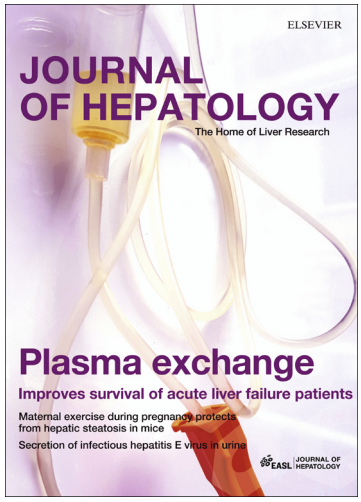

Modelling the impact of deferring HCV treatment on liver-related complications in HIV coinfected men who have sex with men

Cindy Zahnd, Luisa Salazar-Vizcaya, Jean-François Dufour, Beat Müllhaupt, Gilles Wandeler, Roger Kouyos, Janne Estill, Barbara Bertisch, Andri Rauch, Olivia Keiser, The Swiss HIV and the Swiss Hepatitis C Cohort Studies,

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Modelling the impact of deferring HCV treatment on liver-related complications in HIV coinfected men who have sex with men

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Abbreviations

HCV:	Hepatitis C virus
PWLH:	People who live with HIV
MSM:	Men who have sex with men
DC:	Decompensated cirrhosis
HCC:	Hepatocellular carcinoma
PEG-IFN:	Pegylated-interferon-α
RBV:	Ribavirin
DAA:	Direct actin antivirals
EASL:	European Association for the Study of the Liver
SHCS:	Swiss HIV Cohort Study

Keywords

Hepatitis C; HIV; Cirrhosis; Hepatocellular carcinoma; mathematical model

Conflicts of interests

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Author's contributions

CZ, JE, AR and OK designed the study. CZ and LS formulated the model. CZ, RDK and GW analysed the cohort data. CZ performed the model analyses. BB, JFD, BM contributed cohort data and enrolled patients. All authors contributed to the interpretation of the data and results. CZ, AR and OK drafted the manuscript, which was then revised by all the other authors. Kali Tal provided editorial assistance. CZ is the guarantor.

ABSTRACT

Background and aims

Hepatitis C (HCV) is a leading cause of morbidity and mortality in people who live with HIV. In many countries, access to direct acting antiviral agents to treat HCV is restricted to individuals with advanced liver disease (METAVIR stage F3 or F4). Our goal was to estimate the long term impact of deferring HCV treatment for men who have sex with men (MSM) who are coinfected with HIV and often have multiple risk factors for liver disease progression.

Methods

We developed an individual-based model of liver disease progression in HIV/HCV coinfected men who have sex with men. We estimated liver-related morbidity and mortality as well as the median time spent with replicating HCV infection when individuals were treated in liver fibrosis stages F0, F1, F2, F3 or F4 on the METAVIR scale.

Results

The percentage of individuals who died of liver-related complications was 2% if treatment was initiated in F0 or F1. It increased to 3% if treatment was deferred until F2, 7% if it was deferred until F3 and 22% if deferred until F4. The median time individuals spent with replicating HCV increased from 5 years if treatment was initiated in F2 to almost 15 years if it was deferred until F4.

Conclusions

Deferring HCV therapy until advanced liver fibrosis is established could increase liver-related morbidity and mortality in HIV/HCV coinfected individuals, and substantially prolong the time individuals spend with replicating HCV infection.

INTRODUCTION

Liver disease has become a leading cause of mortality in people who live with HIV (PWLH); it is often caused by infection with the Hepatitis C virus (HCV) [1, 2]. In high-income countries, about 30% of HIV-positive individuals are coinfected with HCV, though the proportion varies by risk group. As many as 70-90% of HIV-positive intravenous drug users are coinfected with HCV [3]. In the population of HIV-positive men who have sex with men (MSM) [4-6], HCV incidence has increased in recent years. The accelerated fibrosis progression observed in some studies [7-9], and the high incidence of HCV seroconversions and reinfections underscore the need for reliable predictions of the HCV disease burden and of the optimal therapeutic interventions in this population. Successful HCV treatment greatly reduces the risk of decompensated cirrhosis, hepatocellular carcinoma (HCC) and extrahepatic complications, but does not eliminate it [10-15]. Because HIV coinfected individuals have multiple risk factors for liver disease, including drug toxicity and metabolic liver disease, they might be at increased risk to have liver-related complications even after they clear HCV [12, 14, 16]. We do not know if treatment can be deferred until METAVIR stages ≥ F3 without increasing the risk of liver-related complications [17].

For the last decade, the standard of care for people infected with HCV has been treatment with pegylated-interferon-α (PEG-IFN) plus ribavirin (RBV). This IFN-based regimen is challenging to use, especially in HIV coinfected individuals who are at high risk for serious side-effects and have a low probability of cure [18-20]. Recently, new direct acting antivirals (DAAs) have revolutionized the treatment of HCV. These compounds are very effective, easy to use, and have few contraindications. These are factors that greatly increase the proportion of PWLH eligible for HCV treatment [21-24]. Yet the very high cost of the DAAs represents a major barrier to widespread treatment scale up and is a matter of debate [25]. Although the European Association for the Study of the Liver (EASL) now recommends that individuals coinfected with HIV are prioritized for treatment regardless of their fibrosis stage [26], reimbursement of HCV therapy is often restricted to individuals with advanced liver fibrosis [17, 27-29] .

We set out to estimate the impact of deferring HCV treatment on of liver-related complications in HIV coinfected individuals by using a model of liver disease progression and care. Our main outcomes of interest were liver-related morbidity and mortality as well as the time spent with replicating HCV.

METHODS

Data sources

We parameterized the model with data from the Swiss HIV Cohort Study (SHCS) and published literature. The SHCS (www.shcs.ch) is a prospective cohort study of PWLH in Switzerland that includes about 45% of all HIV-positive individuals declared to the public health authorities, and about 70% of all individuals with AIDS [30]. Detailed demographic, clinical and laboratory characteristics, HCV genotypes, treatment rates, and estimated duration of HIV infection are collected at baseline and during follow-up visits every six months.

Model structure and inputs

We developed the model using '*gems*', an R package that enables the creation of multistate models with generalized hazard functions [31, 32]. ***Figure 1*** shows the structure of the model, which is organized in two dimensions: progress of liver disease and cascade of HCV care. We defined the stages of liver disease, from healthy liver to cirrhosis (F0-F4) based on the METAVIR scoring system. Individuals in METAVIR stage F4 could progress to decompensated cirrhosis or HCC. Progression from decompensated cirrhosis to HCC was also possible. At any disease stage, individuals were allowed to progress along the cascade of care: they could be diagnosed, treated, and succeed or fail treatment. Individuals could also spontaneously clear the infection. Death could occur in any state.

We present the model's input parameters in ***Table S1.*** Simulated individuals were assigned the following characteristics at time of HCV infection: age, HCV genotype, and METAVIR stage *(see*

details in appendix). We derived the distribution of these characteristics from the SHCS dataset (***Table 1***). When we calculated the HCV diagnosis rate, we assumed that individuals were screened annually for HCV antibodies, with a sensitivity that increased from 25% at time of HCV infection to 95% after one year [33], and that elevated liver enzymes would reveal 88% of infections within the first three months of infection [33]. We assumed the progress of liver disease was the same across the METAVIR stages, and increased with older age at time of infection with HCV [34]. We assumed that clearing HCV decreased the rate at which fibrosis progressed from F0 to F4 (rate ratio RR=0.1), from F4 to decompensated cirrhosis (RR=0.1), and from F4 to HCC (RR= 0.38) [10] (*see details in appendix*). The probability of spontaneously clearing HCV followed a logistic decrease over a year, with an overall probability of 32%. Treatment rates and outcomes differed across scenarios.

We modelled one baseline scenario ("SHCS scenario") and 5 interventions ("DAA scenarios"). The SHCS scenario was designed to reproduce current practice in the SHCS before second-generation DAAs were introduced. Individuals were treated with PEG-IFN/RBV. Those with chronic HCV genotype 1 infection also received a first-generation DAA. We assumed that adding a first generation DAA (telaprevir, boceprevir or faldaprevir) to PEG-IFN/RBV increased the probability of treatment success (RR=2.17) [35]. The probability of treatment success followed a logistic decrease from 0.9 at the time of HCV infection to the genotype-dependent probabilities described for chronic HCV two years after infection *(see details in appendix)*. Treatment response rates were lower in people who had compensated cirrhosis than in non-cirrhotic people (RR= 0.74) [36].

In our DAA scenarios, all diagnosed individuals were treated with second generation DAAs; the probability of treatment success differed by HCV genotypes and cirrhosis status (Table S1). We modelled five scenarios, in which individuals were treated when they reached METAVIR stages F0, F1, F2, F3 or F4.

Model outcomes

The clinical outcomes of the model were cirrhosis, decompensated cirrhosis, HCC, liver-related deaths, and time spent with replicating HCV.

Sensitivity analysis

The uncertainty around the key parameter, the fibrosis progression rate by age at HCV infection (Table S1) was taken into account in the main analysis by sampling these parameters from a multivariate normal distribution. To assess the robustness of our main results, we investigated the effect of modifying our assumptions on the following parameters: progress of liver-fibrosis between F0 and F4 before and after HCV clearance, and progression from F4 to the outcomes *(see details in appendix).*

The impact of HCV reinfections was assessed by building an alternative model. In this model we assumed that either 9% of the individuals who had cleared an HCV infection were reinfected after a median time of 3.3 year as observed in the SHCS [37], or that 22% were reinfected after a median time of 2.1 years as described by Martin et al. [38]. In these scenarios, reinfected individuals were not retreated in order to obtain an estimate of the "worst-case-scenario".

Cost calculations

We calculated the cost per 100 HCV infections in our five DAA scenarios by adding the cost of disease stages to the treatment costs. We estimated the mean patient cost by disease stage based on data collected at the University Hospital Zurich, Switzerland. The data included the whole population of HCV infected individuals (not only HIV-coinfected). We used the cost of a 12-week course regimen with sofosbuvir + ledipasvir in Switzerland.

RESULTS

The SHCS scenario

This scenario is based on current HCV treatment strategies prior to the availability of second generation DAAs. We estimate that 46% of the simulated HIV/HCV-infected individuals developed liver cirrhosis over their lifetime, 11% experienced decompensated cirrhosis and 17% HCC ***(Figure 2)***. Of the simulated individuals 27% died of liver-related causes, and 0.8% died of liver-related complications after they cleared HCV.

The second generation DAAs scenarios

The effect of deferring HCV treatment until later stages of liver fibrosis is shown in ***Figure 3a***. The percentage of simulated individuals who died of liver-related complications was 2% if treatment was initiated in F0 or in F1. It rose to 3% if treatment was deferred until F2, 7% if deferred until F3, and 22% if deferred until F4.

Of individuals who died of liver-related complications, less than 1% died after clearing HCV if they were treated as they reached F0 or F1. This percentage increased to 2% if treatment was deferred until F2, 6% if it was deferred until F3, and 17% if it was deferred until F4 ***(Figure 3b).*** A large proportion of liver-related deaths occurred in individuals without replicating HCV if treatment was deferred until advanced fibrosis or cirrhosis as the model assumed that SVR substantially reduces the risk of liver disease progression but does not eliminate it [10-15]. The median time spent with replicating HCV increased from 5 years if treatment was initiated in F2 to almost 15 years if treatment was deferred until F4 ***(Figure 4)***. The percentages of individuals who died from liver-related complications depending on the follow up time since HCV infection are shown in Supplementary ***Table S2***.

Sensitivity analysis

Figure S1 shows the impact of varying the key input parameters on the percentage of individuals who die of liver-related complications. Our base analysis is the one described above (all 5 DAA scenarios).

Results are described in the appendix. The claim that early treatment can prevent liver-related deaths was true in most analyses, unless we assumed an extremely high rate of fibrosis progression (*Figure S1e*), or that liver disease never progressed after HCV was cleared (*Figure S1b*).

Figures S2 and S3 show the impact of HCV reinfections. Assuming that 9% of the individuals who cleared HCV infection were reinfected [37], the difference in the proportion of liver related deaths between the different scenarios was lower compared to the base scenarios. The percentage of individuals who died of liver-related complications was 7% if individuals were treated in METAVIR stage F0 or F1 and 8% if they were treated in F2. It increased to 12% if treatment was deferred until F3 and to 26% if it was deferred until F4. When we assumed that 22% experienced a reinfection as observed by Martin et al. [38], the percentage of individuals who died of liver-related complications was 15% if individuals were treated in F0, F1 or F2. It increased to 18% if treatment was deferred until F3 and to 30% if it was deferred until F4.

Cost calculations

The total cost, including disease and treatment costs, per 100 HCV infections only varied between 4.8 and 5.9 million Euros, depending on the timing of HCV treatment ***(Table S3, see appendix for details).***

DISCUSSION

Principal findings

Over a lifetime, deferring HCV treatment until advanced liver disease stages is likely to substantially increase liver-related complications, increase the time individuals spend with replicating HCV, and may not save money.

In many settings, cost considerations and related limitations in reimbursement by health insurances have led the authorities to recommend that HCV treatment be deferred until METAVIR stage F3 or more. Our model showed that initiating HCV therapy in METAVIR stage F2 instead of deferring treatment until stage F3 or F4 could prevent 4-19 liver-related deaths per 100 HCV infections. In the scenario where all diagnosed individuals are treated with DAAs in METAVIR stages F3 or F4, most liver-related deaths were caused by liver disease progression after HCV clearance, rather than because of treatment failure or a lack of diagnosis. Thus, if treatment is deferred until advanced fibrosis or cirrhosis has developed, most liver-related deaths will occur after HCV is cleared. HCV clearance is often associated with fibrosis regression, but liver fibrosis may progress in some individuals after HCV clearance [10, 12, 16, 17, 39-42]. Accordingly, deferring treatment until advanced fibrosis increased liver-related morbidity and mortality in all scenarios except when we assumed that liver fibrosis never progressed after SVR, or in a scenario with an extremely fast fibrosis progression. This is plausible since many risk factors associated with fibrogenesis, including drug toxicity, alcohol use, coinfections or metabolic liver disease, persist after cure. HCC can occur in those with cirrhotic livers even after they clear HCV [10]. Reinfections have been observed in up to 22% of patients following spontaneous or treatment-induced HCV clearance [38]. As expected, the benefit of treating individuals earlier was partially offset through reinfections and the proportion of patients who experienced liver related events was higher if reinfections were considered (see Figures S2 and S3). However, even in a worst-case-scenario assuming a very high reinfection rate and no retreatment, treating earlier reduced liver-related complications.

We show that initiating HCV therapy in F2, instead of F3 or F4, reduced the time individuals spent with replicating HCV by 47-64% as compared to when therapy is started in F1. Initiating therapy in F1, instead of waiting until F3 or F4 reduced the median time spent with replicating HCV by 85-90%. Early treatment reduced the median time with replicating HCV even in our worst case scenario where reinfected individuals were not retreated. This may decrease the risk of further HCV transmission in those with high-risk behavior. This is particularly important for HIV-positive MSM since this population is in the midst of an increase in HCV transmissions. Earlier initiation of treatment could be a valuable preventive strategy, akin to the concept of treatment-as-prevention in HIV, which was established as a very effective measure to reduce HIV transmissions [43]. A recent study in the SHCS found that increased treatment uptake and efficacy can reduce the proportion of individuals with replicating HCV infection [37].

Our cost calculations suggest that, despite the very high cost of treatment, early treatment might not increase total spending, since the increase in treatment cost is balanced by the savings in health care costs. This is assuming that prices of DAA therapy do not decrease in the coming years.

Comparison with other studies

Three other studies modelled the effect of timing of HCV therapy. The first investigated the effect of deferring HCV therapy in HCV-genotype 1 monoinfected individuals [44]. Researchers compared the cost-effectiveness of initiating therapy in different stages of liver disease and found it did not have much impact on the life expectancy. The second study examined the cost-effectiveness of early HCV treatment for individuals with HCV monoinfection and concluded that treating those with moderate or advanced fibrosis was cost-effective; the cost-effectiveness of treating those with minimal or no fibrosis depended on the cost of treatment [45]. The third study estimated the quality-adjusted life-years for a 40 years old patient to increase from 23.9 if treatment was started in F4 to 33.7 if treatment started in F0 assuming and SVR rate of 90% [46]. These studies considered only cohorts of HCV monoinfected individuals. The first assumed that successful HCV treatment would eliminate further risk of liver disease progression, the second and the third assumed that only individuals treated in F4

were still at risk of liver-disease progression after HCV clearance. In contrast, our model assumes that liver fibrosis progresses in some individuals [13, 14, 16, 40], which led to an increase in liver-related events if therapy was deferred until F3.

Of note, a recent cost-effectiveness analysis among HIV/HCV coinfected patients suggested that IFN-free regimens will be cost-effective if treatment costs were below 109'000 USD, which is now the case in many settings [47]. For the Swiss setting, a recent study suggested that DAA-based therapies were cost-effective even at current prices if a threshold of 100,000 CHF per QALY was assumed [48]. Another study published in 2015 demonstrated that cost-effectiveness is highly sensitive to drug prices and that treating patients in F0 would be cost-effective if treatment costs were below 50'000 USD [49]. A recent study [50] showed that the life-expectancy of HCV-monoinfected individuals who had been successfully treated in an advanced liver-disease stage was comparable to that of the general population. The apparent inconsistency between this finding and our results can be explained by the differences between the cohorts, including different patient characteristics and very different follow-up times. The median follow-up time in that study was 8.4 years, while we make predictions over a life-time. In fact, when we simulated a cohort of individuals cured in an advanced stage of the disease, our model predicted a very low percentage (1.2%) of liver-related deaths after 8.4 years of follow-up *(see appendix)*. A recent meta-analysis [10] estimated a 5-year risk of HCC after SVR of 2.9% in the overall population, and 5.3% among cirrhotic individuals.

Strengths and limitations

Our study was strengthened by our access to observed data from a large and nationally representative cohort of PWLH. Data were collected prospectively during regular follow-up visits and include detailed demographic, clinical and laboratory data on HIV and HCV infections. The individual-based design of our model enabled us to exploit this detailed information. The use of the R package '*gems*' allowed us to model time-dependant transition rates for spontaneous HCV clearance and treatment success. The very flexible structure of the model also allowed us to adapt parameters quickly as new data became available.

Our study also has several limitations. First, we derived some input parameters from the literature, which implies heterogeneity in both data collection and reporting. Second, the results apply primarily to HIV-positive MSM and might not be generalizable to HIV-positive people who acquired HCV through injecting drug use with different demographic and clinical characteristics. Third, disease-costs for each fibrosis stage were calculated as total health-care costs excluding treatment as described before [51]. As these costs include potential costs due to interferon-related side effects, the disease stage costs could overestimate the true costs in the interferon-free DAA era. Fourth, cost calculations are highly dependent on the future developments in DAA prices and differ substantially between countries and recommended regimens. Therefore, cost estimates from this study might not be applicable to other settings. Fifth, the costs averted by preventing complications after secondary HCV infections was not considered, leading to an underestimation of the benefit of early treatment on costs. Sixth, we did not explicitly model that, after cure, liver fibrosis regresses in some individuals while it progresses in others [12, 39-41]. We instead used an average between individuals who continue to have liver fibrosis progression, those who remain stable, and those who regress their fibrosis, corresponding to a tenfold reduction in fibrosis progression after HCV clearance. Given published data on liver-disease progression in both HIV-monoinfected individuals, as well as in HIV/HCV coinfected individuals after SVR, this is a conservative estimate of the risk of liver-disease progression after HCV clearance. Seventh, we did not consider possible discrepancies between the measured and the real stage of liver-disease, though we are aware that non-invasive diagnostic tools are not ideal predictors of liver fibrosis [52]. People classified as F3 could already be cirrhotic, but this is only an additional argument against deferring HCV therapy. Eighth, in the SHCS scenario, we did not model explicitly the side effects of IFN-based treatment. However, to some extent this was accounted for by the lower cure rates in the SHCS if side effects were present. Ninth, the impact of resistant variants emerging after relapse on the effectiveness of DAA therapies could not be investigated with the present model.

Implications of findings

Deferring HCV therapy until advanced liver fibrosis is established may increase the percentage of liver-related complications in people who have multiple risk factors for liver disease progression, such as HIV-coinfected MSM. Our model predicts that the time individuals spend with replicating HCV can be greatly shortened by early treatment. This may decrease further HCV transmissions in those with high-risk behavior. Both findings support arguments that HCV therapy should be accessible to everyone at an early stage. To make this affordable for health insurances and governments, the costs for DAA drugs need to be lowered substantially. Our findings support current recommendations to start HCV treatment irrespective of fibrosis stage in those with risk factors for accelerated fibrosis progression including HIV-coinfected MSM, and in persons at elevated risk of HCV transmission [26].

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Ethical approval:

This study has been approved by all local ethical committees of the SHCS. The data are gathered by the five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in http://www.shcs.ch/180-health-care-providers). Members of the Swiss HIV Cohort Study: Aubert V, Battegay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Nicca D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rickenbach M (Head of Data Centre), Rudin C (Chairman of the Mother & Child Substudy), Schöni-Affolter F, Schmid P, Schüpbach J, Speck R, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.

FIGURES LEGENDS:

Figure 1: Model structure

Individuals can progress vertically through the METAVIR fibrosis stages (F0 to F4) and the endpoints: DC (decompensated cirrhosis) and HCC (hepatocellular carcinoma). From any of those stages individuals can also progress horizontally along the care cascade and be diagnosed, put onto treatment, fail treatment or be cured. Individuals who clear HCV, either spontaneously or because they were succeeded treatment have undetectable HCV. The rates of progression through the METAVIR stages depends on several factors including whether the individual has undetectable HCV (upper right block) or not (all other blocks).

Figure 2: The SHCS scenario

a) Cumulative incidence of any METAVIR fibrosis stages (F0-F4), decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) over time.

b) Percentage of individuals who experience F4, DC, HCC over their lifetime or die of liver related complications.

Figure 3: The DAA scenarios

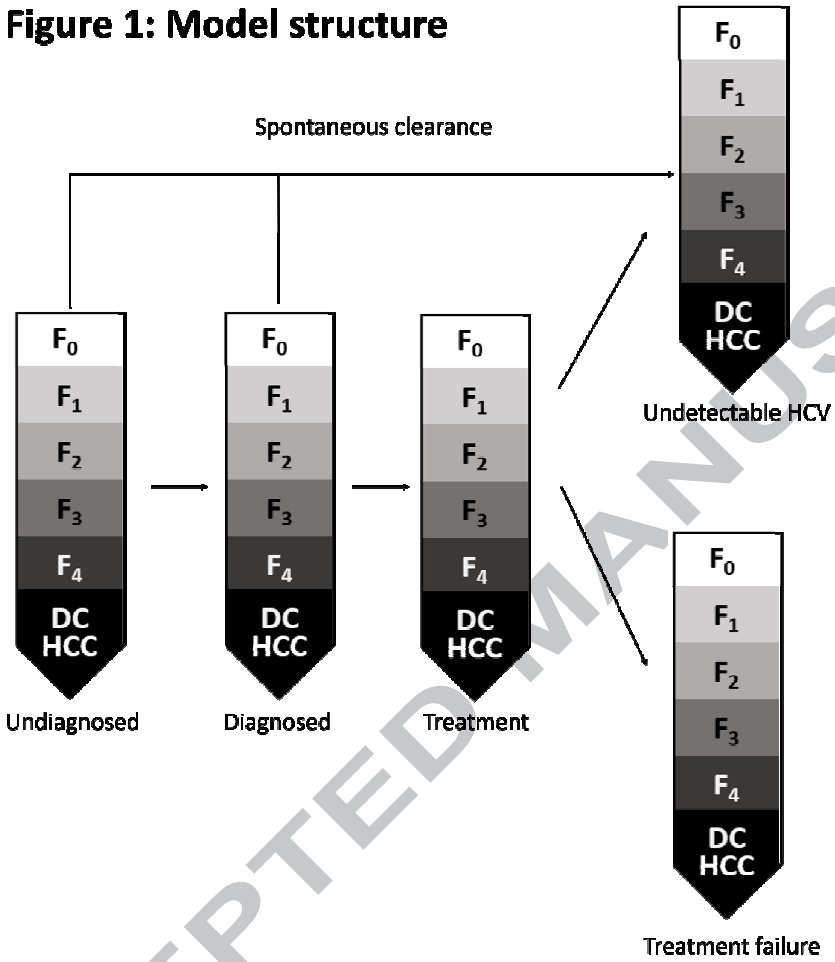
a) Impact of deferring HCV treatment on liver-related complications. The figure shows the percentage of individuals who experience F4 (cirrhosis), DC (decompensated cirrhosis), HCC (hepatocellular carcinoma) and liver-related deaths for different treatment scenarios.

b) Percentage of individuals who die of liver-related complications with or without replicating HCV infection. F0-F4: METAVIR fibrosis stages.

Figure 4: Median years with replicating HCV infection, by treatment scenarios

FIGURES

Figure 1: Model structure



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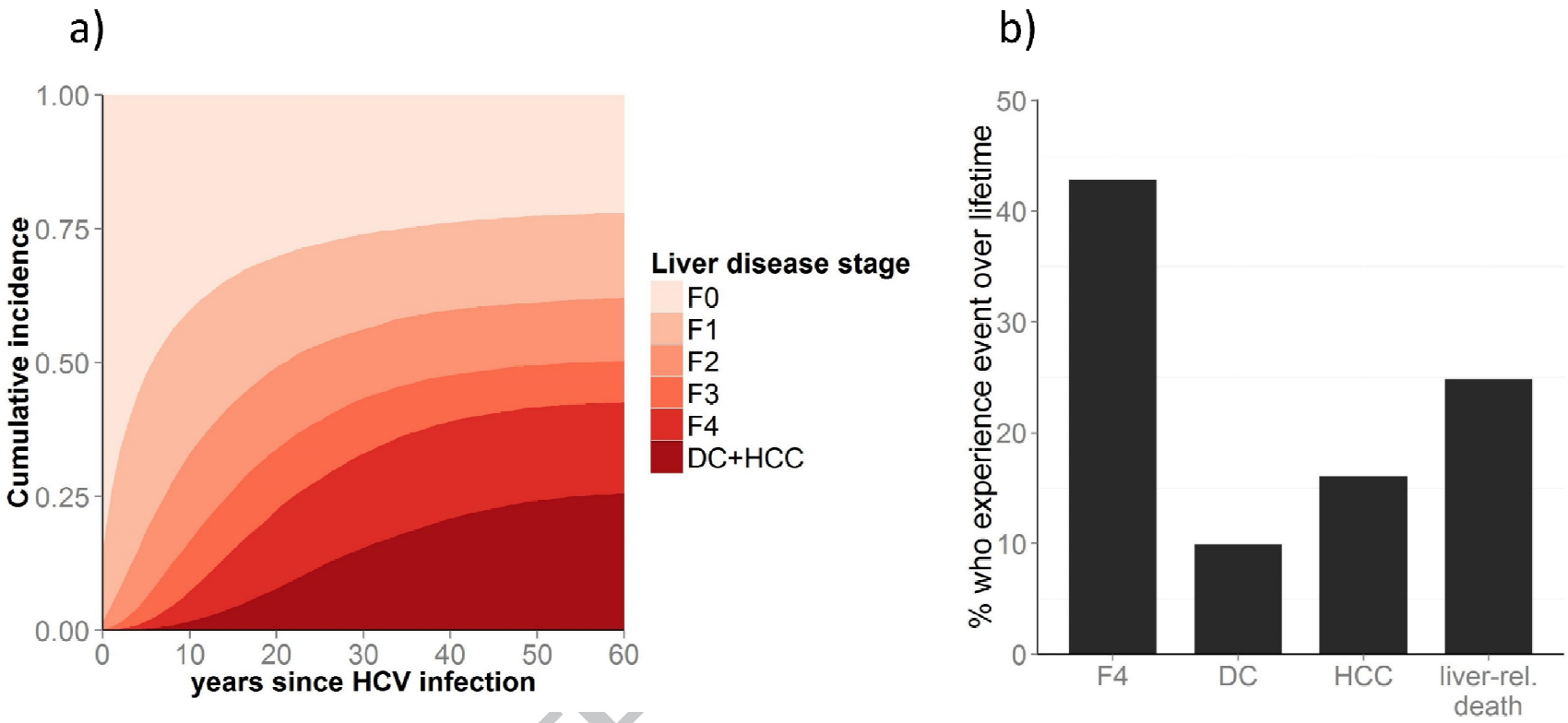
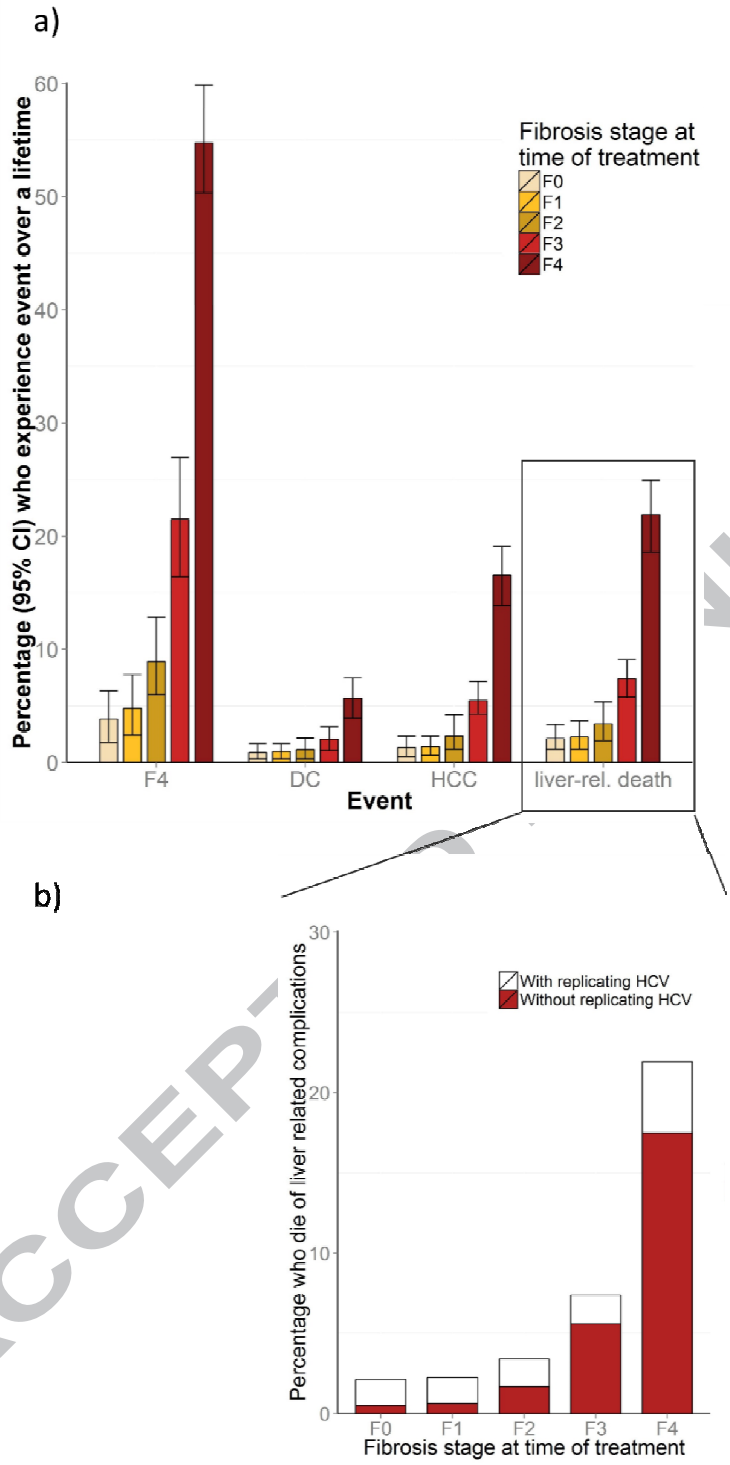


a) Cumulative incidence of any METAVIR fibrosis stages (F0-F4), decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) over time. **b)** Percentage of individuals who experience F4, DC, HCC over their lifetime or die of liver related complications.

Figure 3: The DAA scenarios



a) Impact of deferring HCV treatment on liver-related complications. The figure shows the percentage of individuals who experience F4 (cirrhosis), DC (decompensated cirrhosis), HCC (hepatocellular carcinoma) and liver-related deaths for different treatment scenarios. **b)** Percentage of individuals who die of liver-related complications before and after clearing HCV.

F2, F3 and F4: METAVIR fibrosis stages.

Figure 4

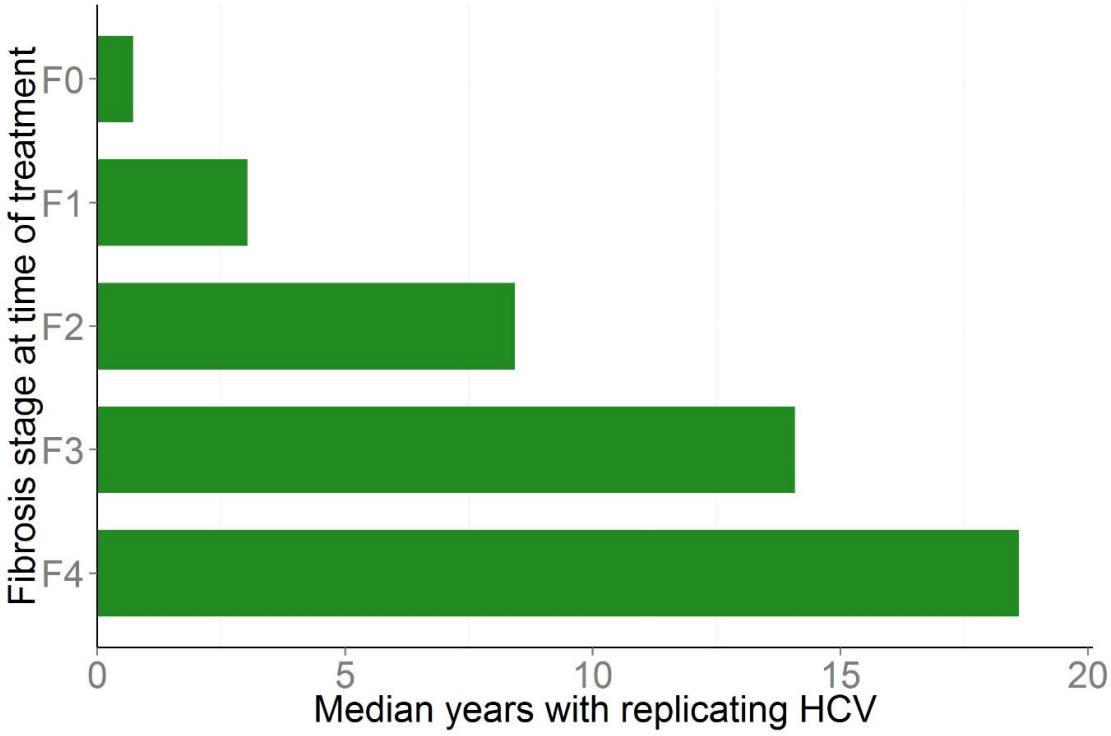


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TABLE 1.

CHARACTERISTIC AT HCV DIAGNOSIS	Value	Reference
Median age in years (IQR)	34 (21-47) [i]	SHCS data
Duration of HIV infection in years (%)		SHCS data
≤ 5	32.7	
6-10	26.2	
11-15	18.7	
16-20	16.8	
>20	5.6	
Median CD4 cells/µl (IQR) [ii]	459 (320-649)	SHCS data
With suppressed HIV RNA (%) [ii]	81	
HCV Genotype (%)		[1]
1	66.7	
2	1.6	
3	12.7	
4	19.0	
METAVIR stage at HCV infection (%)		Simulated using duration of HIV infection and RR of liver fibrosis progression (*see appendix for details*)
F0	85.9	
F1	15.1	
F2	1.8	
F3	0.2	
F4	0.02	

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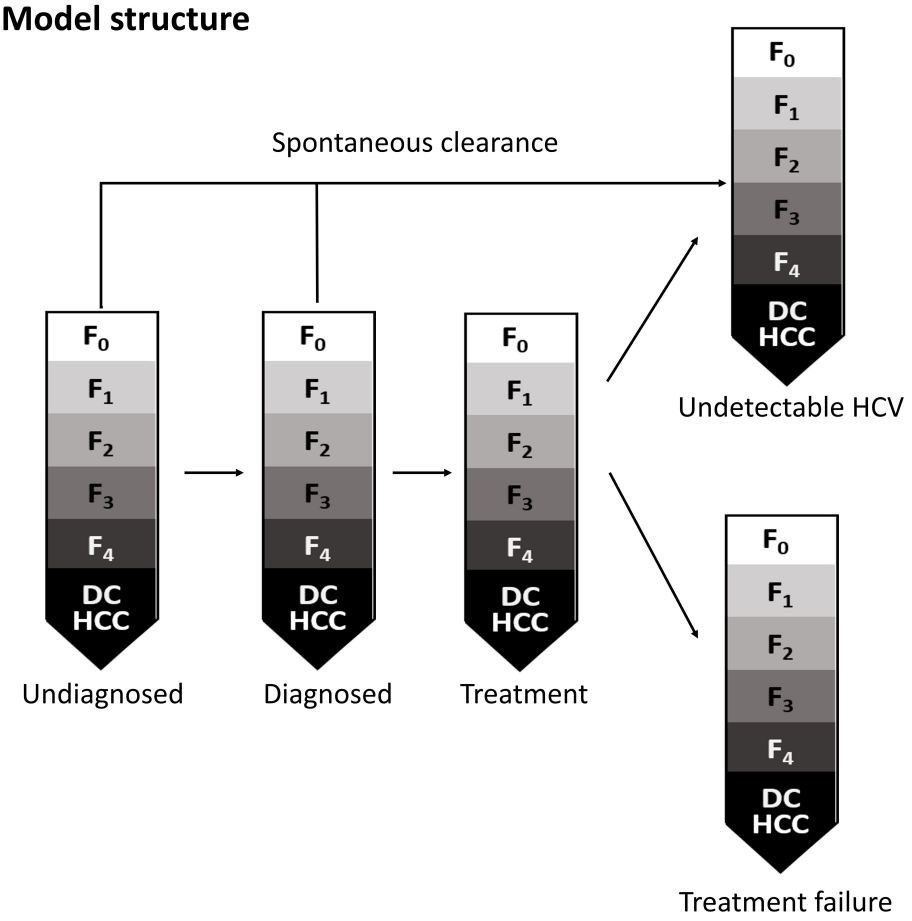
[i] modelled with a Weibull function of the form $f = \frac{\kappa}{\lambda}\frac{t}{\lambda}^{\kappa-1} e^{-\frac{t}{\lambda}^{\kappa}}$ with κ=4.23 and λ=40.22

[ii] not used in the model

Model structure



Results