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TITLE:

Strategies for the treatment of Hepatitis C in an era of interferon-free therapies: what public-health outcomes do we value most?

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ABSTRACT

OBJECTIVE:

The expense of new therapies for Hepatitis C Virus (HCV) infection may force health systems to prioritise the treatment of certain patient groups over others. Our objective was to forecast the population impact of possible prioritisation strategies for the resource-rich setting of Scotland.

DESIGN: We created a dynamic markov simulation model to reflect the HCV infected population in Scotland. We determined trends in key outcomes (e.g. incident cases of chronic infection, and Severe Liver Morbidity (SLM)) until the year-2030, according to treatment strategies involving prioritising, either: a) persons with moderate/advanced fibrosis, or b) Persons Who Inject Drugs (PWID).

RESULTS:

Continuing to treat the same number of patients with the same characteristics, will give rise to a fall in incident infection (from 600 cases in 2015, to 440 in 2030) and a fall in SLM (from 195 cases in 2015 to 145 in 2030). Doubling treatment-uptake and prioritising PWID will reduce incident infection to negligible levels (<50 cases per year) by 2025, whilst SLM will stabilise (at 70-75 cases per year) in 2028. Alternatively, doubling the number of patients treated, but prioritising instead persons with moderate/advanced fibrosis will reduce incident infection less favourably (only to 280 cases in 2030), but SLM will stabilise by 2023 (i.e. earlier than any competing strategy).

CONCLUSION:

Prioritising treatment uptake among PWID will substantially impact incident transmission -however, this approach foregoes the optimal impact on SLM. Conversely, targeting those with moderate/advanced fibrosis has the greatest impact on SLM but is suboptimal in terms of averting incident infection.

KEYWORDS: CHRONIC HEPATITIS; EPIDEMIOLOGY; HCV; HEPATITIS C; LIVER

SUMMARY BOX:

What is already known?

1) Hepatitis C virus infection affects in excess of 140 million persons globally, and causes half a million deaths each year.

2) A new era of highly effective and tolerable therapy is imminent for resource-rich settings.

3) However, new treatments will be costly, and patient demand will likely exceed what health systems can afford to supply.

4) Health systems may need to consider prioritising certain patient groups over others.

What this study adds?

1) Treatment strategies that prioritise Persons Who Inject Drugs (PWID) have the optimal impact on averting incident chronic infection, but fall short in terms of limiting new cases of Severe Liver Morbidity (SLM).

2) Conversely, strategies prioritising persons with more advanced liver fibrosis have the most advantageous impact on SLM, but are suboptimal in terms of curtailing incident transmission.

3) A trade-off between these competing impacts (curtailing SLM or curtailing incident infection) must be reached.

How might it impact on clinical practice in the foreseeable future?

1) To fully profit from new therapies, policy makers should consider which population goals they value most (i.e. impact on incident infection or SLM) and engineer treatment strategies accordingly.

INTRODUCTION:

Globally, in excess of 140 million persons are chronically infected with the hepatitis C virus (HCV) [1]- an infection that leads to half a million deaths each year from liver cirrhosis and liver cancer.[2]. A course of Pegylated Interferon and Ribavirin (PIR), permanently clears the infection in 50-60% of instances, and has been available to patients in resource-rich countries for more than a decade [3]. Yet, owing to significant adverse effects [4, 5] and a high rate of contraindication [6], PIR uptake has been inadequate (only 0.5-4.6% of viremic cases is treated each year [7]). Accordingly, over the last decade, we have seen little curtailment in HCV-related sequelae. On the contrary, HCV-related mortality is rising, and de-facto, more people now die from HCV than from HIV in resource rich settings such as the UK and the US [8, 9]. By this token then, PIR has proven an ineffective means of managing the HCV infection burden.

It is highly significant then, that we stand today, at the cusp of a pharmacological revolution [10-12]. From 2015, HCV therapy will entail higher response rates, fewer contraindications, shorter durations, and greater tolerability (i.e. for most patients, interferon will be dispensed with altogether, and for the rest, used sparingly). With these patient-friendlier attributes, demand for treatment will conceivably reach unprecedented heights. But will health services be able match this demand with supply? HCV antiviral therapy is not cheap; the current going rate, which new therapies are likely to exceed, stands at ~US$100,000 per treatment course [13]. So, with in excess of 250,000 persons living with chronic infection in the UK alone [14], clearly we cannot afford, at least immediately, to treat everyone. Now then is a provident time to consider possible post-2015 national treatment strategies, in terms of their expected population-level impact.

In most resource-rich settings (in particular, Western Europe, North America, and Australia) HCV transmission is driven by intravenous drug use [15]. Perhaps not surprisingly then, Treatment-To-Prevent (TTP) – i.e. concentrating treatment resources on Persons Who Inject Drugs (PWID) - is attracting support [16-19]. The appeal is simple: treating a PWID benefits not just that individual (i.e. in terms of minimising their risk of liver complications) but the wider PWID population as a whole (i.e. by preventing that individual from transmitting the infection to their future injecting partners). But, by necessity, TTP targets a younger population, not in great danger of progressing to symptomatic liver disease (in the near future at least). With the continuing rise in HCV-related mortality, an alternative approach might be, to instead set our sights on treating those with the highest risk of near-term liver morbidity.

The principal of distributive justice holds that when "determining the appropriate level of health care to make available for one set of patients, we must take account of the effect of such a use of resources on other patients"[20]. With this in mind, we forecast population-level trends in a resource-rich setting, according to possible national treatment strategies. Our aim is to stimulate discussion as to how we can capitalise on the opportunities (whilst avoiding any ethical pitfalls) that new therapies will bring.

METHODS:

GENERAL MODEL OVERVIEW

To forecast population-level outcomes according to alternative treatment strategies, we created a dynamic Markov model. The model has a compartmental structure, with each compartment representing a pertinent health state (as per the known natural history of HCV infection and disease progression; see eFig.1). Scotland was chosen as the setting for this model given her rich data sources; in particular, Scotland has a national HCV diagnosis database [21], electronically linked to a national HCV treatment database [22], and conducts regular epidemiological surveys of her PWID population (to note, throughout this paper, the "PWID" acronym refers specifically to *on-going* injecting drug use). [23].We drew upon these data sources in order to estimate the number of Scottish persons residing in each model compartment in the year 2009 (See Table.1 and Appendix A). Then, we used inter-compartment transfer rates obtained from the scientific literature (outlined in Table.2), to project liver-related disease/deaths and incident transmission over a twenty year timeframe (i.e. 2010-2030), in the context of interferon-free/sparing treatment regimens, available from 2015-onwards [10-12].

DETAILED MODEL OVERVIEW

INCIDENT INFECTION

The model incorporates an inflow of new injecting initiates each year (entry via PWID states; see eFig.1). The number of subjects entering PWID states equals the number exiting (where exit occurs through death or through ceasing injecting); hence, an implicit assumption underpinning this model is a stable PWID population size (i.e. ~15,300 persons[24]), in Scotland, over the timeframe of this model. The hallmark of PWID states is that uninfected subjects risk acquiring chronic infection with genotype 1-3 HCV (N.B. genotypes 4-6 account for <1% of infections in Scotland [25], and thus, for simplification, were omitted from this model). We assumed that PWID mix randomly, regardless of their HCV infection status, and so we model incident chronic infection using a mass-action transmission function [26].We calibrated this transmission function to an estimate of 600 incident chronic infections (95% CI: 400-800) – equating to an incidence of 10 (7-14) per 100 person years – occurring in the year-2009 among all PWID in Scotland [27]; see appendix B for further details. The average injecting "career" is 9.1 years (i.e. an 11% per-annum chance of cessation) [17]. Upon ceasing injecting drug use, model subjects transfer permanently to former/never PWID states where incident HCV transmission no longer occurs (see eFig.1).

LIVER DISEASE PROGRESSION

Model subjects differ according to the extent of fibrosis incurred to their liver (as per the Ishak score [28]: Ishak 0-1=mild fibrosis; Ishak 2-5=moderate; and Ishak 6=compensated-cirrhosis). Under chronic infection, fibrosis advances from a mild to moderate severity at a rate of 1.8% per annum; then from moderate severity to compensated-cirrhosis at a rate of 2.7% per

annum (see Appendix C.1 for derivation). On average, these progression rates equate to 7% of persons developing cirrhosis within 20 years of initial infection (consistent with community-level observational data [29]; as is appropriate in a population-level model [30]). Subjects with compensated-cirrhosis are at risk of developing decompensated cirrhosis (defined as ascites, bleeding varices, jaundice or encephalopathy) and liver cancer. These two Severe Liver Morbidity (SLM) states carry a marked risk of a liver-related death (43% per annum with liver cancer; 13% per annum with decompensated cirrhosis [31]). Although this bleak prognosis can be improved through liver transplantation, suitable donors are scarce (hence our model incorporates only a 2% chance, per annum, of transplantation [32]). Of those that do receive a transplant, 85.6% survive the first year; thereafter the risk of a liver death falls to 4.4% [32]. Patients with chronic infection and compensated liver disease are eligible for antiviral treatment. Those attaining the optimal treatment outcome (a sustained viral response [SVR], defined as testing undetectable for viral RNA at least six months after terminating treatment) move into "Treatment-induced viral clearance" states and exhibit an improved prognosis vis-à-vis risk of subsequent liver disease progression (See eFig.1). In post-SVR Ishak-6 states, decompensated cirrhosis and liver cancer occur at a diminished rate (the per annum risk of decompensated cirrhosis falls from 6.5% to 0.8%; the risk of liver cancer falls from 1.4% to 0.4%). Subjects in post-SVR Ishak 0-5 states can still advance through to cirrhosis (Ishak 6), but at a far-reduced rate relative to their chronic counterparts (see Appendix C.2). Of note, we assume SVR does not benefit PWID apropos re-infection risk and the subsequent chance of spontaneous clearance. Finally, at every stage of the model, death from non-liver related causes occurs at a rate of 1.8% [33] and 1.4% per annum, in PWID and former/never PWID states, respectively (see Appendix D regarding estimation of the latter mortality rate).

MODELLED TREATMENT STRATEGIES

On average, one-thousand patients have commenced a course of antiviral therapy, each year in Scotland, between 2010 and 2013. Of these treatment initiates, an estimated 12% were PWID (10% with mild fibrosis, and 2% with moderate-advanced fibrosis); 49% were former/never PIWD with mild fibrosis; and 38% were former/never PWID with moderate or advanced fibrosis (see Appendix E). We assume treatment-uptake and patient-composition remains unchanged in 2014. From 2015 onwards, we model eight distinct treatment strategies. The first strategy is simply a continuation of the status-quo (i.e. treating the same number of patients, with the same case mix, as per 2010-2014). The remaining seven are *alternative* treatment strategies, appropriate and feasible in the context of the impending IFN-free/sparing era. Each alternative strategy differs in terms of treatment uptake intensity, and patient case mix; see Table.3 and eTable.9

MODELLED TREATMENT EFFICACY

The status-quo SVR rates (via current standard-of-care – pegylated-interferon, ribavirin ± telaprevir/bocepreivr) are taken to continue until the end of 2014 (see Appendix F). Thereafter, we anticipate the availability of IFN-free/IFN-sparing regimens. For patients infected with genotypes 1-2, we surmise that these regimens will deliver SVR rates of 95% regardless of fibrosis stage [34-35]. Patients with genotype-3 infection will see marginally lower efficacy levels (90% for Ishak 0-5, and 80% for

Ishak 6 [36, 37]). Of note, in our base-case, persons that fail a course of therapy in 2010-2014 are eligible for re-treatment, but only with a post-2015 IFN-free/sparing regimen (and we make the simplifying assumption that the re-treatment patient has the same chance of an SVR as their treatment-naïve counterpart). However, persons that fail a post-2015 course of therapy are not considered re-treatable (although we remove this latter assumption in sensitivity-analysis 4).

PERFORMANCE OUTCOMES:

We considered the performance of each treatment strategy in terms of the following outcomes occurring over a short-term (defined as 2015-2020), medium-term (2015-2025), and long-term (2015-2030) time horizon.

i. Number of incident cases of SLM (i.e. decompensated cirrhosis and liver cancer) among persons with past/current chronic HCV infection.
ii. Number of liver-related deaths among persons with past/current chronic HCV infection
iii. Number of incident chronic HCV infections among PWID.

UNCERTAINTY ANALYSIS

PROBABILITSTIC SENSITIVITY ANALYSIS

We performed a probabilistic sensitivity analysis, to gauge total uncertainty attributable to the sampling error, inherent in our Table.1 parameters. This involved: (i) assigning, to each parameter an appropriate uncertainty distribution (see Table.1); (ii) selecting, for each parameter, a random value from this distribution; (iii) generating all specified outcomes under this unique set of parameter selections; and (iv)repeating this process 10,000 times. Hence, the 95% credible interval represents the range within which, the central 95% of these 10,000 data points lie.

ONEWAY SENSITIVITY ANALYSES:

We performed various one-way sensitivity-analyses (SA) to test our conclusions against uncertain assumptions. These are outlined in detail in Appendix J.

RESULTS:

DISEASE FORECASTS ASSUMING CONTINUATION OF EXISTING S1000-SQ STRATEGY (see Fig.1):

With the continuation of Scotland's existing treatment strategy (i.e. S1000-SQ), liver-related deaths increase from 130 cases in 2015, up to 150 cases in 2020, and stabilise thereafter. New instances of SLM peak at 195 cases in the year 2015 (i.e. the year we assume new treatments will be introduced), then declines continuously to 145 cases in 2030. Similarly, incident chronic infections fall steadily from 565 cases in 2015, to 440 cases by 2030.

PERFORMANCE OF ALTERNATIVE TREATMENT STRATEGIES (VERSUS EXISTING S1000-SQ STRATEGY)

(I) REDUCING INCIDENT CASES OF SEVERE LIVER MORBIDITY (see Fig.1-3, and Table .4):

Strategies prioritising persons with moderate and advanced fibrosis (i.e. S1000-ADV and S2000-ADV) exerted the optimal impact on SLM. Over the long-term time horizon (i.e. 2015-2030) cumulative SLM cases are 36.1% lower (95% CI: -41.4 to -23.4) with S2000-ADV, than under S1000-SQ. PWID-focused strategies also reduce SLM, but to a lesser extent; for example, analogously, S2000-PWID leads to a 26.2% reduction (95% CI: -32.3 to -14.7). A no-prioritisation approach increases the number of SLM cases, relative to a status-quo case mix. In-fact, in the long-term, treating 2000 patients a year without prioritisation, had an equivalent impact on SLM as treating half that number under a fibrosis prioritising strategy. That is to say, incident SLM was 11.4% lower (95% CI: -17.9 to +27.7) under S2000-NP, but 12.8% lower (95% CI: -19.8 to-6.8) with S1000-ADV. Notably, SLM does not decline indefinitely towards zero. For example, even under our maximum S2000-ADV strategy, SLM stabilises at 70 cases per year. Of these 70 cases, the majority (40-45 cases per year) arise in patients who have previously attained SVR.

(II) REDUCING LIVER MORTALITY (see Fig.1-3, and Table.4):

Similarly, strategies targeting those with moderate and advanced fibrosis have the greatest impact on curtailing liver mortality, whilst a no-prioritisation approach increased liver deaths (relative to S1000-SQ). Thus performance with respect to liver mortality was a mirror image of performance with respect to SLM. A key difference between SLM and liver mortality however, is that the latter is less amenable to change than the former. Particularly, in the short-term, where even with the S2000-ADV strategy, only a 2.4% mortality reduction (95% CI: -5.0 to -1.5) is seen relative to S1000-SQ. Nevertheless, important differences do emerge thereafter; for example, over the longer term, a 21.4% mortality reduction (95% CI: -24.9 to -13.4) occurs with S2000-ADV, relative to S1000-SQ. (but this decline remains notably less than the 36.1% reduction in SLM seen under the same S2000-ADV strategy, and over the same time period).

(III) REDUCING INCIDENT CHRONIC INFECTIONS (see Fig.1-3, and Table.4):

PWID-focused strategies bring about rapid steadfast declines in incident infection. Over the long-term, S2000-PWID leads to a 52.2% (95% CI: -55.9 to -23.9) reduction in incident infections relative to S1000-SQ. This performance far exceeds rival strategies – i.e. analogously, only a 13.3%-20.4% reduction occurred with S2000-ADV, S2000-SQ and S2000-NP. Of further mention, under S2000-PWID, the important public-health goal of reducing incident chronic infection to negligible levels (i.e. to less than 50 cases per year) is achieved in 2025.

POST-HOC ANALYSES:

1. COMBINATION STRATEGIES (see eTable.7-8, eFig.2-3)

   Under the S2000-ADV strategy, Scotland evidently begins to run out of patients with advanced fibrosis from the year 2025 onwards (see eTable.10). The consequence then is that in these latter years, less than the 2000 persons are treated per annum in our model under this strategy. Similarly, with the S2000-PWID strategy, Scotland runs out of infected PWID from ~2025, and so overall, less than 2000 patients are treated each year. Given this, we created a post-hoc combination strategy, whereby we first target those with advanced fibrosis in 2015-2022, and then change our focus to PWID in 2023-2030 (we also consider the vice-versa strategy). This combination approach offers an improved compromise between minimising both liver-related complications *and* new chronic infections over the 2015-2030 timeframe.

2. RAPID DEVASTATION OF SLM (see eTable.10)

   The S2000-ADV strategy stabilises SLM at 70-75 cases by the year 2023 (i.e. within our medium-term time horizon). We explored, in a post-hoc interrogation of our model, how this same reduction in SLM might be expedited. More specifically, we posed the following question: How many patients would Scotland need to treat under a moderate/advanced fibrosis prioritising strategy, in order to effect a rapid devastation of SLM? We defined a "rapid devastation" as reducing incident SLM to <75 cases within our short-term time horizon (2015-2020). On that basis, the minimum such treatment uptake necessary to achieve this goal was 3250 patients per year (i.e. a 3.25-fold increase from existing uptake levels, which amounts to treating 1980 individuals with moderate/advanced fibrosis per year).

DISCUSSION

Our model demonstrates the population impact of alternative treatment strategies during the landmark era of improved Hepatitis C therapies. What is immediately evident from these projections is that no single approach is optimal with regard to all public-health relevant outcomes; in other words, each involves a trade-off. For instance, targeting PWID will have the most advantageous impact on disease transmission, but falls short in terms of averting overt liver disease and death. Conversely, prioritising patients with moderate and advanced liver disease will have the maximum impact on liver-related complications and liver fatalities, but is suboptimal in terms of curtailing incident transmission. In more tangible terms, by doubling treatment uptake and targeting PWID, we have the opportunity to reduce incident infection to negligible levels (i.e. < 50 cases a year) in the year 2025. On the flip-side, through likewise doubling uptake, but instead prioritising those persons with moderate and advanced fibrosis, we can stabilise SLM (at ~70 cases per year) by the year 2023.Thus, new therapies afford public-health policy makers great opportunities, but equally, pose dilemmas too. Population priorities need to be debated and ultimately, certain trade-offs accepted.

In an ideal world, the most tolerable and efficacious therapies would be immediately available to every patient in want. Yet, in the face of finite health budgets and "sticker-shock" [38] drug prices (i.e. the reality today), some system of prioritisation, whereby SVR is pursued with greater urgency in some, is strategically sensible and ethically justifiable. An important finding from this projection model is that liver-related deaths were at their highest when no prioritisation system was in place. In fact, treating 2000 patients randomly (i.e. as per S2000-NP) would have less impact on liver deaths than treating half that number under a fibrosis-prioritising strategy (i.e. as per. S2000-ADV); see Fig.4. Of course, prioritisation intrinsically means treating less of one group, in order to treat more of another. Here, our strategies are centred on directing therapy *away* from mildly fibrotic former/never PWID. But how would a policy of shepherding treatment away from this low-priority group work in practice? -Particularly when there are no drawbacks of toxicity to temper demand (as has always been the case with HCV therapies, until now).Ultimately, the success or failure of any prioritisation approach will rest on whether a societal consensus can be reached as to which patients merit greatest precedence. Yet in parallel, clinicians should be more explicit in articulating to patients what they stand to gain from a SVR – in effect, managing expectations. Until recently, this has been difficult because the prognosis-improvement an SVR confers has been vague (other than perhaps being able to say to patients that SVR lowers the risk of liver complications and death). [39] However a recent simulation model, synthesising the existing literature in a novel and patient-centred way, provides clearer direction. For instance, the sixty-year old patient with mild fibrosis has just a 1.6% and 2.9% probability of gaining additional life years and healthy life years, respectively (where "healthy" is defined as being free from liver decompensation). [40] More realistic expectations may lead to patients making more conservative treatment choices if the benefits on offer are accepted to be modest (as has been noted in other areas of medicine [41]). Measured expectations are needed too, on the part of health-care policy makers. Our model demonstrates that new therapies, targeted at those with advanced fibrosis, can dramatically reduce and stabilise SLM, nevertheless it will remain, going forward, an important feature of this population. Partly, this reflects a well-noted

continued risk of HCC among SVR patients with moderate to advanced fibrosis. More fundamentally however, post-SVR SLM reflects harmful lifestyle exposures intrinsic to the general HCV infected population (i.e. 90% of HCV infections are acquired through injecting drug use, [42] and a history of heavy alcohol use is reported in >1/3 of persons attending treatment services in Scotland [43]). It is often assumed, that the entirety of liver disease occurring within the chronic HCV infected population, is de-facto attributable to chronic infection *per se*. In-fact, if one examines the health outcomes of persons who spontaneously resolve HCV (i.e. a group who are commensurable to chronic patients in terms of lifestyle exposures, but who crucially, will have harboured viral RNA for a <6 month duration) one finds here too, vastly elevated rates of adverse liver outcomes, relative to population controls.[44-46] Our model then, foreshadows the rise of "post-SVR" disease, the corollary of which is that continued engagement with this population to tackle lifestyle factors will be necessary to drive SLM down further, and in effect, win the wider war. To that end, no magic-bullet medicines exist; rather an age-old, complex web of psychosocial factors to unpick.

Although the results of this model are intended to be illustrative, we endeavoured to build treatment strategies that were realistic vis-à-vis implementation at a national, or even pan-national, level. However, whilst increasing the fraction of PWID treated each year by 20% will be seen as achievable, the same scale-up for moderate/advanced fibrotics may be viewed as a greater challenge. PWID for example, conveniently attend specific sites; in particular, needle exchanges and opiate substitution centres. Thus, they are readily accessible to outreach initiatives - the implementation of dried-blood-spot testing in addiction clinics being one such case-in-point [47-49]. Moderate to advanced fibrotics, on the other hand, are a more diffuse population, that do not similarly gather at any one particular site. As such case-finding is more challenging. To rise to this challenge, we need action at both primary and secondary levels of care. For instance, at the secondary care level, services could prioritise specific individuals known to be at high risk of moderate/advanced fibrosis. From the Scottish clinical database (described previously, for example in [22]), we can identify >2,000 patients with chronic HCV who: (i) have attended a specialist secondary-care appointment for management of their infection, (ii) are not currently receiving treatment, (iii) have an APRI score >0.7 (which is indicative of moderate-advanced cirrhosis[50]), (iv) are alive (as of Nov 2013), and (v) do not have liver decompensation or liver cancer. Targeting these individuals alone, would go some way towards fulfilling the treatment quotas set out in S1000-ADV and S2000-ADV. At the primary-care level, age-targeted testing in the GP setting[51, 52] is worth consideration (on the logic that patients with advanced fibrosis tend to be older in age). Further, there are many individuals, who although previously diagnosed with HCV, have never gone onto attend a secondary-care appointment (in Scotland, we know of 4,000 such living persons aged more than 50 years). Could primary-care play a greater role in re-signposting these specific individuals towards therapy? Overall, our contention is that despite their dispersed nature, we are not powerless to increase treatment uptake in this special interest group. A recent analysis illustrates a steady decline in the fraction of Scottish patients with liver cirrhosis receiving therapy over the last decade. [53] The open question then, becomes whether in this decade, and equipped with a bolstered armamentarium, we should aspire to

reverse this trend. Alternatively, we may decide that the prospect of curtailing incident infection is a more worthy near-term priority. Clearly, a debate needs to be had.

Our model is parameterised using observational data from the scientific literature and from Scotland's national surveillance databases. It is reassuring, that our modelled outcomes are in line with observational record-linkage data on liver-related sequelae so far (i.e. up until 2013[14]). Yet, there are specific uncertainties and limitations of this model that we must underscore. Firstly, fibrosis progression rates in unselected community patients are underdetermined. Indeed, the overwhelming majority of what we know about the speed of fibrosis accretion emanates from individuals attending specialist services [54] who are unlikely to be representative of the wider general-infected population (as per the disease iceberg phenomenon). Secondly, the real-world efficacy of future therapies is uncertain. In our base case scenario, we assumed treatment is equally effective for cirrhotic and non-cirrhotic genotype 1-2 patients (based on encouraging initial trial data [34, 35]). For genotype 3 patients we factored in a 10% differential, yet the emergence of a large efficacy-differential between cirrhotic and non-cirrhotic patients could impugn a fibrosis prioritising strategy. These uncertainties must be monitored, and models updated accordingly as more robust data becomes emerges. Thirdly, we apply a homogeneous force of incident infection across our PWID population; a considerable simplification of the reality, where the risk of infection will vary according to numerable co-factors. The transmission aspect of our model is indeed more rudimentary than some contemporary models [17, 55], but is sufficient we think, to capture the broad trends and trade-offs apparent when choosing a TTP strategy over alternatives. A further complicating scenario that our model does not account for is a rising force of infection over time. This might occur if at risk individuals perceive HCV to pose a diminished threat. In other words, in the "treat and forget" therapeutic era, PWID may not take the same precautions to avoid infection, if it is regarded as an easily treated condition. This sort of attitude shift may render our projections on declining transmission overly optimistic. Injecting risk behaviours should be closely monitored for signs of change. Fourthly, our model is based on the population of Scotland; a typical resource-rich setting where contemporary transmission is driven by injecting drug use. To note however, that we would not expect our results (i.e. the broad trade-offs outlined here) to extend to settings with different transmission profiles (namely Japan, and low-middle income countries). Fifthly, we did not consider the cost-effectiveness of the strategies we examined; rather, only their broad-level impact at the population level in terms of outcomes that are societally important. Although cost-effectiveness data would not trump this work (i.e. there is more to selecting the right treatment approach than simply considering the bottom line cost per QALY), it would add an important dimension, and should be a focus for the future. Sixth, we did not model fibrosis progression according to co-factors such as older age, male gender and heavy alcohol consumption, but assumed a blanket rate for all. We concede that this could introduce an important bias here because these co-factors accelerate fibrogenesis [56], and may be more prevalent (heavy alcohol use and older age in particular) among those with more advanced disease, than in competing priority groups such as PWID. Thus in reality, disease progression in these two groups may not occur at the same rate. In this respect, the outlined impact of prioritising moderate/advanced fibrotics on liver-related sequelae might be seen as conservative. Finally, although therapies capable of

80-95% SVR rates are set to be approved by 2015, “sticker shock” prices [38] may mean they are used selectively, with inferior therapies continuing to be prescribed to lower priority groups (or perhaps to groups for which inferior regimens still offer a reasonable chance of SVR). These eventualities are not considered in our model.

The major strength of this study lies in the combined modelling of incident infection *and* liver disease progression. In contrast, previous models have tended to consider one or the other, such that they inevitably end up arriving at one-sided view vis-à-vis which patient group is the treatment priority. [16, 17, 57-60] Combining the two herein is an important advancement that lends crucial insight and a more complete picture for health-care policy makers. In summary, this work highlights the opportunities but also opportunity costs of new therapeutic advancements. Now is the provident time to carefully consider our population-level priorities and engineer our treatment strategies accordingly.

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TABLE.1: Parameters to populate each model compartment at inception (year-2009)

Parameter/data item		Symbol	Mean value	Data source	Sampling distribution	95% credible interval
Number of PWID in Scotland (in 2009)		α	15,300	[24]	Sampled from the posterior distribution of Prevost et al [24]	13,270-17,180
Number of PWID in Scotland with HCV antibodies (in 2009)		γ	7,550			6,620-8,550
Number of ever-PWID with HCV antibodies in Scotland (in 2009)		δ	47,650			33,480-67,130
Proportion of persons with HCV antibodies in Scotland that have ever injected drugs (in 2009)		ε	85%	[42]	N(0.85, 0.02)	82.0-88.2
Proportion of persons with HCV antibodies that spontaneously clear infection		φ	26%	[61]	N(0.26, 0.018)	22.6-29.5
Number of Scottish persons living (in 2009) with treatment-induced viral clearance		η	2000	*	^	
Fibrosis distributio in overall chronical infected population 2009)	PWID	Mild	θ_1	83.5%	[32]	Sampled from the Posterior distribution of Hutchinson et al [32]	56.2-92.0
		Moderate	ξ_1	15.4%			7.4-42.0
		Cirrhosis	$\ddot{Y}_1$	1.1%			0.5-2.2
	ormer/never PWID	Mild	θ_2	55.4%			42.1-66.7
		Moderate	ξ_2	37.3%			27.2-50.3
		Cirrhosis	$\ddot{Y}_2$	5.8%			4.4-7.9
		Decomp cirrhosis	Ψ	1.3%			1.1-2.0
		HCC	π	0.12%			0.07-0.18
Genotype distribution (%) in overall chronically infected population (2009)		1	λ_1	48.9%	[25]	Non-parametric bootstrapping (See Appendix G)	48.0-49.9
		2	λ_2	5.1%			4.7-5.5
		3	λ_3	46.0%			45.1-46.9
Fibrosis distribution in infected population receiving treatment (2009)	WID	Mild	θ_{1RX}	81.1%		See Appendix E	
		Moderate	ξ_{1RX}	16.5%			
		Cirrhosis	$\ddot{Y}_{1RX}$	2.4%			
	ormer/never PWID	Mild	θ_{2RX}	56.0%			
		Moderate	ξ_{2RX}	26.5%			
		Cirrhosis	$\ddot{Y}_{2RX}$	17.5%			
Number of PWID treated, per annum in Scotland (2007 onwards)		τ	120	[17]	U (60, 180)	64-181

Total persons treated for chronic HCV in Scotland, per annum (2009-2013)	μ	1000	[14]	^

^ Not varied, * Unpublished data from the Scottish Clinical database

TABLE.2: Parameters defining inter-compartment transfer rate, 2010-2030.

Parameter/data item	Symbol	Mean value	Data source(s)	Sampling distribution	95% credible interval
Mild →moderate fibrosis (under chronic infection)	(a)	1.8%	[29, 62] - See Appendix C.1	Beta (19.87, 1083.88)	1.1-2.7
Moderate fibrosis→compensated cirrhosis (under chronic infection)	(b)	2.7%		Beta (14.07, 514.12)	1.4-4.2
Mild→moderate fibrosis (post-SVR)	(c)	0.4%	[46] See appendix C.2	Beta (19.87, 1083.88) & Norm(0.22, 0.05)	0.2-0.7
Moderate fibrosis→compensated cirrhosis (post-SVR)	(d)	0.6%		Beta (14.07, 514.12) & Norm(0.22, 0.05)	0.3-1.1
cirrhosis →decompensated cirrhosis (under chronic infection)	(e)	6.5%	[32]	Norm (6.5,1.3)	3.9-9.1
cirrhosis→liver cancer (under chronic infection)	(f)	1.4%	[31]	Beta (1.92, 135.12)	0.5-2.8
Cirrhosis→decompensated cirrhosis (post-SVR)	(g)	0.8%	[40] See appendix C.2	Norm (6.5,1.3) & U(0.07-0.19)	0.4-1.5
cirrhosis/decomp cirrhosis→liver cancer (post-SVR)	(h)	0.4%		Beta (1.92, 135.12) & U (0.18, 0.46)	0.05-1.3
Decompensated cirrhosis→liver death	(i)	13%	[31]	Beta (146.9, 983.1)	11.2-15.1
HCC→liver death	(j)	43.0%	[31]	Beta (116.67, 154.66)	37.0-48.8
DC/HCC→liver transplant	(k)	2%	[32]	Beta (10.18, 498.71)	0.9-3.4
Liver transplant death in first year	(l)	14.6%	[32]	N (14.6, 1.81)	11.0-18.2
Liver transplant death post year 2+	(m)	4.4%	[32]	N (4.4, 0.46)	3.5-5.3
Annual mortality rate [redacted]rmer PWID/never PWID	(n)	1.4%	See appendixD		
[redacted]WID	(o)	1.8%	[30]	N (1.8, 0.55)	0.8-2.9
Annual probability of ceasing injecting	(p)	9.1%	[33]	Tri (0.05, 0.17, 9.1)	5.4-11.1

Table 3: Post-2015 treatment strategies modelled*

	Strategy Name	Treatment Quota (patients per year)	Case mix		Strategy description (treatment quota; case mix)
			Risk group	fibrosis distribution	
Existing strategy adopted (2010-2014)	S1000-SQ	1000	PWID	10% mild; 2% moderate; <1% cirrhotic	Maintain status-quo uptake; maintain status-quo case mix
			former/never PWID	49% mild, 23% moderate, 15% cirrhotic	
Alternative treatment strategies appropriate in a new treatment era	S2000-SQ	2000	PWID	As per S1000-SQ	Double uptake; otherwise, as per S1000-SQ
			former/never PWID		
	S1000-PWID	1000	PWID	27% mild; 5% moderate; 1% cirrhotic	Maintain status-quo uptake;divert 20% of total initiations *away* from mildly fibrotic former/never PWIDs *towards* PWID
			former/never PWID	29% mild; 23% moderate; 15% cirrhotic	
	S2000-PWID	2000	PWID	As per S1000-PWID	Double uptake;otherwise, as per S1000-PWID
			former/never PWID		
	S1000-ADV	1000	PWID	10% mild; 2% moderate; <1% cirrhotic	Maintain status-quo uptake;divert 20% of total initiations *away* from mildly fibrotic former/never PWIDs *towards* moderate fibrotics and compensated-cirrhotics
			former/never PWID	29% mild; 35% moderate; 23% cirrhotic	
	S2000-ADV	2000	PWID	As per S1000-ADV	Maintain status-quo uptake; otherwise, as per S1000-ADV
			former/never PWID		
	S1000-NP	1000	PWID	NA	Mantain status quo uptake; Treat patient groups according to their prevalence in the overall infected population. For example, if in any given year, active PWIDs represent 20% of the total infection pool, then 200 PWID (i.e. 20% of the 1,000 treatment quota) will be treated in that year. This is a hypothetical benchmark strategy, broadly akin to a first-come-first-served distribution approach in an era of universal diagnosis and treatment demand.
			former/never PWID		
	S2000-NP	2000	PWID	NA	Double uptake; otherwise, as per S1000-FCFS
			former/never PWID		

* Where appropriate, over the 2015-2017 period, all strategies factor in a phased/gradual transition towards the specified uptake level/case mix

Table.4: Cumulative modeled number* of: (I) incident cases of Severe Liver Morbidity (II) Liver deaths and (III) incident chronic infections, according to treatment strategy and time horizon.

Time Horizon	Strategy	(i) Severe Liver Morbidity		(ii) Liver deaths		(iii) Incident chronic infections	
		Cumulative number (95% CI)	% change relative to S1000-SQ (95% CI)	Cumulative number (95% CI)	% change relative to S1000-SQ (95% CI)	Cumulative number (95% CI)	% change relative to S1000-SQ (95% CI)
Short term (2015-2020)	S1000-SQ	1140 (500, 2085)	REF	845 (415, 1500)	REF	3270 (1695, 5025)	REF
	S1000-PWID	1135 (500, 2080)	-0.4 (-0.9, 0)	845 (415, 1500)	0 (-0.7, 0)	3145 (1575, 4960)	-3.8 (-7.3, -1.1)
	S1000-ADV	1100 (470, 2040)	-3.5 (-7.0, -1.8)	840 (410, 1495)	-0.6 (-1.5, 0)	3270 (1695, 5025)	0.0 (0.0, 0.0)
	S1000-NP	1200 (570, 2140)	+5.3 (1.6, 16.5)	860 (425, 1510)	+1.8 (0.4, 3.8)	3260 (1715, 5010)	-0.3 (-1.8, 2.3)
	S2000-SQ	1065 (440, 1995)	-6.6 (-13.6, -3.5)	835 (405, 1485)	-1.2 (-2.7, -0.6)	3190 (1620, 4990)	-2.4 (-4.6, -0.6)
	S2000-PWID	1060 (435, 1990)	-7.0 (-14.5, -3.7)	835 (405, 1485)	-1.2 (-2.8, -0.7)	2910 (1365, 4785)	-11.0 (-20.5, -3.8)
	S2000-ADV	995 (390, 1910)	-12.7 (-23.8, -7.0)	825 (395, 1470)	-2.4 (-5.0, -1.5)	3190 (1620, 4990)	-2.4 (-4.6, -0.6)
	S2000-NP	1135 (535, 2045)	-0.4 (-3.9, 9.4)	845 (420, 1490)	0 (-1.0, 2.4)	3115 (1610, 4885)	-4.7 (-8.5, -1.4)
Medium term (2015-2025	S1000-SQ	2005 (820, 3740))	REF	1605 (750, 2880)	REF	5755 (2625, 9270)	REF
	S1000-PWID	1995 (810, 3725)	-0.5 (-1.4, -0.3)	1600 (745, 2875)	-0.3 (-0.6, 0)	5080 (2025, 8935)	-11.7 (-24.5, -2.7)
	S1000-ADV	1845 (700, 3560)	-8.0 (-16.0, -4.4)	1555 (710, 2820)	-3.1 (-5.9, -1.8)	5755 (2625, 9270)	0.0 (0.0, 0.0)
	S1000-NP	2175 (1060, 3850)	+8.5 (1.8, 33.7)	1670 (825, 2930)	+4.0 (1.0, 12.2)	5720 (2810, 9205)	-0.6 (-3.0, 8.5)
	S2000-SQ	1685 (630, 3375)	-16.0 (-25.9, -8.8)	1505 (680, 2760)	-6.2 (-10.5, -3.6)	5350 (2250, 9085)	-7.0 (-15.4, -1.4)
	S2000-PWID	1660 (620, 3350)	-17.2 (-27.3, -9.4)	1495 (675, 2750)	-6.9 (-11.1, -3.9)	3695 (1470, 7955)	-35.8 (-45.1, -12.3)
	S2000-ADV	1405 (565, 3045)	-29.9 (-36.1, -17.6)	1405 (645, 2635)	-12.5 (-16.3, -7.2)	5350 (2250, 9085)	-7.0 (-15.4, -1.4)
	S2000-NP	1915 (935, 3510)	-4.5 (-10.8, 18.9)	1585 (780, 2810)	-1.2 (-4.3, 6.8)	5120 (2525, 8780)	-11.0 (-15.9, 0.3)
Long term (2015-2030)	S1000-SQ	2770 (1030, 5250)	REF	2340 (1020, 4245)	REF	8040 (3275, 13405)	REF
	S1000-PWID	2735 (1010, 5225)	-1.3 (-2.2, -0.5)	2330 (1010, 4225)	-0.4 (-1.1, -0.2)	6225 (2150, 12685)	-22.6 (-35.5, -3.9)
	S1000-ADV	2415 (870, 4870)	-12.8 (-19.8, -6.8)	2190 (925, 4065)	-6.4 (-10.4, -3.7)	8040 (3275, 13405)	0.0 (0.0, 0.0)
	S1000-NP	3045 (1510, 5450)	+9.9 (1.4, 52.1)	2480 (1225, 4355)	+6.0 (1.1, 23.4)	7940 (3840, 13325)	-1.2 (-3.5, 20.1)
	S2000-SQ	2075 (790, 4445)	-25.1 (-30.9, -13.8)	2035 (875, 3890)	-13.0 (-17.2, -7.4)	6970 (2435, 13035)	-13.3 (-26.3, -1.9)
	S2000-PWID	2045 (770, 4400)	-26.2 (-32.3, -14.7)	2015 (865, 3865)	-13.9 (-18.1, -7.9)	3845 (1555, 9910)	-52.2 (-55.9, -23.9)
	S2000-ADV	1770 (720, 3735)	-36.1 (-41.4, -23.4)	1840 (830, 3570)	-21.4 (-24.9, -13.4)	6970 (2435, 13035)	-13.3 (-26.3, -1.9)
	S2000-NP	2455 (1250, 4670)	-11.4 (-17.9, 27.7)	2230 (1115, 4035)	-4.7 (-9.3, 12.8)	6405 (3380, 12445)	-20.3 (-21.5, 8.9)

* rounded to the nearest five