Patient-important benefits of clearing the hepatitis C virus through treatment

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MANUSCRIPT TITLE: Patient-important benefits of clearing the hepatitis C virus through treatment: a simulation model

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STRUCTURED ABSTRACT

IMPORTANCE:
Given an appreciable risk of adverse-effects, chronic hepatitis C virus (HCV) patients face a dilemma regarding whether to accept or forego a course of therapy that can permanently clear their viral infection.

OBJECTIVE
To inform this decision point, we explored (via simulation modelling) patient-important benefits of treatment-induced viral-clearance according to individualised patient factors.

DESIGN:
We created the HCV Individualised Treatment-decision model (the HIT-model) to simulate, on a per patient basis, the lifetime course of HCV-related liver disease.

SETTING:
The HIT-model is applicable to settings where chronic HCV patients are considered for antiviral therapy; by and large secondary referral specialist care centres.

PARTICIPANTS:
Hypothetical persons with chronic HCV infection aged 30-60 years with varying degrees of liver fibrosis (mild, moderate and severe).

EXPOSURE:
The lifetime course of liver disease was simulated, on a per patient basis, according to two distinct scenarios: (i) treatment-induced viral-clearance attained, and (ii) treatment-induced viral-clearance not attained. Then, for each model subject, the course of liver disease under these alternative scenarios was compared.

MAIN OUTCOMES:
Emphasis was on patient-important outcomes; in particular: (1) Probability of viral-clearance conferring additional total life years, and (2) Probability of viral-clearance conferring additional life years spent in compensated health states (i.e. the avoidance of liver failure).

RESULTS:
The probability of benefiting from treatment-induced viral-clearance varied strikingly. It was lowest among patients at 60 years of age with initially mild fibrosis; 1.6% (95% CI: 0.8-2.7) and 2.9% (95% CI: 1.5-4.7) regarding outcome 1 and 2, respectively. It was highest among patients with compensated cirrhosis aged 30 years; 57.9% (95% CI: 46.0-69.0) and 67.1% (95% CI: 54.1-78.2) regarding outcome 1 and 2, respectively.

CONCLUSIONS:
For older patients with less advanced liver fibrosis, viral-clearance is less likely to confer benefit when measured in terms of averting liver failure and premature death. These data have important implications. Foremost, they will inform the contemporary patient quandary of immediate treatment with existing therapies (that have poor adverse-effect profiles) versus deferring until more tolerable (and more efficacious) regimens become available.
INTRODUCTION

Chronic hepatitis C virus (HCV) infection leads to progressively worsening degrees of liver fibrosis (i.e. scarring of the liver). Eventually (over a period of many decades), fibrosis can become so extensive, that liver function is compromised.\(^1\) Often, it is only at this point of hepatic decompensation that HCV infection becomes evident to the patient. Hereafter, in the absence of a liver transplant, long-term prognosis is bleak.\(^2\) It is this typical sequence of events that has led to HCV being dubbed the "silent killer"\(^3-4\).

Chronic HCV infection is treatable. Current treatments regimen (consisting of a 16-48 week course of pegylated interferon, ribavirin ± a protease inhibitor in genotype-1 patients) can permanently eradicate the infection in 67-75% of persons (based on the sustained viral response [SVR] proxy).\(^5-7\) The number of people treated every year is substantial; approximately 5,000-6,000, and 60,000-80,000 initiates each year in the UK and US, respectively.\(^8,9\) However current therapies are not a panacea; adverse-effects can be appreciable\(^10,11\) and sometimes severe.\(^12-14\) Moreover, patients failing first generation protease inhibitors can develop resistance to the class.\(^15\)

Accordingly, before embarking on a course of therapy, the patient (and their clinician) should carefully consider the risk-benefit ratio. Particularly given that, de-facto, the majority with infection are unlikely to develop overt liver disease, within the course of their lifetime.\(^16,17\) So, to assist this patient-decision we simulated the lifetime course of liver disease according to SVR status and individualised patient factors. We envisage that these data, in conjunction with information regarding: (i) the probability of SVR, (ii) the adverse-effect profile, and (iii) the prospect that more tolerable and efficacious therapies will be available in the future\(^18\), will arm patients and clinicians alike, with a more complete picture when considering therapy with current (and future\(^18\)) treatment regimens.
METHODS

MODEL PURPOSE:
To delineate the value of treatment-induced viral clearance, we created the Hepatitis-C
Individualised Treatment-decision model (the HIT-model). The HIT-model simulates lifetime
liver disease outcomes for individual model subjects, henceforth from two distinct scenarios:

(i) SCENARIO-1: Treatment-induced viral-clearance attained - i.e. the patient accepts a
course of antiviral therapy and attains SVR.
(ii) SCENARIO-2: Treatment-induced viral-clearance not attained - i.e. the same patient
alternatively either declines therapy or fails, hence their chronic infection persists
over their remaining life course.

For each model subject, we then compared the course of liver disease under scenario-1 versus
scenario-2.

MODEL OVERVIEW:

The HIT-model is a markov-chain model that simulates the lifetime course of HCV-related liver
disease according to viral-clearance status. The model is run as a first order Monte-Carlo
simulation, otherwise known as a microsimulation.19,20 The structure and parameterisation it
assumes (see Fig-1 and Table-1) is typical of existing HCV simulation models (be they cost-
effectiveness21-24 or burden forecasting models25-27) and draws on a wide array of empirical
research data.

As per the schematic in Fig.1, subjects under scenario-2 (persisting chronic HCV infection) face
progressive hepatic fibrosis, culminating in compensated cirrhosis (i.e. Ishak-6). Probabilities
used to inform the progression of model subjects through these early stages were derived from a
well-described cohort of chronic HCV patients attending a UK tertiary referral clinic.24 These
same progression rates (based on 12% of persons developing compensated cirrhosis within 20 years of acquiring infection) have been adopted in hitherto HCV simulation models.21,23,24 Once (if at all) subjects reach Ishak-6, they then risk the development of decompensated liver cirrhosis and hepatocellular carcinoma (HCC). If either of these two health states are attained, subjects may then die a HCV liver-related death (occurring at an annual risk of 43% and 13% from HCC and decompensated liver cirrhosis states, respectively28), but are also eligible for a liver transplantation (occurring according to a 2% annual probability26), which can improve long-term prognosis (i.e. 14.6% risk of a HCV-related death during the year transplant occurs, but 4.4% for every year thereafter26). In scenario-1 (attainment of viral-clearance), we assumed subjects with mild/moderate fibrosis could not progress to more advanced states of liver disease. In contrast, subjects with initial cirrhosis (Ishak-6) could progress to decompensated cirrhosis or HCC health states (and downstream states thereafter), but at a reduced rate relative to scenario-229 (see Table-1). At every stage of the model (for both scenarios equally), subjects were susceptible to death from causes unrelated to HCV infection. Based on empirical data, we assumed these deaths occurred at an increased rate relative to the general population.30-34 Finally, disease progression was simulated in annual cycles, until a maximum age of 90 years.

INDIVIDUALISED PATIENT FACTORS:
Outcomes were stratified according to individualised patient factors; these being initial fibrosis stage (Ishak 0-2, 3-5 and 6) and age (30, 45 and 60 years). Thus in total, disease course was simulated separately according to nine distinct patient types (i.e. all possible permutations of fibrosis stage and age).

PRIMARY OUTCOMES:
These reflected: patient-important events (those "perceptible to the patient and of sufficient value that changing their frequency would be of value to the patient"35); the inceptive rationale for
therapy (i.e. to prevent HCV-related complications and death); and the chief concerns of patients (premature-death and disease progression). Hence as follows:

(i) OUTCOME-1: The likelihood of viral-clearance conferring additional years of life

(ii) OUTCOME-2: The likelihood of viral-clearance conferring additional years of life in compensated health states (i.e. the avoidance of liver failure).

The rationale for outcome-2 is that in compensated disease states, the functioning of the liver is (by and large) unimpaired (i.e. by its very definition, the liver is able to compensate for the damage incurred). Accordingly, patient preferences for mild, moderate and compensated cirrhosis states do not differ.38,39

EXPRESSING OUTCOMES THROUGH PROBABILITY DISTRIBUTIONS:
Regarding outcome-1, we assembled the probability distribution for total life years gained (i.e. all life years gained in non-absorbing disease states) through attaining viral-clearance (versus the alternative scenario of persisting chronic infection). From the resulting distribution, we draw particular attention to the probability of gaining >0 additional life-year(s). Similarly with regards to outcome-2, we compiled the probability distribution for life years gained in compensated health states, and emphasise the probability of gaining >0 additional year(s).

EXPRESSING OUTCOMES THROUGH THE NUMBER-NEEDED-TO-SVR:
We determined the number needed to attain SVR in order to prevent one patient dying a premature HCV-related death (NNS1); calculated as the reciprocal of the probability of gaining >0 additional life-years. Equally, we calculated the number needed to attain SVR in order to avert one patient from prematurely developing overt liver disease (NNS2); calculated as the reciprocal of the probability of gaining >0 additional years in compensated health states.

The NNS is a HCV bespoke version of the number needed to treat (NNT). The NNT (referring to the number of patients that need to be treated in order to avert one additional adverse outcome) is
well-regarded among clinicians as a meaningful measure of the effectiveness of a medical
intervention.\textsuperscript{40,41} Thus, the rationale for additionally framing the benefit of viral-clearance in an
NNS format is to assist interpretation by clinicians and their patients (the target audience of this paper).

\textbf{UNCERTAINTY DUE TO SAMPLING ERROR:}
To quantify the overall uncertainty in our outcomes attributable to sampling error, we assigned
probability distributions to model parameters (as specified in Table-1), and sampled randomly
from these. As is recommended for microsimulation models,\textsuperscript{20} we adopted a stratified sampling
approach (Latin hypercube) enabling a more efficient coverage of the sampling space than non-
stratified sampling alone (thus permitting fewer replications and a less onerous computational
intensity). For each set of random parameter draws (1000 performed in total) we ran each type of
patient through the model 10,000 times (thus equating to 10 million simulations in total for each
patient type). The variability (expressed as the 2.5\textsuperscript{th} and 97.5\textsuperscript{th} percentiles) of each outcome
across these 1,000 parameter draws was used derive a 95\% uncertainty interval.

\textbf{SENSITIVITY ANALYSES:}
We performed three one-way sensitivity analyses (SA) to assess the variability of our outcomes to
pivotal parameters. As follows:

1. \textbf{SA-1}: We increased our base case fibrosis progression parameters, pro rata, to reflect
16\% progression to cirrhosis at 20 years (as per alternative progression data on liver
clinic attendees\textsuperscript{42}).

2. \textbf{SA-2}: We decreased our base case fibrosis parameters, pro rata, to reflect 7\% progression
to cirrhosis at 20 years. The lower 7\% progression rate\textsuperscript{43} is appropriate when modelling
the general infected population\textsuperscript{44} (i.e. as for the US birth cohort screening intervention\textsuperscript{45}).
3. SA-3: we assumed no excess risk (compared to the general population) for non HCV-related mortality.

RESULTS

OUTCOMES IN TERMS OF PROBABILITY DISTRIBUTIONS:
Gains in total life-years (outcome-1) and life-years spent in compensated disease states (outcome-2) attributable to viral-clearance, exhibited highly skewed distributions (see eFigure 1-2). For patients with initially mild or moderate fibrosis these probability distributions bespeak a situation where the majority gains minimally, but the minority gains considerably. Gains were more likely and more substantial for those treated at advanced fibrosis stages and younger ages. Patients with mild fibrosis at age 60 years of age had the lowest probability of benefiting from a SVR; a 1.6% (95%CI: 0.8-2.7) and 2.9% (95%CI: 1.5-4.7) chance in relation to outcome-1 and outcome-2, respectively (see Table-2). In contrast, patients with compensated cirrhosis at 30 years of age had the greatest probability of benefiting from a SVR; a 57.9% (95%CI: 46.0-69.0) and 67.0% (95%CI: 54.1-78.2) chance in relation to outcome 1 and 2, respectively. Notwithstanding the probability of benefiting from viral-clearance being small (particularly so for patients with mild and moderate fibrosis), amongst those who did benefit, the magnitude of this benefit was considerable; for example 6.2-14.5, 7.8-19.3, and 9.8-23.7 additional life-years for persons initially with mild fibrosis, moderate fibrosis and compensated cirrhosis, respectively.

OUTCOMES IN TERMS OF NUMBER-NEEDED-TO-SVR:
The number needing to attain SVR in order to avert adverse outcomes was highly heterogeneous across individualised patient factors (Table-3). For example, on average, only two patients with cirrhosis at 30 years would (on average) need to attain SVR in order to avert one HCV-related
Whereas for mildly fibrotic patient aged 60 years, 65 such patients would need to attain SVR in order to avert that same one death. Similarly, on average, only two persons (with cirrhosis at 30 years of age) would need to attain SVR in order for one patient to gain at least one additional year in a compensated health state. This compares to 35 patients (with mild disease at 60 years of age) that would need to attain SVR in order to achieve that same effect.

SENSITIVITY ANALYSES:

The likelihood of benefiting from viral-clearance was increased under SA-1 and SA-3, but reduced under SA-2 (see Table-4, and eTables 1-6). Nevertheless, for all SAs, the probability of benefiting from viral-clearance (in terms of either outcome 1 or 2) remained ≤20% (or analogously NNS≥5) for patients with mild fibrosis (at all ages) and moderate fibrosis (at age 60 years).
DISCUSSION

Treating populations with chronic HCV is highly cost-effective\textsuperscript{21-24}, nevertheless, for the individual patient, there are clearly a range of benefits to be had. At its most extreme, the probability that a mildly fibrotic person at 60 years of age will benefit from viral-clearance (in terms of clinically apparent outcomes) is just 2-3\%, whilst it is 58-67\% for a cirrhotic person at 30 years of age (Table-2). This contrast is tantamount to a clinician needing to clear infection in, on average, $\sim$35 times as many persons of the former description (versus persons of the latter) in order to avert the same number of HCV-related deaths (Table-3). Variation in the merit of a SVR is acknowledged neither in clinical guidelines,\textsuperscript{36,46} nor in information made available to patients.\textsuperscript{47,48} With this perspective, the use of current treatment regimens (with poor adverse-effect profiles \textsuperscript{10-14}) to treat older patients with minimal fibrosis, becomes a moot point and a challenging decision for patients and physicians.

The view that, in the absence of treatment, severe liver disease is not an inevitable outcome of chronic HCV infection is not new. Seeff and Alter have speculated that two thirds of chronic HCV patients will not develop severe liver-related manifestations of infection within their lifetimes.\textsuperscript{16} Moreover, Yoshida and colleagues calculated the mean gain in HCC-free survival attributable to SVR in Japanese patients according to age and fibrosis stage.\textsuperscript{49} Their findings mirror ours. More specifically they too noted: (i) the gain in HCC-free survival varies markedly according to age and fibrosis stage, and (ii) older patients with mild fibrosis have less to gain from treatment. However, Yoshida's study was based entirely on data from Japanese patients and only considered HCC-free survival as an outcome. Further, \textit{mean} gain in HCC-free survival is a somewhat misleading summary measure for the individual patient (i.e. the benefit distributions presented in Fig 2-4 are heavily skewed). Finally, although clinical guidelines urge that treatment
decisions be individualised,\textsuperscript{36,46} the literature is bereft of data delineating the benefits of therapy according to patient factors. Hence, all in all, we consider this study a valuable contribution to the evidence base.

Presently, SVR is labelled a "cure"\textsuperscript{48} (language a patient would generally associate with an outcome that restores health). Analogously, pre-treatment discussions (between patient and clinician) weigh only the probability of SVR against the risk of adverse-effects.\textsuperscript{47} In these ways, SVR can be portrayed as an outright benefit in itself. We caution that framing viral-clearance in this way (without consideration of age or disease-stage) may misguide patients apropos the value of therapy. At the same time, HCV initiatives are increasingly geared towards widening access to treatment. A simple utilitarian logic underpins this strategy: The more persons treated, the more cases of end-stage-liver-disease, in time, will be averted. Screening US baby boomers (persons born between 1945 and 1965) for HCV infection (with a view to treating those that screen positive) is a case-in-point.\textsuperscript{45} This initiative will identify \~1.6 million patients with chronic infection, here-to-fore unaware of their condition. It is estimated that of these 1.6 million, more than 50\% will be aged 45 years+ with mild fibrosis, or aged 60 yrs+ with moderate fibrosis\textsuperscript{50}; in other words, patient-groups that gain less from a SVR (assuming SVR is attained at all). Thus, on one hand, at the population level, birth-cohort screening will indeed avert a considerable number of end-stage liver disease cases over the years to come. All the same, from the perspective of any one individual patient, the likelihood of benefit may not always be sufficient to offset the adverse-effects of therapy. Ultimately, it is for the patient and their clinician (not the authors of this paper) to decide what is, and is not, an attractive risk-benefit ratio. However, it is for the medical-researcher to arm them with an objective assimilation of the data. Accordingly, the data presented herein have important potential; particularly to inform the treatment decisions of individuals identified with chronic HCV infection via US birth cohort screening.
Hitherto HCV simulation models are pitched at policy makers; insofar as they focus on broad population-level outcomes, far-removed from the individual-level decision-to-treat\textsuperscript{21-27} Our focus on addressing the questions that matter most to patients, in an intuitive way (in effect advocating a new patient-centred modelling approach), is the greatest strength of this paper. Various impediments hinder primary research studies, in their own right, from addressing these issues. In particular, (i) initial infection is asymptomatic (so inception cohorts are rare), (ii) liver damage thereafter occurs gradually over a course of decades (rendering long-term follow-up difficult), (iii) antiviral therapy post-diagnosis is ubiquitous (thus adulterating the picture going forward), and (iv) the gold standard means of assessing liver stage (a liver biopsy) is an invasive procedure and performed sparingly.\textsuperscript{17} The simulation approach adopted here, draws on primary research data to generate the most plausible inference to the question-at-hand. However, results will rest on certain assumptions. In particular, the HIT-model assumes a constant (linear) course of fibrosis progression over the lifetime of the patient (as per hitherto HCV models\textsuperscript{21,23,24,26}, and as is consistent with current observational data\textsuperscript{51}). However, there is uncertainty in this assumption; fibrotic accretion may accelerate with time (particularly after 30 years of infection; a follow-up duration few observational studies exceed) and in this eventuality, our findings may be affected. These uncertainties (not reflected in our confidence intervals) should be made clear. Secondly despite stratifying by age and disease-stage, patients and clinicians may argue that the HIT-model still remains too broad-brush. In particular, alcohol (which contributes to disease progression enormously\textsuperscript{52}) is ignored. Future research should better characterise the course of disease progression in the absence of heavy alcohol use and incorporate these findings into a patient-centred modelling approach. Similarly, differences in disease progression, by gender, should also be considered. Thirdly, the HIT-model frames the benefit of SVR in terms of averting liver failure and premature death; sequelae that concern HCV patients most.\textsuperscript{57} However, these outcomes may not capture the totality of HCV-induced adversities, and as such may understate the benefits of therapy. In particular:
(a) Compensated cirrhosis is frequently asymptomatic, but not always; some patients present with non-specific symptoms (dyspepsia, asthenia, upper abdominal discomfort, etc). The precise symptomatic-asymptomatic ratio is undetermined. Fattovich et al report that among patients referred to tertiary clinics following diagnosis of compensated cirrhosis, 43% demonstrated such symptoms, and 57% did not (although, N.B, a referral bias in favour of symptomatic patients is clearly likely to operate in this type of cohort).

(b) HCV infection can predispose one to various non-liver-related conditions (cryoglobulinaemia, lichen planus, vitiligo, porphyria cutanea tarda and B-cell lymphomas) which are not considered in our model (although, barring cryoglobulinemia, these conditions are relatively infrequent).

(c) Our simulation model does not include the possibility that SVR benefits the patient vis-à-vis non-liver-related mortality. An association between chronic HCV infection per se and increased non-liver mortality is equivocal and not supported by many key studies. Ongoing scrutiny however, particularly with regard to vascular disease, is required.

There are important implications to these data. In the short-term, this work will inform the contemporary patient dilemma of immediate treatment with existing therapies (that have poor adverse-effect profiles) versus awaiting interferon-free regimens that promise higher SVR rates with better tolerability. Longer-term, it urges that broadened access to therapy be twinned with efforts to more objectively communicate (to the individual patient) the risk-benefit ratio of treatment.
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Authors contributions: Hamish Innes and Prof. Sharon Hutchinson had full access to all of the data generated by this model and take full responsibility for the integrity and accuracy of the analysis.

Study concept and design: Innes and Hutchinson.

Analysis and interpretation of data: Innes, Dusheiko, Goldberg, Hayes, Mills, Dillon, Aspinall, Barclay and Hutchinson

Drafting of the manuscript: Innes, Dusheiko, Goldberg, Hayes, Mills, Dillon, Aspinall, Barclay and Hutchinson

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(12) US Food and Drug Administration. Drug safety communication.


(61) Life Tables for Great Britain, 2008-2010.


FIGURE LEGENDS

Fig.1: Chronic HCV natural history schematic assumed in the Hepatitis-C Individual-based Treatment-decision model
### Table-1: Parameters incorporated into the HIT-model

<table>
<thead>
<tr>
<th>Health state transition /scenario(s) applicable to/</th>
<th>Mean annual probability of transition</th>
<th>Data source(s)</th>
<th>Sampling distribution</th>
<th>2.5-97.5 percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-decompensated health states</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild fibrosis to Moderate fibrosis [2]</td>
<td>2.5%*</td>
<td>Wright et al 24</td>
<td>Beta (38.06, 1484.38)</td>
<td>1.8-3.3</td>
</tr>
<tr>
<td>Mild fibrosis to Moderate fibrosis [1]</td>
<td>0.0%</td>
<td>†</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>Moderate fibrosis to Cirrhosis [2]</td>
<td>3.7%§</td>
<td>Wright et al 24</td>
<td>Beta (26.87, 699.30)</td>
<td>2.5-5.2</td>
</tr>
<tr>
<td>Moderate fibrosis to Cirrhosis [1]</td>
<td>0.0%</td>
<td>†</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>Compensated cirrhosis to decompensated cirrhosis [2]</td>
<td>3.9%</td>
<td>Fattovich et al 28</td>
<td>Beta (14.58, 359.21)</td>
<td>2.2-6.1</td>
</tr>
<tr>
<td>Compensated cirrhosis to decompensated cirrhosis [1]</td>
<td>0.43%</td>
<td>Fattovich et al 27 and Chou et al 29**</td>
<td>Beta (14.58, 359.21) &amp; Uniform (0.021)</td>
<td>0.0-1.0</td>
</tr>
<tr>
<td>Compensated cirrhosis to liver cancer [2]</td>
<td>1.4%</td>
<td>Fattovich et al 28</td>
<td>Beta (1.92, 135.12)</td>
<td>0.5-2.8</td>
</tr>
<tr>
<td>Compensated cirrhosis to liver cancer [1]</td>
<td>0.38%</td>
<td>Fattovich et al 28 and Chou et al 29††</td>
<td>Beta (1.92, 135.12) &amp; Uniform (0.18, 0.46)</td>
<td>0.1-1.0</td>
</tr>
<tr>
<td><strong>Post-decompensated health states</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decompensated cirrhosis to liver cancer [1&amp;2]</td>
<td>1.4%</td>
<td>Fattovich et al 28</td>
<td>Beta (5.35, 377.09)</td>
<td>0.5-2.8</td>
</tr>
<tr>
<td>Decompensated cirrhosis to liver related death [1&amp;2]</td>
<td>13.0%</td>
<td>Fattovich et al 28</td>
<td>Beta (146.9, 983.1)</td>
<td>11.1-15.0</td>
</tr>
<tr>
<td>Decompensated cirrhosis/HCC to liver transplant [1&amp;2]</td>
<td>2.0%</td>
<td>Hutchinson et al 26</td>
<td>Beta (10.18, 498.71)</td>
<td>1.0-3.4</td>
</tr>
<tr>
<td>HCC to death [1&amp;2]</td>
<td>43.0%</td>
<td>Fattovich et al 28</td>
<td>Beta (116.67, 154.66)</td>
<td>37.2-48.9</td>
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<tr>
<td>Liver transplant death in first year [1&amp;2]</td>
<td>14.6%</td>
<td>Hutchinson et al 26</td>
<td>Normal (14.6, 1.81)</td>
<td>11.1-18.1</td>
</tr>
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<td>Liver transplant survival post year 2+ [1&amp;2]</td>
<td>4.4%</td>
<td>Hutchinson et al 26</td>
<td>Normal (4.4, 0.46)</td>
<td>3.5-5.3</td>
</tr>
<tr>
<td><strong>non-HCV related mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age specific probability of non-HCV related mortality for UK general population [1&amp;2]</td>
<td>E.g. from 0.06% (aged 30-39yrs) to 7.8% (aged 80+ yrs)</td>
<td>UK all-cause mortality life tables: Years 2007-2009 61</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td>Factor increase (relative to general population) assumed for HCV persons 30-39 yrs [1&amp;2]</td>
<td>7.7 §§</td>
<td>McDonald et al 33</td>
<td>Normal (7.66, 0.60)</td>
<td>6.49-8.85</td>
</tr>
<tr>
<td>Factor increase (relative to general population) assumed for HCV persons 40-49 yrs [1&amp;2]</td>
<td>4.9 §§</td>
<td>McDonald et al 33</td>
<td>Normal (4.90, 0.58)</td>
<td>3.8-6.0</td>
</tr>
<tr>
<td>Factor increase (relative to general population) assumed for HCV persons 50+ yrs [1&amp;2]</td>
<td>1.7 §§</td>
<td>McDonald et al 33</td>
<td>Normal (1.67, 0.18)</td>
<td>1.3-2.0</td>
</tr>
</tbody>
</table>

*Modified to be 3% and 1.8% for sensitivity analysis 1 and 2, respectively
† Assumed 0% is based on a conservative assumption in the absence of robust empirical data
§ Parameter not varied
¶ Modified to be 2.6% and 4.4% for sensitivity analysis 1 and 2, respectively
** Systematic review by Chou et al 29 describes a 79-100% factor reduction in the annual risk of decompensated cirrhosis post SVR
† † Systematic review by Chou et al 29 describes a 54-82% factor reduction in the annual risk of liver cancer with SVR
§§ Modified to 1 for sensitivity analysis 3
Table 2: Impact of treatment-induced viral clearance in terms of: (i) total life years gained, and (ii) years gained in compensated disease states, according to individual patient factors

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Initial fibrosis stage</th>
<th>Initial age (years)</th>
<th>(i) Total life years gained</th>
<th>(ii) Years gained in compensated disease states</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Distribution: Median (IQR)</td>
<td>% Probability of gaining &gt;0 years (95% interval)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Distribution: Median (IQR)</td>
<td>% Probability of gaining &gt;0 years (95% interval)</td>
</tr>
<tr>
<td><strong>Mild (Ishak 0-2)</strong></td>
<td>30</td>
<td>0 (0-0)</td>
<td>13.6 (8.5-19.4)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>0 (0-0)</td>
<td>6.3 (3.5-9.6)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0 (0-0)</td>
<td>1.6 (0.8-2.7)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate (Ishak 3-5)</strong></td>
<td>30</td>
<td>0 (0-14)</td>
<td>40.0 (27.9-51.7)</td>
<td>0 (0-20)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>0 (0-1)</td>
<td>26.0 (16.7-36.1)</td>
<td>0 (0-7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0 (0-0)</td>
<td>10.6 (6.2-16.2)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Compensated cirrhosis (Ishak 6)</strong></td>
<td>30</td>
<td>7 (0-26)</td>
<td>57.9 (46.0-69.0)</td>
<td>13 (0-32)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>0 (0-15)</td>
<td>49.3 (36.7-60.9)</td>
<td>7 (0-21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0 (0-4)</td>
<td>31.6 (21.5-42.1)</td>
<td>0 (0-9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table-3: Number needed to attain sustained viral response in order, on average: (i) to avert one patient from a dying a HCV-related death (NNS₁), and (ii) for one patient to spend at least one additional year in a compensated health state (NNS₂), according to initial fibrosis stage and age.

<table>
<thead>
<tr>
<th>Initial fibrosis stage</th>
<th>Initial age (years)</th>
<th>NNS₁ (95% interval)* to 1 decimal place</th>
<th>NNS₂ (95% interval)* to 1 decimal place</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (Ishak 0-2)</td>
<td>30</td>
<td>7.4 (5.1-11.7)</td>
<td>5.6 (4.0-8.7)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>16.1 (10.4-28.4)</td>
<td>10.8 (7.1-18.5)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>64.9 (36.8-125.0)</td>
<td>35.0 (21.1-64.5)</td>
</tr>
<tr>
<td>Moderate (Ishak 3-5)</td>
<td>30</td>
<td>2.5 (1.9-3.6)</td>
<td>2.1 (1.6-2.9)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>3.9 (2.8-6.0)</td>
<td>2.9 (2.1-4.3)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>9.5 (6.1-16.2)</td>
<td>5.9 (4.0-9.6)</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>30</td>
<td>1.7 (1.4-2.2)</td>
<td>1.5 (1.3-1.8)</td>
</tr>
<tr>
<td>(Ishak 6)</td>
<td>45</td>
<td>2.0 (1.6-2.7)</td>
<td>1.6 (1.4-2.2)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>3.2 (2.4-4.6)</td>
<td>2.2 (1.7-3.1)</td>
</tr>
</tbody>
</table>

*distribution positively skewed so central estimate presented as the median
Table 4: Probability that treatment-induced viral clearance confers: (i) additional life year(s), and (ii) additional year(s) spent in compensated health states, according to sensitivity analyses (SA) 1-3.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Initial fibrosis stage</th>
<th>Initial age (years)</th>
<th>(i) Probability of gaining &gt;0 additional life years (95% interval)</th>
<th>(ii) Probability of gaining &gt;0 addition years in compensated disease states (95% interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SA 1 - 16% cirrhosis progression at 20 years</td>
<td>SA 1 - 16% cirrhosis progression at 20 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SA 2 - 7% cirrhosis progression at 20 years</td>
<td>SA 2 - 7% cirrhosis progression at 20 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SA 3 - no excess non-HCV related mortality assumed</td>
<td>SA 3 - no excess non-HCV related mortality assumed</td>
</tr>
<tr>
<td>Mild (Ishak 0-2)</td>
<td>30</td>
<td>17.4 (11.5-24.1)</td>
<td>8.4 (4.3-13.9)</td>
<td>18.8 (12.0-26.2)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>8.4 (5.0-12.4)</td>
<td>3.7 (1.7-6.6)</td>
<td>8.8 (5.1-13.0)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>2.2 (1.1-3.5)</td>
<td>0.9 (0.4-1.8)</td>
<td>2.5 (1.4-4.0)</td>
</tr>
<tr>
<td>Moderate (Ishak 3-5)</td>
<td>30</td>
<td>44.1 (32.4-55.2)</td>
<td>32.6 (20.1-45.7)</td>
<td>50.4 (36.2-63.7)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>29.3 (19.6-39.4)</td>
<td>20.5 (11.6-30.8)</td>
<td>32.5 (21.5-44.0)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>12.3 (7.1-18.2)</td>
<td>8.1 (4.1-13.3)</td>
<td>14.8 (9.0-21.7)</td>
</tr>
<tr>
<td>Compensated cirrhosis (Ishak 6)</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>66.7 (54.2-78.2)</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>NA</td>
<td>NA</td>
<td>55.6 (42.5-67.8)</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>NA</td>
<td>NA</td>
<td>38.1 (27.1-49.3)</td>
</tr>
</tbody>
</table>