype; Duration of IFN-free DAA treatment: 12 weeks regardless of genotype; Duration of the Best Case Scenario treatment: 1 week regardless of genotype. [2, 4, 6, 7, 18-21] |
| $\sigma_{c_a}$ | Status Quo treatment rate for individuals in the $C_a$ compartment: 8 per 1000 PWID per year; Intervention scenarios for the treatment rate for individuals in the $C_a$ compartment: 20, 40 and 80 per 1000 PWID per year [16, 17] |
| $\sigma_{c_n}$ | Treatment rate for individuals in the $C_n$ compartment: $\alpha \sigma_{c_a}$ |
| $\alpha$ | Reduction in the treatment rate for $C_n$ due to treatment ineligibility: Based on Peg-IFN + RBV treatment: 0.10; Based on Peg-IFN + RBV plus (BOC or TPV) treatment: 0.20; [4, 16, 22] |
Based on IFN-free DAA treatment: 0.75;
Based on Best Case Scenario treatment: 1.00.
These numbers were derived based on the unstable
housing and drug use patterns in these reports,
counter-indications for the use of each of these drugs
and the Canadian HCV treatment guidelines.

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<td>ζ</td>
<td>Proportion of PWID not eligible for treatment:</td>
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<tr>
<td></td>
<td>Based on Peg-IFN + RBV treatment: 90%;</td>
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<tr>
<td></td>
<td>Based on Peg-IFN + RBV plus (BOC or TPV) treatment: 75%. This is probably optimistic due to the fact that BOC/TPV are not very well tolerated [23];</td>
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<td>Based on IFN-free DAA treatment: 20%. We have no data on this other than phase 3 reports.</td>
</tr>
<tr>
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<td>Based on Best Case Scenario treatment: 0%.</td>
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Based on IFN-free DAA treatment:
Based on Peg-IFN + RBV treatment: 90%;
Based on Peg-IFN + RBV plus (BOC or TPV) treatment: 75%. This is probably optimistic due to the fact that BOC/TPV are not very well tolerated [23];
Based on IFN-free DAA treatment: 20%. We have no data on this other than phase 3 reports.
Based on Best Case Scenario treatment: 0%.

Recruitment rate into susceptible PWID. For lack of better data, this constant was fit in the model to maintain a constant population. It was estimated using:
\[
\sum_{j=0}^{2} \left( \mu \cdot \left( S_j + I_j + C_{uj} + C_{uj} + C_{aq} + T_j + R_j \right) \right),
\]
with \( j \) representing the 3 risk categories (i.e., zero, low and high risk).

| \( \lambda_{S_i} \) | Force of infection for the high and low risk categories: |
\[ \lambda_{S_k} = h_k \beta \sum_{i=1}^{2} \left( \sum_{j=0}^{4} I_{ij} + \chi_0 \left( C_{u_{ij}} + C_{a_{ij}} + C_{n_{ij}} \right) + \chi_1 T_{ij} \right) / N \]

with \( k = 1 \) (low risk), 2 (high risk), \( i = 1 \) (low risk), 2 (high risk), and \( j = 0, \ldots, 4 \) fibrosis level.

Force of infection for the zero-risk category: \( \lambda_{S_0} = 0 \)

Average contact rate. This parameter was numerically derived to fit a fixed prevalence. In BC, it is estimated that 65% of the PWID population is HCV RNA positive. With all other parameters fixed, we ran a long-time simulation inside a Nelder-Mead simplex algorithm that determined the optimal value of \( \beta \) that results in a 65% chronic prevalence in the endemic scenario. Note that this parameter includes the background rate of individuals in the population currently accessing harm-reduction programs (53 per 100 PWID per year).

Relative infectivity while chronically infected with respect to the acutely infected stage: 10%. This parameter is to take into account the different phases in the HCV life cycle and their respective infectivity. Thus in this case, the infectivity in the acute infected stage was assumed to be 100%. This means that in

[22, 24, 10, 25, 26]
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<tbody>
<tr>
<td>$\chi_1$</td>
<td>Relative infectivity while on treatment with respect to the acutely infected stage: 5%</td>
<td>[10, 25, 26]</td>
</tr>
<tr>
<td>$N$</td>
<td>Total PWID population was 18,068 and given by $N = \sum_{i=1}^{2} \sum_{j=0}^{4} (S_{ij} + I_{ij} + C_{u_j} + C_{a_j} + C_{n_j} + T_{ij} + R_{ij})$, $i = 1$ (low risk), 2 (high risk), $j = 0, \ldots, 4$ fibrosis level. This was derived from the overall HCV prevalence. The total population including the zero risk category was fit in order for $N$ to match the high and low risk compartments.</td>
<td></td>
</tr>
<tr>
<td>$h_2$</td>
<td>Increased relative risk for high-risk individuals: 1.40</td>
<td>[27]</td>
</tr>
<tr>
<td>$h_1$</td>
<td>Decreased relative risk for low-risk individuals: 0.40</td>
<td>[28]</td>
</tr>
<tr>
<td>$n_2$</td>
<td>Proportion of the PWID that engages in high risk injection drug use: 64%</td>
<td>[22, 24]</td>
</tr>
<tr>
<td>$n_1$</td>
<td>Proportion of the PWID that engages in low risk injection drug use: 36%</td>
<td>[22, 24]</td>
</tr>
<tr>
<td>$\lambda_{n_i}$</td>
<td>Force of re-infection was estimated using: $(1 - \varepsilon_R) \lambda_{S_i}$</td>
<td></td>
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<tr>
<td>Parameter</td>
<td>Description</td>
<td>Reference</td>
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<tr>
<td>( \varepsilon_r )</td>
<td>Re-infection risk reduction due to harm-reduction and natural causes: 79%</td>
<td>[28]</td>
</tr>
<tr>
<td>( \mu_{PWID} )</td>
<td>Status Quo mortality rate for PWID with fibrosis level ( F_0 ): 0.01 per person-years</td>
<td>[14, 29]</td>
</tr>
<tr>
<td>( m_{LD} )</td>
<td>Standardized mortality ratio for liver-related disease: 8.44. This was determined from deaths attributable to viral hepatitis, liver cancer, and alcoholic and non-alcoholic liver disease in a population of HCV infected individuals</td>
<td>[30, 31]</td>
</tr>
<tr>
<td>( \mu )</td>
<td>Population mortality rate range across fibrosis stages. These set of parameters were linearly interpolated between the baseline mortality rate (( \mu_{PWID} )) and the SMR-adjusted value for individuals who died from liver-related disease (( m_{LD}\mu_{PWID} ))</td>
<td></td>
</tr>
<tr>
<td>( c_0 )</td>
<td>Cessation rate for the high and low-risk individuals: 0.18 per PWID per year</td>
<td>[32]</td>
</tr>
<tr>
<td>( c_1 )</td>
<td>Relapse rate back to high-risk drug use: 0.75 per PWID per year</td>
<td>[32]</td>
</tr>
<tr>
<td>( c_2 )</td>
<td>High to low-risk transition rate: 0.32 per PWID per year</td>
<td>[22, 24]</td>
</tr>
<tr>
<td>( c_3 )</td>
<td>Low to high-risk transition rate. This rate was estimate to keep the PWID population constant at</td>
<td></td>
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</table>
64% having high risk and 36% having low risk.

Statistical analysis for the trend in the distribution of fibrosis levels in Figure 3 in the manuscript
References


8. Dalgard O. Follow-up studies of treatment for hepatitis C virus infection among injection drug users. Clinical infectious diseases : an official publication of the Infectious Diseases Society


