Research Article

CrossMark

EASL JOURNAL OF HEPATOLOGY

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

Cindy Zahnd[1], Luisa Salazar-Vizcaya[1], Jean-François Dufour[2], Beat Müllhaupt[7], Gilles Wandeler[1,3,5], Roger Kouyos[4], Janne Estill[1], Barbara Bertisch[1,6], Andri Rauch[5,*,†], Olivia Keiser[1,†], and the Swiss HIV, and the Swiss Hepatitis C Cohort Studies

[1]*Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland;* [2]*Hepatology, University Clinic for Visceral Surgery and Medicine, University Hospital Bern, Bern, Switzerland;* [3]*Department of Infectious Diseases, University of Dakar, Dakar, Senegal;* [4]*Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich and Institute of Medical Virology, University of Zurich, Switzerland;* [5]*Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Switzerland;* [6]*Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital, St-Gallen, Switzerland;* [7]*Swiss Hepato-Pancreato-Biliary Center and Department of Gastroenterology and Hepatology, University Hospital Zürich, Switzerland*

See Editorial, pages 5–6

Background & 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 MSM. 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 a replicating HCV infection.

Keywords: Hepatitis C; HIV; Cirrhosis; Hepatocellular carcinoma; Mathematical model.

Received 27 May 2015; received in revised form 9 February 2016; accepted 15 February 2016; available online 26 February 2016

* Corresponding author. Address: Associate Professor of Infectious Diseases, Department of Infectious Diseases, Inselspital, Freiburgstrasse 4, 3010 Bern, Switzerland. Tel.: +41 031 632 15 74; fax: +41 031 632 31 76.

E-mail address: Andri.rauch@insel.ch (A. Rauch).

† These authors share senior authorship.

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

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 (PegIFN) plus ribavirin (RBV). This interferon (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 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.

Materials and 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 that includes 73% of all diagnosed HIV-infections in Switzerland [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]. Fig. 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 compensated liver 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 Supplementary Table 1. Simulated individuals were assigned the following characteristics at time of HCV infection: age, HCV genotype, and METAVIR stage (details in Supplementary material). 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] (details in Supplementary material). 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 PegIFN/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 PegIFN/RBV increased the probability of treatment success in chronic infection (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 (details in Supplementary material). 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 (Supplementary Table 1). We modelled five scenarios, in which individuals were treated when they reached METAVIR stages F0, F1, F2, F3 or F4.

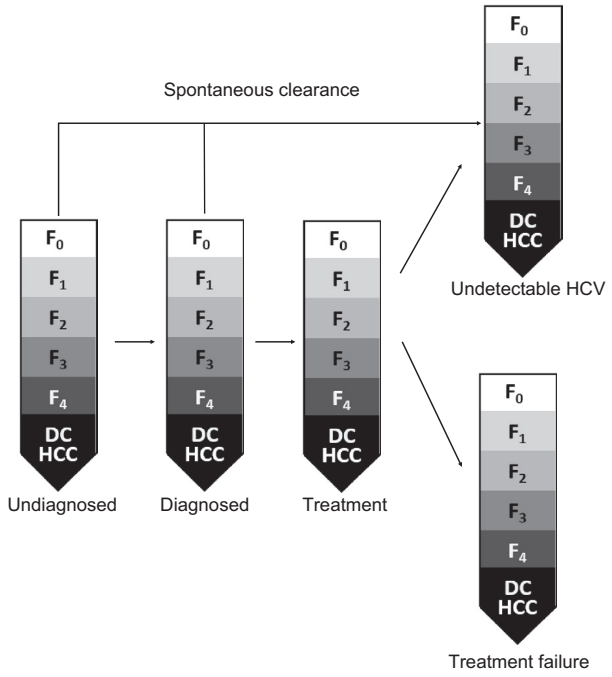

Fig. 1. Model structure. Individuals can progress vertically through the METAVIR fibrosis stages (F0 to F4) and the endpoints: decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). From any of those stages individuals can also progress horizontally along the care cascade and be diagnosed, put onto treatment, fail treatment or be cured. Individuals who clear HCV, either spontaneously or because they succeeded treatment have undetectable HCV. The rates of progression through the METAVIR stages depends on several factors including whether the individual has undetectable HCV or not.

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 (Supplementary Table 1), 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: progression of liver fibrosis between F0 and F4 before and after HCV clearance, and progression from F4 to the outcomes (details in Supplementary material).

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.

Research Article

Table 1. Characteristics at HCV diagnosis.

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 (%)		[5]
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	

[i]Modelled with a Weibull probability density function of the form $f = \frac{\kappa}{\lambda}\frac{t^{\kappa-1}}{\lambda}e^{-\frac{t^{\kappa}}{\lambda}}$ with $\kappa = 4.23$ and $\lambda = 40.22$.
[ii]Not used in the model.
SHCS, Swiss HIV Cohort Study; IQR, Interquartile range.

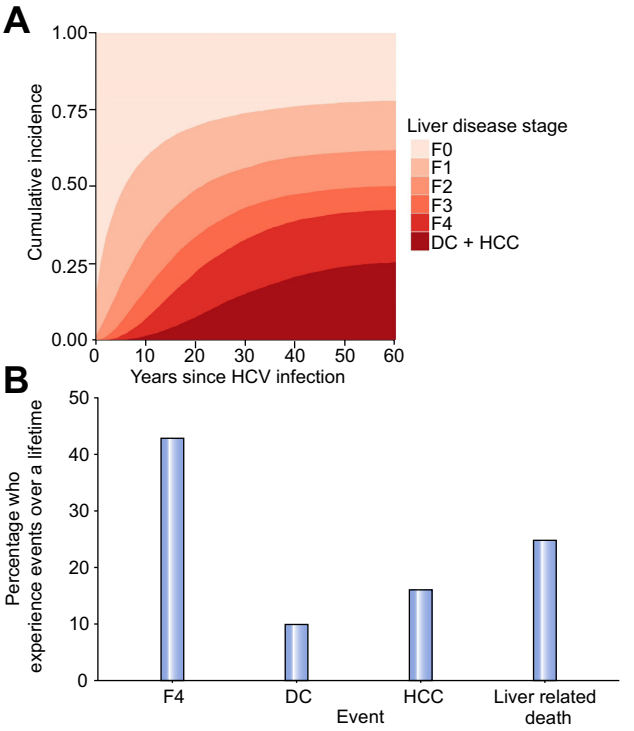

Fig. 2. The SHCS (Swiss HIV cohort study) scenario. (A) Cumulative incidence of any METAVIR fibrosis stages (F0-F4), decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) over time. (B) Percentage of individuals who experience F4, DC, HCC over their lifetime or die of liver-related complications.

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 (Fig. 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 Fig. 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.

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 (Fig. 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 (Fig. 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 2.

Sensitivity analysis

Supplementary Fig. 1 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 (Supplementary Fig. 1E), or that liver disease never progressed after HCV was cleared (Supplementary Fig. 1B).

Supplementary Figs. 2 and 3 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.

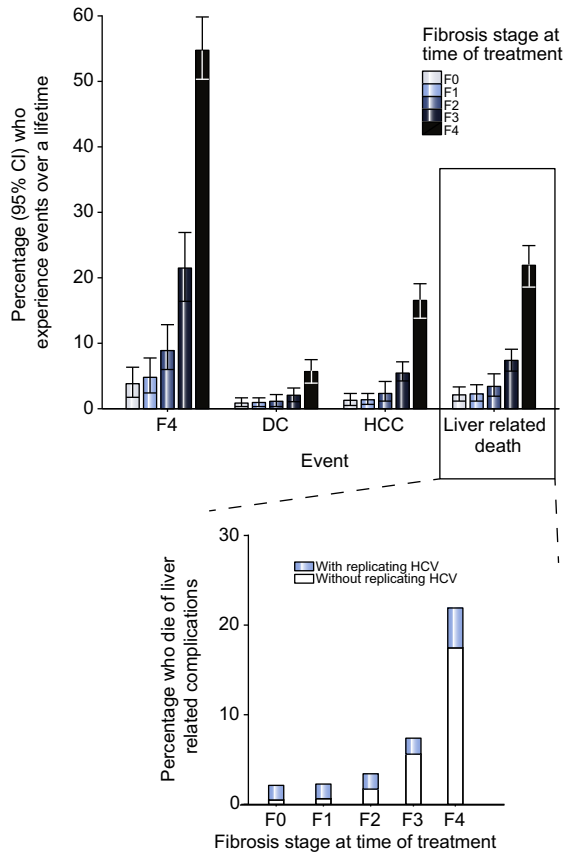

Fig. 3. The DAA scenarios. (A) Impact of deferring HCV treatment on liver-related complications. The figure shows the percentage of individuals who experience cirrhosis (F4), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) and liver-related deaths for different treatment scenarios. (B) Percentage of individuals who die of liver-related complications with or without replicating HCV infection. F0-F4: METAVIR fibrosis stages.

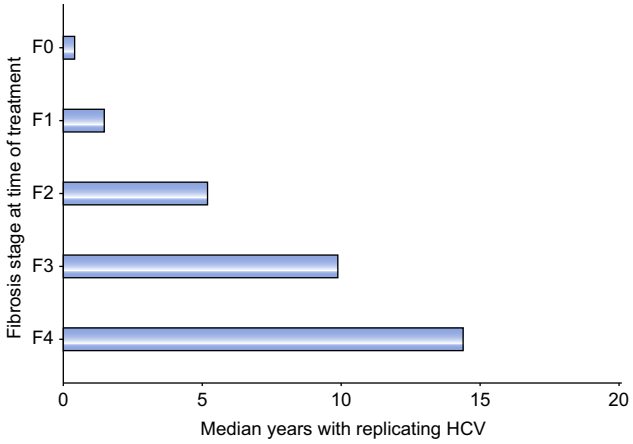

Fig. 4. Median years with replicating HCV infection. Data by treatment scenario.

Cost calculations

The total cost, including disease and treatment costs, per 100 HCV infections varied between 4.8 and 5.9 million Euros, depending on the timing of HCV treatment (Supplementary Table 3; details in Supplementary material).

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 in HIV positive MSM, 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 (Supplementary Figs. 2 and 3). 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 (QALY) 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 study assumed that successful HCV treatment would eliminate further risk of liver disease progression, the second and the third studies 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 lifetime. 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 Supplementary material). 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 IFN-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].

Financial support

This study has been financed within the framework of the Swiss HIV and Hepatitis C Cohort Studies, supported by the Swiss National Science Foundation (SNF grant #148522, #146143 and #148417). Additional funding for this study came from Cancer Research Switzerland (grant #2938-02-2012) and IeDEA Southern Africa (grant #U01AI069924). The funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, and in the decision to submit the article for publication. All authors declare that they are independent from their funders. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

AR reports honoraria for advisory boards and/or travel grants from Janssen-Cilag, MSD, Gilead Sciences, Abbvie, and Bristol-Myers Squibb, and an unrestricted research grant from Gilead Sciences, all remuneration went to his home institution and not to AR personally, and all remuneration was provided outside the submitted work. BM reports grants and personal fees from Gilead, personal fees from Abbvie, personal fees from BMS, personal fees from Roche, personal fees from MSD, personal fees from Janssen, personal fees from Boehringer Ingelheim, outside the submitted work. OK and BB received an unrestricted grant from Gilead outside the submitted work. JE, JFD and GW have nothing to disclose. There are no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

CZ, JE, AR and OK designed the study. CZ and LS formulated the model. CZ, RK 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. CZ is the guarantor.

Acknowledgements

We thank Kali Tal for her editorial assistance. 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.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2016.02.030.

References

[1] Smith C, Sabin CA, Lundgren JD, Thiebaut R, Weber R, Law M, et al. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. Aids 2010;24:1537–1548.
[2] Weber R, Ruppik M, Rickenbach M, Spoerri A, Furrer H, Battegay M, et al. Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. HIV Med 2013;14:195–207.
[3] CDC. HIV and viral hepatitis, [accessed on 02.02.2014] http://www.cdc.gov/hiv/pdf/library_factsheets_HIV_and_viral_Hepatitis.pdf; 2014.
[4] Hagan H, Neurer J, Jordan AE, Des Jarlais DC, Wu J, Dombrowski K, et al. Hepatitis C virus infection among HIV-positive men who have sex with men: protocol for a systematic review and meta-analysis. Syst Rev 2014;3:31.
[5] Wandeler G, Gsponer T, Bregenzer A, Gunthard HF, Clerc O, Calmy A, et al. Hepatitis C virus infections in the swiss HIV cohort study: a rapidly evolving epidemic. Clin Infect Dis 2012;55:1408–1416.
[6] van de Laar T, Pybus O, Bruisten S, Brown D, Nelson M, Bhagani S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology 2009;136:1609–1617.
[7] Vogel M, Page E, Boesecke C, Reiberger T, Schwarze-Zander C, Mauss S, et al. Liver fibrosis progression after acute hepatitis C virus infection in HIV-positive individuals. Clin Infect Dis 2012;54:556–559.
[8] Osinusi A, Kleiner D, Wood B, Polis M, Masur H, Kottilil S. Rapid development of advanced liver fibrosis after acquisition of hepatitis C infection during primary HIV infection. AIDS Patient Care STDS 2009;23:403–406.
[9] Fierer DS, Dieterich DT, Fiel MI, Branch AD, Marks KM, Fusco DN, et al. Rapid progression to decompensated cirrhosis, liver transplantation, and death in HIV-infected men after primary HCV infection. Clin Infect Dis 2012;56:1038–1043.
[10] Hill AM, Saleem J, Heath KA, Simmons B. Effects of Sustained Virological Response (SVR) on the risk of liver transplant, hepatocellular carcinoma, death and re-infection: meta-analysis of 129 studies in 23,309 patients with Hepatitis C infection. Hepatology 2014;60:55A.
[11] van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584–2593.
[12] Labarga P, Fernandez-Montero JV, Barreiro P, Pinilla J, Vispo E, de Mendoza C, et al. Changes in liver fibrosis in HIV/HCV-coinfected patients following different outcomes with peginterferon plus ribavirin therapy. J Viral Hepat 2014;21:475–479.
[13] Innes HA, Hutchinson SJ, Allen S, Bhattacharyya D, Bramley P, Delahooke TE, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatology 2011;54:1547–1558.
[14] Mendeni M, Foca E, Gotti D, Ladisa N, Angarano G, Albini L, et al. Evaluation of liver fibrosis: concordance analysis between noninvasive scores (APRI and FIB-4) evolution and predictors in a cohort of HIV-infected patients without hepatitis C and B infection. Clin Infect Dis 2011;52:1164–1173.
[15] Chaudhry AA, Sulkowski MS, Chander G, Moore RD. Hazardous drinking is associated with an elevated aspartate aminotransferase to platelet ratio index in an urban HIV-infected clinical cohort. HIV Med 2009;10:133–142.
[16] Labarga P, Fernandez-Montero JV, de Mendoza C, Barreiro P, Pinilla J, Soriano V. Liver fibrosis progression despite HCV cure with antiviral therapy in HIV-HCV-coinfected patients. Antivir Ther 2014;20:329–334.
[17] Bani-Sadr F, Lapidus N, Bedossa P, De Boever CM, Perronne C, Halfon P, et al. Progression of fibrosis in HIV and hepatitis C virus-coinfected patients treated with interferon plus ribavirin-based therapy: analysis of risk factors. Clin Infect Dis 2008;46:768–774.
[18] Sulkowski MS. HCV therapy in HIV-infected patients. Liver Int 2013;33:63–67.
[19] Sulkowski MS. Current management of hepatitis C virus infection in patients with HIV co-infection. J Infect Dis 2013;207:S26–S32.

Research Article

[20] Puoti M, Rossotti R, Travi G, Panzeri C, Morreale M, Chiari E, et al. Optimizing treatment in HIV/HCV coinfection. Dig Liver Dis 2013;45S5:S355–S362.
[21] Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: a systematic review. JAMA 2014;312:631–640.
[22] Martel-Laferriere V, Dieterich DT. Treating HCV in HIV 2013: on the cusp of change. Liver Int 2014;34:53–59.
[23] Rockstroh JR, Bhagani S. Managing HIV/hepatitis C co-infection in the era of direct acting antivirals. BMC Med 2013;11:234.
[24] Zeremski M, Martinez AD, Talal AH. Editorial commentary: Management of hepatitis C Virus in HIV-infected patients in the era of direct-acting antivirals. Clin Infect Dis 2014;58:880–882.
[25] Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. Clin Infect Dis 2014;58:928–936.
[26] EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015;63:199–236.
[27] Anthem Health Insurance. [accessed the 23.01.2015 https://www.anthem.com/provider/noapplication/f0/s0/t0/pw_e210963.pdf?na=pharminfo; 2015.
[28] Moradpour D, Rauch A, Fehr J, Müllhaupt B. Treatment of chronic hepatitis C- September 2014 Update. http://www.sginf.ch/ssi/images/ssi/news/SASL-SSI_HepC_EOS_Sept2014.pdf; 2014.
[29] NICE. Sofosbuvir for treating chronic hepatitis C. https://www.nice.org.uk/guidance/ta330; 2015.
[30] Kohler P, Schmidt AJ, Cavassini M, Furrer H, Calmy A, Battegay M, et al. The HIV care cascade in Switzerland: reaching the UNAIDS/WHO targets for patients diagnosed with HIV. AIDS 2015;29:2509–2515.
[31] Luisa Salazar Vizcaya NB, Thomas Gsponer. gems: Generalized multistate simulation model. CRAN, R archive: http://cranr-projectorg/web/packages/gems/indexhtml; 2014.
[32] Blaser N, Salazar Vizcaya L, Estill J, Zahnd C, Kalesan B, Egger M, et al. Gems: an R package for simulating from disease progression models. J Stat Software 2015;64:1–22.
[33] Thomson EC, Nastouli E, Main J, Karayiannis P, Eliahoo J, Muir D, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. Aids 2009;23:89–93.
[34] Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349:825–832.
[35] Sulkowski M, Pol S, Mallolas J, Fainboim H, Cooper C, Slim J, et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. Lancet Infect Dis 2013;13:597–605.
[36] Mira JA, Garcia-Rey S, Rivero A, de los Santos-Gil I, Lopez-Cortes LF, Giron-Gonzalez JA, et al. Response to pegylated interferon plus ribavirin among HIV/hepatitis C virus-coinfected patients with compensated liver cirrhosis. Clin Infect Dis 2012;55:1719–1726.
[37] Wandeler G, Schlauri M, Jaquier M-E, Rohrbach J, Mtzner KJ. Incident hepatitis C Virus infections in the swiss HIV cohort study: changes in treatment uptake and outcomes between 1991 and 2013. Open Forum Infect Dis 2015;2:ofv026.
[38] Martin TC, Martin NK, Hickman M, Vickerman P, Page EE, Everett R, et al. HCV reinfection incidence and treatment outcome among HIV-positive MSM in London. Aids 2013;27:2551–2557.
[39] Lee YA, Friedman SL. Reversal, maintenance or progression: What happens to the liver after a virologic cure of hepatitis C? Antiviral Res 2014;107C:23–30.
[40] Maylin S, Martinot-Peignoux M, Moucari R, Boyer N, Ripault MP, Cazals-Hatem D, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroenterology 2008;135:821–829.
[41] Poynard T, Moussalli J, Munteanu M, Thabut D, Lebray P, Rudler M, et al. Slow regression of liver fibrosis presumed by repeated biomarkers after virological cure in patients with chronic hepatitis C. J Hepatol 2013;59:675–683.
[42] Casado JL, Quereda C, Moreno A, Perez-Elias MJ, Marti-Belda P, Moreno S. Regression of liver fibrosis is progressive after sustained virological response to HCV therapy in patients with hepatitis C and HIV coinfection. J Viral Hepat 2013;20:829–837.
[43] Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493–505.
[44] Deuffic-Burban S, Schwarzinger M, Obach D, Mallet V, Pol S, Pageaux GP, et al. Should we await IFN-free regimens to treat HCV genotype 1 treatment-naive patients? A cost-effectiveness analysis (ANRS 12188). J Hepatol 2014;61:7–14.
[45] Leidner AJ, Chesson HW, Xu F, Ward JW, Spradling PR, Holmberg SD. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. Hepatology 2015;61:1860–1869.
[46] McEwan P, Ward T, Bennett H, Kalsekar A, Webster S, Brenner M, et al. Estimating the clinical and economic benefit associated with incremental improvements in sustained virologic response in chronic hepatitis C. PLoS One 2015;10 e0117334.
[47] Linas BP, Barter DM, Leff JA, Dilorenzo M, Schackman BR, Horsburgh CR, et al. The cost-effectiveness of improved hepatitis C virus therapies in HIV/hepatitis C virus coinfected patients. Aids 2014;28:365–376.
[48] Pfeil AM, Reich O, Guerra IM, Cure S, Negro F, Mullhaupt B, et al. Cost-effectiveness analysis of sofosbuvir compared to current standard treatment in Swiss patients with chronic hepatitis C. PLoS One 2015;10 e0126984.
[49] Rein DB, Wittenborn JS, Smith BD, Liffmann DK, Ward JW. The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus. Clin Infect Dis 2015;61:157–168.
[50] van der Meer AJ, Wedemeyer H, Feld JJ, Dufour JF, Zeuzem S, Hansen BE, et al. Life expectancy in patients with chronic HCV infection and cirrhosis compared with a general population. JAMA 2014;312:1927–1928.
[51] Mullhaupt B, Bruggmann P, Bihl F, Blach S, Lavanchy D, Razavi H, et al. Modeling the health and economic burden of hepatitis C virus in Switzerland. PLoS One 2015;10 e0125214.
[52] Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. Am J Gastroenterol 2007;102:2589–2600.