Research Article

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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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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.

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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; 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.

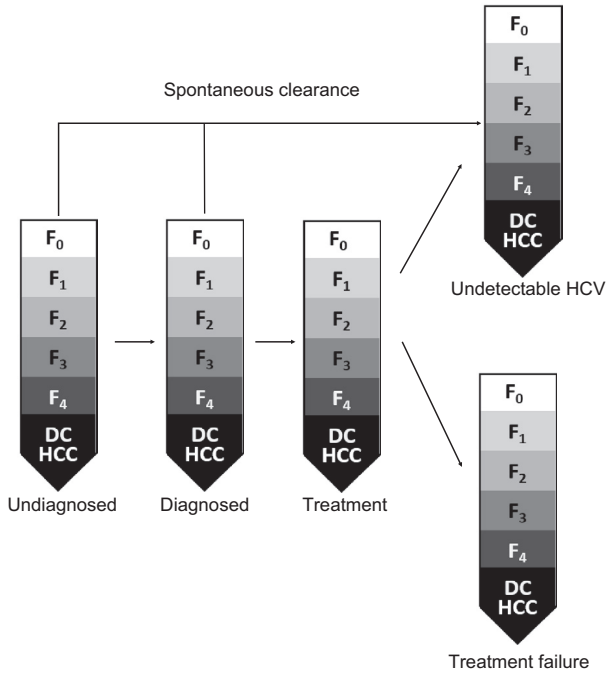

Fig. 1. Model structure. Individuals can progress vertically through the METAVIR fibrosis stages (F0 to F4) and the endpoints: decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). From any of those stages individuals can also progress horizontally along the care cascade and be diagnosed, 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.