This is Exhibit "M" referred to in the
affidavit of Asvini Krishnamoorthy
sworn before me at Toronto, Ontario
this 29th day of January, 2016

A Commissioner for taking affidavits
within the Province of Ontario

Estimating the Prognosis of Canadians Infected With the Hepatitis C Virus Through the Blood Supply, 1986-1990

Fourth Revision of Hepatitis C Prognostic Model Incorporating Data From the Compensation Claimant Cohort

April 2011

Hla-Hla Thein MD MPH PhD
Qilong Yi MD MSc PhD
Murray Krahn MD MSc FRCPC

Corresponding author address:

Hla-Hla Thein
Dalla Lana School of Public Health
University of Toronto
5th Floor 155 College Street Rm 560
Toronto, ON M5T 3M7
Tel: +1-416-978-2020
Fax: +1-416-978-8299
Email: rosie.thein@utoronto.ca

Table of Contents

List of Abbreviations

ALT, alanine aminotransferase

β, coefficient

BMI, body mass index

CASL, Canadian Association for the study of the Liver

CI, confidence intervals

df, degrees of freedom

ESLD, end-stage liver disease

FPR, fibrosis progression rate

HAART, highly active antiretroviral therapy

HAI, histological activity index

HBsAg, hepatitis B surface antigen

HBV, hepatitis B virus

HCC, hepatocellular carcinoma

HCV, hepatitis C virus

HIV, human immunodeficiency virus

IDU, injecting drug use

IDUs, injecting drug users

IFN, interferon

LB, liver biopsy

MMLE, Markov maximum likelihood estimation

PEG-IFN, pegylated interferon

PTCC, Post-transfusion compensation claimant

RCT, randomized controlled trial

RNA, ribonucleic acid

RR, risk ratio/relative risk

SD, standard deviation

SE, standard error

SMR, Standardized Mortality Ratio

SVR, sustained virologic response

Executive Summary

Hepatitis C virus (HCV) is one of the most common causes of liver disease in Canada. Before serologic testing for the presence of hepatitis C became available in 1990, blood transfusion and blood product use were a major source of HCV infection. Between 1986 and 1990, surrogate marker testing was employed to screen blood donors in the United States to reduce the risk of HCV infection in the general population. In Canada, surrogate marker testing was not employed in most jurisdictions.[2] As a result, many individuals in Canada became infected by HCV through blood transfusion and blood products during this time window.

On March 27, 1998 federal, provincial, and territorial governments announced an offer of financial assistance to individuals who were infected with HCV through the blood system between January 1, 1986 and July 1, 1990. In 1999, court orders in British Columbia, Ontario and Québec were obtained approving a settlement agreement which made approximately $1.2 billion available to compensate claimants, who included individuals with transfusion-acquired HCV infection (including hemophilics), those with HIV who became co-infected with HCV, and secondarily infected individuals.

The Canadian compensation program is unique in that it links compensation levels to stage of liver disease. However, the long-term prognosis of HCV infection is uncertain and variable, and experts disagree. In order to assist in ensuring the long-term sufficiency of the fund, a working group was formed in November of 1998 to provide best possible estimates of the prognosis of the HCV-infected post-transfusion compensation claimant (PTCC) cohort. This “medical

model", a Markov state-transition model, served as the basis of the actuarial model which estimated future payments from the compensation fund.

The compensation agreement between governments and plaintiffs calls for an estimate of the sufficiency of the compensation fund every three years. In order to assist in the process of assuring the sufficiency of the fund, the original prognostic model has undergone four subsequent revisions. This document describes the fourth revision of the original model. Serial revision is required because new information regarding both the characteristics of compensation claimants (e.g. HCV stage distribution and size of claimant cohort) and HCV outcome data (e.g. natural history prognostic data, treatment patterns and treatment intensity) continues to become available. Older projections become less accurate as time passes.

The first revision took place in 2002 by a working group which included some members of the original group (Murray Krahn, Jenny Heathcote & Linda Scully) and two new members (Peter Wang & Qilong Yi). There were two major differences in the 2002 prognostic model, in comparison to the original model. The first was that the prognosis of the PTCC cohort was explicitly linked to liver fibrosis stage. This made it considerably easier to use the "medical model" to estimate future payments, as compensation levels were closely linked with fibrosis stage. The second major difference was that we had detailed clinical and demographic data from 2,466 compensation claimants.

The second revision included one new member (Morris Sherman), and differed from the first revision in several aspects. First, the number of compensation claimants increased from 2,446 to

4,530 or by 85%. Thus, the results reflected were more representative of the target cohort. Second, the stage transition probabilities were revised by incorporating data from newly published prognostic studies and transition rates derived directly from the PTCC cohort. In contrast to the previous models, a new method (Markov maximum likelihood estimation, MMLE developed by our group), which does not assume constant fibrosis progression rate, was used to obtain stage-specific transition probabilities. Third, antiviral therapy improved substantially, with combination pegylated interferon (PEG-IFN) and ribavirin therapy proving to be more effective than the standard interferon-based therapies, and became the standard of care in the past few years. A meta-analysis was thus performed to estimate sustained virologic response (SVR) rates in patients treated with PEG-IFN and ribavirin. Fourth, a revised survey of hepatologists to evaluate practice patterns with respect to antiviral therapy was incorporated into the 2005 model.

The third revision included two members from the previous revisions (Murray Krahn & Qilong Yi) and one new member (Hla-Hla Thein). It retains all the objectives of the second revision: i) update literature review regarding transition probabilities; ii) use the most current data from the post-transfusion compensation claimants; and iii) project future outcomes. Besides that the number of compensation claimants increased from 4,530 to 5,004 in this revision, the methodology used is almost the same as in the 2005 revision. However, in order to obtain more precise transition estimates, the stage-specific transition probabilities were revised by performing a new comprehensive meta-analysis involving transition probabilities derived from the 111 literature-based studies (both English and non-English) and from transition probabilities derived directly from the PTCC cohort. Further, these transition probabilities were adjusted, taking into account study design and clinical factors.

The third revision differs from the previous revisions in a number of ways: i) conducted more comprehensive systematic reviews (i.e., transition probabilities, effect of HIV on fibrosis progression, excess mortality associated with HIV infection, and HCV treatment efficacy); ii) adjustment for the effect of study design and clinical factors on disease progression; iii) and revision of the link between compensation level and fibrosis stage distribution (i.e., level 3, non-bridging fibrosis has been distributed to F1/F2 and level 4, bridging fibrosis to F3 instead of F1 and F2/F3, respectfully). This does not appear to change the overall results substantially in the short-term.

This fourth revision was conducted by the same members as in the 2007 revision. It differed from the previous revisions in several aspects: i) in all models, claimants were categorized into different disease stages based on clinical symptoms and laboratory testing results, which is independent of the compensation level. In the previous models, claimants who were classified as Level 2, but had negative RNA or did not have RNA result, other symptoms to support fibrosis, or cirrhosis diagnosis were reclassified as Compensation Level 1 (HCV antibody positive/RNA negative). In our current model, there were 254 claimants who were classified as Level 2; all were HCV antibody positive, but 44 had negative RNA and 210 had missing RNA results. There were 20 deaths and 234 were still alive. These were a group of claimants whose physicians had not confirmed Level 2 but on discussion with the Crawford Class Action Services Administrator, it was confirmed that PCR positive tests had been provided to the Administrator for all claimants approved at Level 2. Therefore, these cases remained classified as Compensation Level 2 (HCV RNA positive); ii) the model was revised with an additional health

state transition from HCC to liver transplantation; iii) annual HCV treatment rates from the cohort rather than expert estimates were used; and iv) previous HCV treatment was considered. Approximately 30% of living patients in 2010 whose current stage between fibrosis stage 1 and fibrosis stage 4 (compensated cirrhosis) were assumed cured after treatment and would have a lower progression rates. Transition probabilities (particularly, clinical stages), age and sex distribution, and initial stage distribution were updated.

For the overall living patients, our model predicts that the prevalence of cirrhosis in August 2010 is 10.0% (Table 8.1.1). The cumulative lifetime incidence of cirrhosis is 38.5%, and 24.0% will ultimately die of liver disease. Our model also predicts that 34.5% of non-hemophilic patients alive in 2010 will ultimately develop cirrhosis, and 20.4% will ultimately die of liver disease. Because hemophilic patients are younger, and are frequently co-infected with HIV, they will have higher cumulative rates of cirrhosis and liver-related death (51.6% and 35.6%, respectively).

Predictions of the current model relative to those of the earlier three models are reported in Tables 7.2 and 7.3. There is no substantial difference in the prognostic projections between the current model and the 2007 model. The differences between more recent revisions (2004, 2007 and 2010) and 2002 revision are attributable to several factors. First, there are now more claimants in early HCV stages (F0 and F1) than in the 2002 model (76.4% in 2004 and 82.6% in 2007 and 79.7% in 2010 vs. 63.9% in 2002) (Table 7.2). Second, the stage transition probabilities used in the recent projections were adjusted downward after incorporating several

newly published studies and data from the compensation cohort. Third, more effective treatment (combination PEG-IFN and ribavirin) is now available.

This document reports specific projections for 10-year age strata for individuals with transfusion acquired hepatitis C infection who are hemophilics as well as those who are non-hemophilics. We also report sensitivity analyses that estimate the degree of uncertainty associated with these projections.

As in the previous reports, the limitation of the prognostic model relates to the availability of biopsy data of PTCC cohort. The true extent of liver damage at the time of claim is unknown in approximately 80% of the PTCC cohort. However, the current model likely represents the state-of-the-art in estimation of HCV prognosis among this cohort. It is possible that the number and stage distribution of compensation claimants might be almost complete as the number of claimants has increased by only 4.4% (from 5,004 in 2007 to 5,225 in 2010). The number of outstanding claims is believed to be relatively small.

This work represents a multidisciplinary effort between experts in hepatitis C clinical care, epidemiology, biostatistics, and decision modeling. It represents a unique application of decision modeling methods to a public policy question of great import to Canadians. It provides separate estimates for hemophilics and non-hemophilics, and allows estimates of the sufficiency of the compensation fund to rest on the best current evidence. The model incorporates meaningful clinical data to estimate stage distribution and the direct estimation of annual treatment rates from the cohort. Analysis of the large PTCC cohort dataset makes it possible to more accurately

estimate the stage distribution of compensation claimants and to estimate patient-derived transition probabilities. The best possible current and future predictions are produced using both literature- and patient-derived stage-specific transition probabilities, taking into account study design and clinical factors. Finally, this work provides uniquely detailed prognostic estimates that will be of value to HCV patients and their physicians who want to know what the future holds for them.

1. Background

Hepatitis C virus (HCV) is one of the most common causes of liver disease in Canada. Recent studies suggest that the prevalence of HCV infection in the Canadian population is about 0.8 % and the estimated number of people with HCV is about 250,000 to 300,000.[3-5] Before serologic testing for the presence of hepatitis C became available in 1990, blood transfusion and blood product use were a major source of HCV infection. Between 1986 and 1990, surrogate marker testing was employed to screen blood donors in the United States to reduce the risk of HCV infection in general population.[6] In Canada, surrogate marker testing was not employed in most jurisdictions.[2] As a result, many individuals in Canada became infected by HCV through blood transfusion and blood products during this time window.[2]

On March 27, 1998, federal, provincial, and territorial governments announced an offer of financial assistance to individuals who were infected with HCV, directly or indirectly through the blood system between January 1, 1986 and July 1, 1990. Up to $1.1 billion was to be made available to compensate claimants, who included hemophilics, secondarily infected HCV claimants, those with HIV who became co-infected with HCV, as well as all others with HCV infection acquired through blood transfusion during the period in question.

In order to settle on an appropriate compensation scheme, the federal and provincial governments as well as the claimants reviewed a number of models of the natural history of hepatitis C. Because of disagreement regarding the natural history of this disease, the Canadian Association for the study of the Liver (CASL), an impartial body with no stake in the outcome of compensation negotiations, was approached by both stakeholders to produce the best available

model of the natural history of HCV. In November of 1998, CASL approached individuals with expertise in hepatitis C epidemiology, hepatitis C clinical care and decision modeling to assist in the construction of a model. As a result, an ad-hoc working group was formed. Drs. Murray Krahn, Jenny Heathcote, Linda Scully, Leonard Seeff and John Wong, were the key members of the working group.

This working group evaluated and accepted the validity of the structure of the Bennet/Wong Markov chain model,[7,8] but subsequently simplified it. Each parameter in the model was reviewed. Key parameters, such as the excess mortality rate, the incidence rates of cirrhosis, hepatocellular carcinoma (HCC) and decompensated cirrhosis, were updated by systematically reviewing and synthesizing the literature. Confidence limits and/or plausible ranges were identified for key model parameters. With this revised model, the cumulative probability of acquiring cirrhosis, decompensated liver disease, and liver death were predicted using baseline characteristics. For the transfusion cohort as a whole, the 20-year and lifetime cumulative probability of developing liver cirrhosis was 13.4% and 24.9%, respectively. Similarly, the 20-year and cumulative lifetime probability of dying of HCV-related liver disease was 2.5% and 12.3%, respectively.

However, the original model had two major limitations. First, it used clinical staging for HCV progression rather than serological and pathological staging, on which the compensation agreement was based. Second, the previous model was developed before any clinical or demographic information was available regarding actual claimants. The model was therefore based only on estimates derived from the literature.

The compensation agreement between governments and plaintiffs calls for an estimate of the sufficiency of the compensation fund every three years. In order to assist in the process of assuring the sufficiency of the fund, the first revision of the original prognostic model was completed in 2002 by a working group consisting of several members of the original research team (Drs. Jenny Heathcote, Linda Scully and Murray Krahn) and two new members, Dr. Peter Wang (Epidemiology) and Dr. Qi-Long Yi (Biostatistics).

The specific objectives for the first revision of the prognostic model were:

i) Create a fibrosis stage-based Markov prognostic model (fibrosis stage 0 [F0], fibrosis stage 1 [F1], fibrosis stage 2 [F2], fibrosis stage 3 [F3], fibrosis stage 4 [F4, cirrhosis];
ii) Review and synthesize the existing literature to derive the transition probabilities between these health states and document the impact of the baseline characteristics on these transition probabilities;
iii) Use the available post-transfusion compensation cohort data to provide independent estimates of transition probabilities and other key probabilities for the model; and
iv) Project the prognosis (expressed in cumulative probabilities of adverse events) of claimants over their remaining lifetimes in accordance with HCV severity levels stipulated in the compensation package.

The second revision of the HCV prognostic model remained to use a fibrosis stage-based Markov model and retained the objectives of the first revision:

i) Update literature review regarding transition probabilities;
ii) Use the most current data from the post-transfusion compensation claimants; and

iii) Project future outcomes.

Efforts to update our projections for the second revision focused mainly on objectives ii and iii. In addition, Dr. Morris Sherman joined the team as an additional content expert and reviewer.

The third revision of the HCV prognostic model in general, continued to retain the objectives of the second revision and fine tune methodology in order to obtain more accurate predictions. The working group included two members from the previous revisions (Drs Murray Krahn & Qilong Yi) and one new member, Dr. Hla-Hla Thein joined the team as a content and modeling expert.

The objectives of this fourth revision remained the same including to further fine tune methodology to reflect more precise estimates.

2. Model Structure and Assumptions

2.1. Model Structure

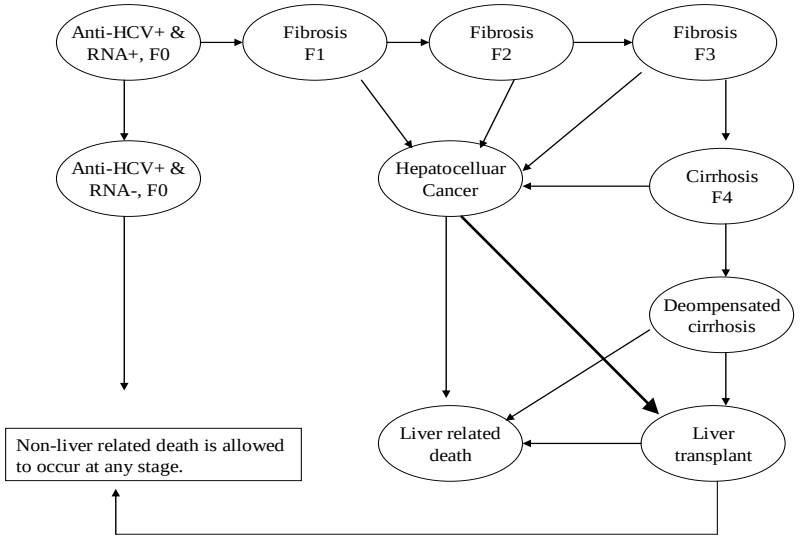
The proposed model (Figure 1 and Figure 2.1), which was revised from the previous Markov models,[9-11] is comprised of two major components: model structure and model parameters. Structure refers to the health states that are represented within the model and the allowable transitions between those health states. Model parameters include the numerical values assigned to transitions between health states (i.e., the transition probability from one stage to another).

Each circle represents a health state for the individuals infected due to blood transfusion in Canada between 1986 and 1990. Each solid arrow represents possible transitions between health

states that may occur each year. (A detailed representation of the tree as programmed in TreeAge Pro is shown in Figure 2.1). The recent models are largely consistent with the one used in the first revision except for the new path from liver transplant to non-liver related death. Futhermore, in the current model, an additional path from HCC to liver transplantation was implemented (Figure 1). In the previous models, post-transplant death was modeled using a cumulative mortality rate for all individuals post-transplant. In the second and third revisions we disaggregate mortality rates into disease-specific and general population mortality rates. This modification is particularly important in the elderly as deaths from competing causes rise with increasing age. The current version of the model adheres closely to the contemporary understanding of the biology of HCV disease by representing fibrosis as the key to defining prognosis. In so doing, it also represents health states that more closely reflect compensation levels defined in the compensation agreement.

In all models, claimants were categorized into different disease stages based on clinical symptoms and laboratory testing results, which is independent of the compensation level. Transitions between fibrosis stages (F0 to F4) are explicitly represented in all four revisions. For patients with F0 stage, a distinction is made between those who are RNA+ and those who are not (a sub-classification of a ***pathological*** category according to ***serology***). Patients with F4 disease are separately considered according to whether they have compensated or decompensated cirrhosis (a ***clinical*** distinction).

Figure 1 Simplified Schematic Markov Model of Natural History of HCV Infection



2.2. Model Assumptions

This model structure involves a number of specific assumptions, which are described below.

2.2.1. There is no excess HCV-related mortality in patients whose liver disease has not yet progressed to F4. Thus, the excess mortality attributable to rare HCV-related events such as B-cell lymphoma, renal failure, and symptomatic mixed cryoglobulinemia are not explicitly represented in the model. The sole exception to this is HCC. Patients are allowed to develop and die from HCC at earlier stages, although this is very uncommon.

2.2.2 The probability of progressing to HCC for an HCV-RNA negative person is extremely low. We assume that it is zero and do not explicitly model this transition.

2.2.3 The only difference between RNA+ and RNA- patients is the transition rate from F0→F1. We assume that transition rate from F0→F1 for a RNA- patient is "0". After the F0 stage, serologic status (i.e., RNA- and RNA+) is not explicitly represented. We assume that future prognosis is determined by fibrosis stage alone.

2.2.4. Our model is unidirectional for chronic disease stage. Thus, regression from a later to an earlier stage (e.g. F1 to F0, F2 to F1, F3 to F2) is not permitted, although there is recent evidence to suggest that this may occur in some individuals. Also, the disease progresses one stage a time. Thus, skipping stages within a single cycle (one year) is not allowed (e.g. F1 directly to F3).

2.2.5. The effect of treatment on disease progression is not explicitly represented in the model diagram, but is incorporated within the model structure in the form of an efficacy parameter modifying the annual probability of disease progression in patients who are treated. The effects of other covariates, such as sex and age are also incorporated into the model, although they also are not explicitly represented in the diagram.

2.2.6 We assume that hemophilic status does not affect HCV disease progression (see section 4.3.6). However, hemophilics account for 25.6% of HCV patients in our cohort (as of 2010), and had very different age and sex distributions (significantly younger and more males), and a high rate of coinfection with HIV (41.3% vs. 0.4% in non-hemophilics). Thus, non-hemophilic patients and hemophilic patients were modeled separately.

2.2.6 Previous models did not include liver transplantation associated with HCC. In the current model, we assume a probability of 0.10 (range, 0.05-0.18). HCV is a major cause of hepatocellular carcinoma,[12] and is now the leading indication for liver transplantation in North America.[13] In Canada, there is evidence of the rising numbers of people infected with HCV receiving liver transplantation, accounting for 35% of the liver transplantations.[14]

2.3. Analytic Method

Prognostic results were generated using first order Monte Carlo simulation, as implemented in TREEAGE PRO.[15] This allows the model to be much more compact, because it allows a large number of prognostic variables to be represented as tracker variables (i.e., variables that are modified for each individual as they progress through the model) rather than having to be explicitly represented in the model as Markov health states. For each combination of age, hemophilic status, and starting distribution, 100,000 simulated patients were run through the prognostic model one at a time. The cumulative proportion in any stage (e.g. cirrhosis, liver death) thus represents the number, out of 100,000, who at any time within the specified interval, entered that health state.

3. Model Parameters - General Approach to Data Synthesis

3.1. Data Sources

Three sources of data were reviewed: the previous models, published data, and data directly collected from the PTCC cohort.

3.1.1. Data from the previous models

Some model parameters as well as most aspects of model structure were carried over from the previous modeling efforts. These included transition probabilities for both early stage of HCV infection (e.g. transition probabilities from HCV RNA- F0 to recovery and from HCV RNA- F0 to F1) and late stage HCV infection, defined as stages of HCV infection after cirrhosis (e.g. transition probabilities from decompensated cirrhosis to liver transplantation, HCC to liver transplantation, liver transplantation to death, decompensated cirrhosis to liver-related death, and HCC to death). After reviewing studies published in the last few years, we were convinced that most of these late stage transition probabilities derived in our last reports remain valid, except for the transition from HCC to liver death (see below). The excess mortality ratios attributable to transfusion itself were derived from Vamvakas.[16,17] As in the previous model, information describing the initial distribution at time of infection, for model simulations that began at the time of infection (not the baseline model) including age, sex and year of exposure were derived from the report by Remis *et. al*.[4] The simulations used for the 2010 (baseline) model, that begin on August 31, 2010, used the actual stage distributions derived from the compensation cohort.

Since some studies on the progression of fibrosis do not present the information exactly as the model requires, transformation of the data was performed to derive the transition probabilities between stages. The method used to derive stage-specific transition probabilities was based on a simplified Markov Chain model using an iteration technique (see section 3.4).[18]

3.1.2. Data from the literature

We updated data on the transition probabilities for stages after cirrhosis, i.e., from cirrhosis to HCC (Table 4.4.1) and from HCC to liver-related death (Table 6) and the effectiveness of pegylated interferon (PEG-IFN) and ribavirin combination therapy in HCV-infected individuals (Tables 4.3.1.1-4.3.1.3). For other data relating to late stages of HCV, we referred to Hutchinson *et al's*[19] report. For the transition from HCC to liver-related death, we found that HCC survival has improved likely due to treatment advancements in recent years or that we may have underestimated in the previous models). For the the current model, the derived transition probability from HCC to liver-related death is 0.350 (range, 0.316-0.699),[19-22] compared to 0.605 (range, 0.545-0.676) in the 2007 model.

3.1.3. Data from the post-transfusion compensation claimant cohort

Data compiled from compensation claim files were used to calculate stage-specific transition probabilities (i.e., F0→F1, F1→F2, F2→F3, and F3→F4), which were compared and also combined with literature-based transition probabilities using the algorithm derived from a meta-regression of covariates associated with liver fibrosis progression in chronic HCV infection.[23]

3.2. Synthesizing published data

In the previous models, published human studies that examined liver fibrosis progression in chronic HCV infection were searched via the MEDLINE, EMBASE, and PubMed databases of both English and non-English language publications covering the period January, 1990 to August, 2007 (up to December, 2006 for non-English articles), with combinations of "hepatitis C", "HCV", "hepatitis non-A", "fibrosis", "cirrhosis", "cohort studies", "case-control studies",

"prognosis", "disease-free survival", "medical: futil", "treatment outcome", "treatment failure", "disease progression", "morbidity", "mortality", "fatal outcome", "hospital mortality", "survival analysis", and "natural history". Citations were cross-checked through review of bibliographies of relevant published papers. Additionally, an expert working in the area was contacted in order to supplement any grey literature.

In the current revision, we extended our literature search from 2007 to 2010 for clinical input data.

3.3. Estimating transition probabilities

Two methods have been generally used in literature to derive transition probabilities between health states from published studies: ***direct*** and ***indirect*** estimation. In ***direct*** estimation, the fibrosis progression rate is defined as the ratio of the difference in fibrosis stage expressed in METAVIR units between two biopsies and the interval between the two biopsies in years. Direct estimation is only possible when serial biopsy information (i.e., at least two biopsies) is available with an accurate estimate of the time interval between biopsies. When only a single biopsy is available (most studies), only ***indirect*** estimation of fibrosis progression is possible. Using the indirect method, the current fibrosis stage in METAVIR units is divided by the estimated number of years of infection. The date of the first blood transfusion is often used to estimate the time at which the initial infection occurred.

Both direct and indirect methods have drawbacks in estimating disease transition probabilities. When the disease transition probability is estimated indirectly, the rate of fibrosis progression is

assumed to be constant between all stages (e.g. $p_{01}= p_{12}= p_{23}= p_{34}$), an assumption which may not be plausible, and which has been questioned in the literature.[24] Although the direct method is able to directly estimate the rate of transition between fibrosis stages, and does not require the assumption of constant transition probabilities, it does require paired liver biopsies, which are only available in a few studies. Thus, its application is greatly limited because of small numbers and unrepresentative samples. In addition, transition probabilities derived from either method are likely influenced by the timing of the biopsies performed. Sampling variation in the time of biopsy within fibrosis stages could result in significant variations in estimated transition rates.

For example, suppose a patient remained in pathologic stages F1 and F2 each for 5 years, and that the transition between stages occurs at the end of year 5. If sampling occurs in years 5 and 6, the estimated population transition rate derived from that single estimate is 1.0, whereas if sampling takes place at years 1 and 10, the estimated transition rate is 0.1. The biases related to the timing of biopsy are of little concern in a population-based study assuming the timing of biopsy is random. However, because biopsies are often triggered by clinical events which may correlate which changing fibrosis stages, an upward bias in transition rates attributable to sampling pattern may exist. Some studies, e.g. Poynard *et. al*.[25] report prognosis in terms of the average (or median) number of ***fibrosis units per year***. This is a variable that could potentially apply either to an individual or to a population. However, what is required for our model is the average ***transition rate*** between stages per year. This value, for an individual, can only take the value of zero or one – either an individual changes stages or not. For a cohort, this value represents the proportion of the cohort transitioning between stages within a given cycle. It is

important to note that we treat these values (***fibrosis units per year*** and ***transition rates***) as being interchangeable.

For a cohort, the mean number of fibrosis units per year is equal to the mean transition rate between stages. If we are considering transitions between two stages, the number of fibrosis units per year change is equivalent to the percentage of subjects that transit to the next stage. Based on an exponential survival model, the mean progression rate, whether it is expressed as the transition rate between stages or as the number of fibrosis unit changes per unit time, is equal to the reciprocal of the mean survival time in one stage (or sojourn time). For example, if the mean rate of fibrosis progression per year was 0.133, then mean survival time is equal to 1/0.133=7.5 years. In other words, the progression time from entering one stage to leaving this stage is equal to 7.5 years. Therefore, the reported progression rates as calculated in fibrosis units from published studies using either the direct or indirect method have the same meaning as the transition rate we defined and can be used as an estimate of the mean transition rate between stages in our model.

Another concern associated with simple direct or indirect estimation is related to the assumption that HCV patients are homogeneous and have similar fibrosis progression rates. Even within individuals, progression rates may vary as a function of fibrosis stage and age.[24] Variation across individuals has also been convincingly demonstrated. Poynard *et al*.,[26] for example, suggests that there are at least three populations in terms of disease progression: rapid, intermediate, and slow progressors. To reflect the inter-group differences in disease progression, the authors have suggested using logistic regression to model disease progression. In this approach, other

covariates, such as age and sex can be incorporated. While this modeling approach has some appealing aspects, it still assumes that the within-group transition rate is consistent across different stages. This is potentially problematic, as the population of any group will change with time. As the "rapid progressors" depart, the mean rate of progression for the residual cohort will fall.

Our model uses a single transition rate for each modeled transition between health stages. This rate represents a mean rate that takes into account variation across individuals, although it does not fully represent the prognosis of any single individual. This mean rate also does not explicitly take time dependency into account. If transition rates fall over time, as one would expect with the changing composition of fibrosis health states (fast progressors depart more quickly leaving more slow progressors over time), the model as currently specified may overstate progression rates in the very long term.

3.4. Estimating stage-specific transition probabilities: The Markov Maximum Likelihood Method

According to the Markov chain model, the HCV stage distribution of patients after T years of follow-up, P_T=(P0,P1,P2,P3,P4), depends on a transition matrix, M_T, and the initial distribution, P_o=(p0,p1,p2,p3,p4).

$$P_T = P_o * (M_T)^T. \qquad (1)$$

$$M_T = \begin{bmatrix} 1-p_{01} & p_{01} & 0 & 0 & 0 \\ 0 & 1-p_{12} & p_{12} & 0 & 0 \\ 0 & 0 & 1-p_{23} & p_{23} & 0 \\ 0 & 0 & 0 & 1-p_{34} & p_{34} \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}.$$

where p_{ij}, which is unknown but assumed to be fixed, is the transition probability from ith stage to jth stage. Given P_o, T and observed P_T, the unknown transition probabilities, p_{01}, p_{12}, p_{23} and p_{34}, can be estimated through an iteration process.

At the first step, M_T^0, an initial set of transition probabilities, ($p_{01}^0, p_{12}^0, p_{23}^0$ and p_{34}^0) are given for p_{01}, p_{12}, p_{23} and p_{34}, to calculate an expected stage distribution, $\hat{P}_T^0$. The differences (residual) between the expected and observed distributions are compared against a pre-set convergence criterion, usually a very small value (e.g. 0.0001). After each iteration, the previous transition probabilities are revised in order to minimize the differences between the expected and observed HCV stage distributions. The same process is repeated until a set of transition probabilities are found (converged) which best reproduces the observed HCV disease distribution.

Assuming that we are doing the ''ith iteration and have $p_{01}^i, p_{12}^i, p_{23}^i$ and p_{34}^i

$$\hat{P}_T^i = P_o * \begin{bmatrix} 1-p_{01}^i & p_{01}^i & 0 & 0 & 0 \\ 0 & 1-p_{12}^i & p_{12}^i & 0 & 0 \\ 0 & 0 & 1-p_{23}^i & p_{23}^i & 0 \\ 0 & 0 & 0 & 1-p_{34}^i & p_{34}^i \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}^T.$$

The differences, Residual (Res), between the expected and the observed stage distribution is

$$\text{Res} = \hat{P}_T^i - P_T = \begin{bmatrix} \hat{P}0 - P0 \\ \hat{P}1 - P1 \\ \hat{P}2 - P2 \\ \hat{P}3 - P3 \\ \hat{P}4 - P4 \end{bmatrix}$$

and the squared residual sum is Res`*Res, where Res` is a row vector. In our analysis, 0.000001 was defined as the convergence criterion. If the residual sum is greater than 0.000001, $p_{01}^i, p_{12}^i, p_{23}^i$ and p_{34}^i will be modified to be $p_{01}^{i+1}, p_{12}^{i+1}, p_{23}^{i+1}$ and p_{34}^{i+1}.

The transition probabilities are modified according to the sign of the residual. If the expected proportion for stage S is less than the observed proportion, we will decrease the probability of transition from stage S to stage S+1. Otherwise, we would increase the corresponding transition probability. That is:

$$p_{s,s+1}^{i+1} = p_{s,s+1}^{i} + sign(\hat{P}s - Ps) * \Delta,$$

where sign(.) =-1 if $\hat{P}s - Ps$ is negative, and sign(.)=1 if $\hat{P}s - Ps$ is positive. Δ is the step width. For this model, 0.0001 was used.

With this approach we are able to estimate the stage-specific transition probabilities from F0 to F1, …, F3 to F4 based on the stage distribution from one biopsy examination.

For example, Kenny Walsh *et. al*.[27] reported data with 17 years of follow-up. At the end of the study, the stage distribution was 49% in F0, 34% in F1, 10% in F2, 5% in F3, and only 2% in F4. The initial distribution is given as (1,0,0,0,0), that is, we assume that all subjects had no fibrosis at beginning. The initial transition probabilities are given as (0.10,0.10,0.10,0.10).

At the first step, we have expected stage distribution,

$$\hat{P}_T^0 = (1,0,0,0,0) * \begin{bmatrix} 0.9 & 0.1 & 0 & 0 & 0 \\ 0 & 0.9 & 0.1 & 0 & 0 \\ 0 & 0 & 0.9 & 0.1 & 0 \\ 0 & 0 & 0 & 0.9 & 0.1 \\ 0 & 0 & 0 & 0 & 1.0 \end{bmatrix}^{17} = (0.1668,0.3150,0.2800,0.1556,0.0826)$$

Res=(0.1668,0.3150,0.2800,0.1556,0.0826)- (0.49, 0.34, 0.10, 0.05, 0.02)

Since expected P0, P1 are less than observed P0, and P1, we need to decrease transition probabilities, p_{01}, p_{12}, but p_{23} and p_{34} need to be increased. We then pursue the next iteration.

Convergence was achieved after 1384 iterations: the expected stage distribution is (0.4899, 0.3402, 0.1000, 0.0498, 0.0200) and the squared residual is 0.0000001. The estimated transition

probabilities are (0.0411, 0.0469, 0.1029, 0.0877). The probabilities tell us that disease progression is slow from F0 to F1, and F1 to F2, but faster from F2 to F3 and F3 to F4.

In the second revision, we adapted the iteration approach to incorporate maximum likelihood estimation. The maximum likelihood approach can use individual data and produce an approximated variance of the estimated stage-specific rates. In addition, this approach results in more rapid convergence. Details for this method and the corresponding SAS codes for the above statistical calculations are provided in the paper by Yi *et al.*[18] and in Appendix B.

In the third and fourth revisions, we use this Markov maximum likelihood estimation (MMLE) method to estimate stage-specific transition probabilities.

3.5. Using the Markov Maximum Likelihood Method to estimate stage-specific transition probabilities from the literature

The proposed method can be applied to either prospectively gathered data, or to cross-sectional studies. In either case, all that is required is an estimate of the starting distribution and of the final distribution. However, estimating stage-specific transition probabilities for non-prospective data is potentially problematic, as follow up for most non-prospective cohorts will be incomplete. Various selection pressures may result in certain fibrosis stages being over-represented in the cases that are ultimately gathered for study. For example, if patients with more advanced disease are more likely to come to clinical attention and be included in a non-prospective study, late-stage transition probabilities will tend to be biased upward. Underrepresentation of patients with stage F0 disease will lead to a higher transition probability

from F0 to F1. Missing patients in F2 and F3 will cause higher proportions with cirrhosis relative to F2 and F3, even higher than the patients in F3. This will lead to very high transition probability from F3 to F4, and lower transition probabilities from F1 to F2 and F2 to F3.

4. Estimating Model Parameters from the Literature

4.1. Seroconversion from HCV RNA+ to HCV RNA- status

Research has shown that HCV infection may be self-limited or persist[27-34] and the transition from HCV RNA+ to HCV RNA-, i.e., clearance of the virus, is a part of natural course of disease during the acute period of hepatitis.[35] In a prospective study of 43 hepatitis C patients with a history of illicit drug use, Villano *et al*.[33] concluded that approximately 85% of people with acute hepatitis C infection develop persistent viremia after a 72-month follow-up. In a review by Hoofnagle,[35] the proportion of patients infected by HCV developing chronic hepatitis was estimated to be 85%. Among 41 patients with post-transfusion hepatitis C, 10 (25%) recovered and 31 (75%) progressed to chronic liver disease after 6 years.[29] Alter *et al*.[28] reported a study on community acquired hepatitis C, in which chronic hepatitis developed in 60 (62%) of 97 HCV-infected patients at a follow-up period ranging from 9 to 48 months. Wiese *et al*.[36] reported that 55% of HCV-infected women were positive for HCV RNA after 20 years of follow-up. In a more recent report, Wiese *et al*.[37] reported that 46% of HCV-infected patients were positive for HCV RNA after 25 years of follow-up. In a recent systematic review, Micallef *et al*.[34] examined 31 studies involving 9 studies of post-transfusion hepatitis, 19 of acute clinical hepatitis, and three of seroincident cases. In total, data was available for 675 subjects. The mean study population was 22 (range 4–67) and the mean duration of follow-up was approximately 3 years.

The authors reported that the proportion with viral clearance ranged from 0.0 to 0.8, with a weighted mean of 0.26 and a 95% CI of 0.22 to 0.29.

Theoretically, all patients should experience the HCV-RNA positive stage, and individuals who are HCV-RNA negative were presumably converted from the RNA positive state sometime following the period of acute infection (i.e., after six months). However, estimating the rate of seroconversion within the first six months, and estimating the annual rate of seroconversion thereafter is not straightforward. It is not even clear that ***any*** seroconversion takes place after the acute period. All seroconversion may be taking place during the acute infection period.

Most published studies, and our own data describing the 1986-1990 PTCC cohort, simply describe serologic status some years after HCV infection was acquired. Our own data describe RNA+ and RNA- status approximately 23 years post-transfusion. Except for young women cohorts (assumed 20% seroconversion),[27,36,37] we assumed that 15% of individuals seroconvert within the first 6 months, based on the published estimate of Hoofnagle.[35] For each published study, we estimated the subsequent annual rate of seroconversion from RNA+ to RNA- based on the remaining cumulative rate and the mean duration of follow-up in the study. The weighted transition rate, incorporating the data from 21 published studies, is 0.020 (95% CI, 0.013-0.027) (Table 4.1).

In our compensation cohort, there were 138 HCV RNA- among 1,935 claimants who have both transfusion dates and RNA tests available in 2004. With an average duration of 17 years in 2004, the estimated transition rate from HCV RNA+ to HCV RNA- was 0.0042 (Table 4.1). When

published data were pooled with our own data from the compensation cohort, the weighted transition rate from HCV RNA+ to HCV RNA- was 0.017 (95% CI, 0.011-0.022) (Table 4.1). We used this data in the 2007 and 2010 prediction models. In the simulation study by Salomon *et al.*[1] the transition rate range used was 0-0.01. In our previous models, we used a rate of 0.006.

4.2. Progression of liver fibrosis

4.2.1. Search strategy and selection criteria

Studies were included if they satisfied the following criteria: (1) full-length and peer-reviewed original articles; (2) chronic HCV infection defined as the presence of anti-HCV antibody detected by second or third generation enzyme-linked immunosorbent assay and at least one of the following: HCV RNA detected by polymerase chain reaction, recombinant immunoblot assay positivity, an elevated alanine aminotransferase (ALT) level without an alternative cause of chronic liver disease, liver biopsy consistent with chronic hepatitis C; and (3) no HCV treatment prior to the first liver biopsy or between subsequent biopsies. Studies were excluded if there were reports of fewer than 20 cases of chronic HCV infection, or if fibrosis progression rates could not be calculated (e.g. duration of HCV infection not reported). If duplicate publications represent several updates of the data, the most recent data or studies with more complete information were included.

Our primary inclusion criterion for prognostic studies of patients with chronic HCV infection was the presence of liver biopsy data expressed using the METAVIR staging system in which the extent of liver fibrosis is expressed in METAVIR units on a scale of 0 (no fibrosis) to 4 (cirrhosis) system.[38] We also included studies in which fibrosis stage was expressed using a

staging system (e.g. Ishak) that could readily be converted to the METAVIR system. This excluded most studies published prior to 1996. Thus, the dataset from which the most important prognostic dataset was derived differs quite significantly from our 1998 study. The new dataset also differs from our 2002 and 2004 studies is that it is more comprehensive including both English and non-English studies.

We considered the taxonomy of Seeff[39] which we used in our 1998 study to aggregate individual studies characterizing the prognosis of HCV infection. Seeff identified 4 types of study: post-transfusion studies, chronic liver disease studies, retrospective analyses of historically defined transfusion-associated hepatitis, and retrospective-prospective non-A non-B and C hepatitis studies. Post-transfusion studies are studies in which individuals who develop post-transfusion hepatitis are prospectively followed. Chronic liver disease studies are prognostic studies that select individuals for inclusion who present for clinical care, usually at tertiary care centres. Retrospective analyses of historically defined transfusion-associated hepatitis studies are case series in which an attempt is made to ascertain the time elapsed from infection by determining the date of transfusion at which time the infection was presumably acquired. Retrospective-prospective studies are those in which a post-transfusion or post-infection cohort is identified retrospectively, and then prospectively followed.

4.2.1.1. Non-cohort studies

The two study designs, chronic liver disease and retrospective analyses of historically defined transfusion-associated hepatitis both suffer from potentially significant biases. Chronic liver disease studies, while often prospective, are usually cases identified in the clinical care, often in

the tertiary care setting. Thus selection bias attributable to more severe illness, and referral filter bias, attributable to the clinical care setting, potentially serve to select an unrepresentative stage distribution of HCV liver disease. Moreover, the true date of infection is usually not known with certainty, but is inferred from the transfusion history. Thus, recall bias is also potentially a problem.

The largest and perhaps best known retrospective study (n=2,235) was that of Poynard and colleagues.[25] The annual progression rate in this study was estimated by using a presumptive date of infection, and calculated using the indirect method. It was reported as 0.133 (95% CI 0.125-0.143) fibrosis units per year. Similar results were reported by Matsumura *et al*.[40] in a Japanese retrospective study of 239 clinical patients. In this study the authors also calculated transition rates ranging by stage: from F0 to F1, 0.11; F0 to F2, 0.12; F0 to F3, 0.16; and F0 to F4, 0.15. Several other studies[41-43] reported annual rates of fibrosis progression similar to that reported by Poynard *et al*.[25] Some studies reported transition rates using the direct method where two or more liver biopsies were performed. The initial stage of these individuals may not start from F0, but from F1, F2, or a more advanced stage. Most studies with repeated biopsies have relatively small sample sizes.

In the 2004 study, published disease transition rates from retrospective studies were calculated using both ***direct*** and ***indirect*** methods. These transition rates across fibrosis stages varied from 0.129 to 0.134, which are very close to the 0.133 fibrosis units per year calculated from Poynard's data.[25] In addition, we used MMLE method to derive stage-specific transition probabilities for studies[25,40,44-47] that reported intermediate stages. We observed lower rates of

disease progression in the intermediate stages, and higher in the early and particularly in the later stages: F0→F1, 0.127; F1→F2, 0.091; F2→F3, 0.154; and F3→F4, 0.226.

There were a number of new studies on HCV stage transition probabilities published after our 2002 report. Ryder and colleagues[46] published fibrosis transition probability results based on a prospective repeat liver biopsy study of 214 British HCV-infected patients. All patients were untreated. The mean inter-biopsy interval was a median of 2.5 years with the rate of progression of 0.17 Ishak fibrosis points per year. Similar studies were also reported by others.[44,47]

4.2.1.2. True cohort studies

In prospective studies, a distinct ***inception cohort*** is identified by exposure to or infection with HCV. Thus all members of the cohort are identified at the same time, and selection, referral and recall biases, which are potential problems inherent in the use of retrospective data, are mitigated.

In general, there was a paucity of disease transition rates from cohort studies. Findings derived from the available studies suggest that disease transition rates were lower than those reported in non-cohort studies. In two different cohort studies in healthy women infected with contaminated anti-D immune globulin, Kenny-Walsh[27] and Wiese *et al*.[36,37] reported that only 2% or less of the initial infected population developed cirrhosis 17-25 years after infection.

In 2004 study, estimation of transition probabilities using the MMLE technique on Kenny-Walsh[27] and Wiese *et al's*[36] data showed that the weighted mean transition probabilities were

0.046, 0.054, 0.096, 0.117 for transition from F0 to F1, F1 to F2, F2 to F3, and F3 to F4, respectively. Thus, there appears to be a clear distinction between transition rates in early fibrosis stages (F0-F2), which are lower, and transition rates between late fibrosis stages (F3-F4), which are relatively higher, a pattern that is also present in the non-cohort studies. Our committee believed that this pattern is most likely reflective of the true pattern of fibrosis transition probabilities, as these data are least affected by bias. This pattern, however, may be at least in part attributable to the effects of increasing age and body mass index as cohorts age. Our method was unable to separately estimate the effects of these variables, but implicitly does capture their effects.

It is instructive to observe that transition rates within true cohort studies are approximately half of those observed in the non-cohort studies, providing a rough guide as to the magnitude of the effects of potential bias on observed transition rates.

4.2.1.3. Studies stratified by study design, setting and population

In our new systematic review (Table 4.2.1), in order to capture the effects of study design factors, we grouped all the eligible studies by: (1) study design – cross-sectional/retrospective, retrospective-prospective, and prospective; (2) setting – clinical- and non-clinical; and (3) study population – blood donors, community, patients on dialysis, female cohorts, injecting drug users (IDUs), liver clinic series, paediatric population, post-transfusion cohorts, and renal transplant recipients.

See description of study design in section 4.2.1. Studies conducted in clinical settings refer to where individuals were identified and/or assessed for their HCV status and liver disease in a clinical/tertiary care setting, and those conducted in non-clinical settings refer to where individuals were screened for HCV in a non-clinical setting, for example, blood donation centre or regional centre.

Data were collected for each study that included relevant items identified in previous studies: i) study-related factors – name of the first author, publication year, study design, country, setting, method of recruitment, number of participants and those who underwent liver biopsy, duration of follow-up; ii) host-related factors – age at assessment, gender, body mass index (BMI), age at HCV infection, estimated duration of HCV infection, mode of HCV acquisition (injecting drug use, blood or blood product transfusion, sporadic/other), alcohol consumption, HIV or hepatitis B virus (HBV) coinfection, history of diabetes mellitus, and presence of hepatic steatosis; iii) virus-related factors – HCV genotype, HCV RNA positivity, and HCV viral load; iv) liver-related factors – ALT level, fibrosis stage based on established histopathologic criteria,[38,48-50] clinical and/or histological diagnosis of cirrhosis, and histological activity index (HAI). We accepted the definitions of elevated ALT level and excess alcohol consumption reported in the studies. We collected the past history of alcohol consumption where possible.

The mean age at HCV acquisition was calculated by taking the difference between the mean age at assessment of liver disease and the mean duration of HCV infection when direct information about age at infection was not available. Ishak[49] fibrosis stages (S0-S6) were converted to the well-validated METAVIR scoring system,[38] where stage of fibrosis is assessed on a five-point

scale: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with rare septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis (i.e., S0=F0; S1=F1; S2=F2; S3-S4=F3; S5-S6=F4). Where studies (n = 16) reported collectively for two immediate fibrosis stages, for example, F0 or F1/F3 or F4, a 50:50 distribution was made conservatively for each stage (e.g., 20 cases of F0 or F1, was distributed to 10 F0 and 10 F1). For the Knodell scoring system (F0 to F4 without F2 stage), F3 was distributed similarly to F2 and F3. Stage distribution was not performed if three or more stages were reported collectively.

A total of 111 reports of HCV natural history studies, involving 33,121 individuals with chronic HCV infection were included in the meta-analysis. A hundred of 111 studies had a cross-sectional/retrospective design. Most studies (n = 97) were performed in clinical settings. Only 14 studies were performed in non-clinical settings. The population studied was most frequently liver clinic patients (n = 79). Relevant data for individual studies are reported in Table 4.2.2.

We used MMLE method to derive stage-specific transition probabilities and performed a meta-analysis to estimate pooled transition rates. Individual study estimates are reported in Table 4.2.3 and pooled estimates in Table 4.2.5. Similar to the pattern observed in the non-cohort studies in 2004, we observed lower rates of disease progression in the intermediate stage, and higher in the early and later stages: F0→F1, 0.117; F1→F2, 0.085; F2→F3, 0.120; and F3→F4, 0.116.

4.3. Factors affecting fibrosis progression

4.3.1. Hepatitis C treatment efficacy

Treatment-induced sustained virological response (SVR, defined as undetectable HCV RNA in serum 24 weeks after the end of treatment)[51,52] to either interferon (IFN) alone or to IFN in combination with ribavirin has been proven to be very effective in delaying or reversing fibrosis progression.[53,54] Effective treatment is associated with long-term clinical and economic benefits, including a low probability of HCV re-infection,[55-57] reduced injury to the liver,[58] normalisation of liver enzymes, cessation of the progression (and even regression)[59] of severe liver disease,[41] improvement in health-related quality of life and productivity,[60] reduced rates of decompensated cirrhosis,[61] HCC,[62] and improved survival.[61,63]

However, not every patient responds to treatment. According to Sobesky *et al*.,[41] the SVR rate for IFN therapy alone is about 20%. In patients treated with combination therapy, the response rate is higher, but varies by stage of disease. Pooled efficacy data from two randomized trials reported in our original report[9] showed that patients with mild chronic hepatitis, moderate chronic hepatitis, and cirrhosis have SVR rates of 36%, 43%, and 21% respectively.

Published reports also suggest that response rates vary by genotype. Combination therapy using standard IFN yields SVR rates of approximately 25-28% in genotype 1 patients and 62% in non-1 genotypes.

The newly approved PEG-IFN or peginterferon has a much longer half-life than the standard IFN and is more effective, though not all patients can tolerate the side effects associated with therapy.

SVR rates among HCV monoinfected individuals have increased from 10-15% with IFN monotherapy to 40-50% with IFN and ribavirin combination therapy,[64] and to 60-65% with PEG-IFN alfa-2a and ribavirin combination therapy.[65,66] Results from a large international randomized clinical trial[51] suggest that the SVR rate in the group treated with PEG-IFN was approximately double that of the group treated with IFN alfa-2a alone. Results from four randomized controlled trials of HCV treatment in HIV/HCV coinfected individuals have shown SVR rates of up to 40% with PEG-IFN and ribavirin therapy.[67-70]

In order to accurately incorporate the effect of combined PEG-IFN and ribavirin treatment on HCV progression rates, a new meta-analysis of the effectiveness of PEG-IFN and ribavirin on chronic hepatitis C was performed in 2007. After a literature search, 49 clinical trials evaluating the efficacy of PEG-IFN-based therapies were identified (Tables 4.3.1.1-4.3.1.3). Ten of the 49 studies were non-randomized trials, and were therefore excluded from the meta-analysis. Twenty-four additional studies were also excluded: 9 studies used PEG-IFN monotherapy only; and 15 studies included highly selected patients (e.g. patients who did not respond to monotherapy, an exclusively African-American population, or genotype-specific study). Fifteen randomized controlled trials among treatment naïve individuals were ultimately included to derive the overall effect of PEG-IFN and ribavirin treatment on hepatitis C. As the sample sizes vary from one study to another, the SVR for each individual study was weighted by its sample size in the intervention group. Based on the 15 studies, the effects are: 49%, 60%, and 45% for overall (n=14), F0-F1 (n=3), and F3-F4 (n=6), respectively (Tables 4.3.1.1-4.3.1.3). In the current model, the SVR rates used were: for F1 to F3 49% and for cirrhosis (F4) 31%. The SVR rate for HCV-infected people with cirrhosis (F4) was derived from a large multicerter

retrospective cohort study,[71] involving 568 patients (70% HCV genotype 1). We did not consider genotype-specific treatment response since the PTCC cohort data lacks information about genotype.

Disease progression rates are very low or zero in those who respond to treatment. Sobesky *et al*.[41] compared patients treated with IFN to untreated patients and found the median fibrosis progression rate based on paired biopsies to be 0.000 METAVIR units/yr in 150 treated patients, and 0.1333 in 86 untreated controls. Poynard *et al*.[72] investigated the impact of a combination regimen or IFN alone on the progression of liver fibrosis, and found that after treatment, the progression rates become negative or zero for either IFN alone or IFN combined with ribavirin. Both studies above reported that the patients receiving treatment had a zero mean progression rate. However, patients with a sustained response had higher regression rates and lower progression rates, than patients without a response. Since most studies examining progression of liver pathology in treated patients have a short time horizon, we employed a conservative assumption in the 2004 model. We very conservatively assumed that the treatment decreases the progression rate (in sustained responders) of liver fibrosis to 10% of that in untreated patients. Like the 2002 model, we also assumed that this treatment effect occurs only in patients with sustained response, and there was no fibrosis regression. This assumption results in the net effect of potentially overestimating the rate of progression to late stage disease in the entire PTCC cohort. In the current model, we used similar treatment efficacies as in the 2007 model, and tracked those individuals who had been treated (though retreatment of non-responders or relapsers was not considered). Approximately 30% of living patients in 2010 whose current stage

between fibrosis stage 1 and fibrosis stage 4 (compensated cirrhosis) were assumed cured after treatment and would have a lower progression rates.

4.3.2. Patterns of treatment by disease stage, age, and co-morbidity

In 2002, we repeated our 1998 survey of Canadian hepatologists to understand patterns of antiviral therapy for HCV patients in Canada. Forty-four (of approximately 50) hepatologists in Canada were contacted and faxed or e-mailed a survey questionnaire. Thirty-eight of 44 responded, for an overall response rate of 86.4% (Table 4.3.2). Based on the survey data, the treatment rate for patients with and without fibrosis is 80% (median) and 14%, respectively. Patients with decompensated cirrhosis are usually not offered treatment.

In 2004, we again surveyed Canadian hepatologists to see whether patterns of antiviral therapy had changed using a brief questionnaire. Appendix C provides the survey covering letter, questionnaire as well as the summary results. As the results from the 2004 survey are virtually identical to those in the 2002 survey, the 2002 survey results were used in both 2004 and 2007 models as it has a larger sample size (Table 4.3.2).

In the current model, we used annual treatment rates of the PTCC cohort instead of the survey cumulative estimates. Approximately a quarter of the cohort has been treated over time and the rates have not changed substantially between 2007 (21.6%) and 2010 (23.8%). We believe that the hepatologist survey estimates were an overestimate of the actual treatment rates. The annual treatment rates for those age < 65 years were: F0 0%; F1-F3 10%; and F4 10%. The respective rates for those age 65 years and above were 0%, 3.3%, and 3.3%, respectively (Table 6). We

assume the possibility of similar treatment rates in the future and therefore used these rates for model projections.

4.3.3. Age, sex and alcohol

The effect of age, sex and alcohol on disease progression has been consistently demonstrated in the literature (Table 4.3.3). It has been suggested that HCV elimination after infection may be faster in females than in males.[73] Based on a large retrospective data set, Poynard *et al*.[25] found that sex, age at first transfusion and alcohol are important prognostic factors. If age at transfusion is >40 years, the progression rate will be 1.5 times of that in people with age <40 years. The risk ratio (RR) of progression in men as compared to women is approximately 1.39.[25] As compared to patients with no alcohol intake, patients with alcohol intake ≥50g per day and <50 g per day have a RR of progression of liver fibrosis of about 1.14 to 1.61. Other studies have also found alcohol to be a very significant risk factor for the progression of liver fibrosis[74-80] irrespective of study design or definition of alcohol abuse. The effects of age, sex and alcohol on disease progression are implicitly incorporated in the model.

4.3.4. HIV coinfection

Studies have shown that coinfection with the HIV virus may accelerate progression of HCV-related liver disease (Table 4.3.4.1 and Figure 4.3.3). Some studies have demonstrated that patients with HIV/HCV coinfection have higher serum and liver HCV RNA levels than those with HCV infection alone.[81] Studies have also suggested that HCV patients with HIV coinfection are more likely to develop end-stage liver disease (ESLD). Ragni and co-workers[82] followed 157 hemophilics, 54% of whom were infected with HCV, for a period of 24 years. The authors

found that the rate of ESLD was higher in HIV positive than HIV negative patients (12.9% vs 9.7%). The adjusted RR for HIV infection was 3.72 (95% CI, 1.25-11.09). Benhamou *et al.*[74] directly studied the impact of HIV coinfection on the progression rate of HCV infection. The authors compared a cohort of 122 HIV-HCV co-infected patients with a control group of 122 HIV-negative HCV-infected patients. The median fibrosis progression rate in co-infected patients was 0.153 (95% CI, 0.084-0.125) and in control patients was 0.106 (95% CI, 0.084-0.125) fibrosis units per year. This suggested a rate ratio for progression of about 1.5 for HCV patients with HIV coinfection, in comparison to patients infected with HCV alone.

In the previous models, a HIV-related RR of fibrosis progression (1.44) reported by Benhamou *et al.*[74] was used. Because this study did not consider the effect of antiretroviral therapy, we conducted a new systematic review to investigate the impact of HIV on fibrosis progression in HCV-infected individuals in the era of highly active antiretroviral therapy (HAART) (Figure 4.3.3). Studies were included if they satisfied the following criteria: (1) full-length and peer-reviewed original articles; (2) chronic HCV infection defined as the presence of anti-HCV antibody detected by second or third generation enzyme-linked immunosorbent assay and at least one of: HCV RNA as detected by polymerase chain reaction, recombinant immunoblot assay positivity, an elevated ALT level without an alternative cause of chronic liver disease or liver biopsy consistent with chronic hepatitis C; (3) HIV infection determined by the positivity of both enzyme-linked immunosorbent assay and Western blot assays; (4) no HCV treatment prior to the first liver biopsy or between subsequent biopsies; and (5) where the infected groups were directly compared.

We extracted adjusted relative risks or RRs and 95% CIs of cirrhosis among HCV monoinfected and HIV/HCV coinfected individuals from the papers when available.[82-90] For other studies, RRs and 95% CIs were estimated using the number of individuals with cirrhosis in each infection group and the corresponding estimated duration of HCV infection. RRs were reported as adjusted values where HCV monoinfected and HIV/HCV coinfected individuals were matched for specific covariates. For two studies where there were no reports of cirrhosis in the HCV monoinfected group[83] or the HIV/HCV coinfected group,[91] an event in each group was attributed to facilitate the calculation of RRs. A meta-analysis of RRs for cirrhosis was performed to obtain pooled estimate.

A total of 27 reports of natural history studies, involving 7,666 individuals with HCV monoinfection (n = 4,970) and HIV/HCV coinfection (n = 2,636) were included in the meta-analysis (Figure 4.3.3). There were 74% and 80% males, 54% and 72% of individuals reporting injecting drug use as mode of HCV acquisition, 36% and 20% reporting receipt of blood or blood product, 20% and 22% reporting excess alcohol consumption, 89% and 83% with HCV RNA positivity, and 51% and 45% with genotype 1, respectively in each group. The mean age of HCV monoinfected individuals was 39.5 years compared to 36.9 years in the HIV/HCV monoinfected individuals, and the duration of HCV infection was 16.5 years and 15.5 years, respectively. Among HIV/HCV coinfected individuals, CD4 cell count at liver disease assessment was reported in 17 studies. The mean CD4 count was 429 cells/μL. There were no reports of HAART in 13 studies. In studies reporting HAART (n = 13), 74% of the individuals were receiving HAART for at least one year at the time of liver disease assessment.

The estimated pooled RRs of cirrhosis for the 27 studies are shown in Figure 4.3.3. Based on the fixed effects model, the RR of cirrhosis among HIV/HCV coinfected patients, relative to HCV monoinfected patients was 1.89 (95% CI, 1.65-2.16). The RR in the random effects model was 2.11 (95% CI, 1.51-2.96). For the non-HAART group, the RR for both fixed and random effects models were 2.49 (95% CI, 1.81-3.42). The RR of cirrhosis in the HAART group was 1.75 (95% CI, 1.06-2.80).

Mortality rates also seem to be strongly affected by HIV/HCV coinfection (Table 4.3.4.2). Yee *et al*.[92] studied a cohort of 310 hemophilic patients infected with HCV between 1961 and 1985, and found that the progression rate to death related to liver disease is 3% and 21% for those HIV negative and positive, respectively, over a 13.3 year interval, with an HIV-related RR of mortality of approximately 7.

In considering how to incorporate this information in the model, we had to take account of the fact that prognostic studies often do not report HIV status. Therefore, our overall stage-specific transition rates undoubtedly incorporate information from some individuals who are HIV positive. Separately estimating the prognosis of those with HIV infection might run the risk of double counting. However, for hemophilic patients, HIV status usually is reported. In our own data, 41.0% (Table 5.3.2) of hemophilic patients are HIV positive. Though HIV testing information is available in few non-hemophilics, we assumed that HIV positivity was more common in hemophilics since they received blood products repeatedly and were exposed to blood products much earlier. In our model for hemophilics, therefore, we incorporated the effect

of HIV status by assuming that fibrosis transition rates between F0 and F4 were increased, on average by our new factor of 2.11.

We also updated excess mortality associated with HIV in 2007 to adjust upward the risk of non-liver death in HIV/HCV coinfected patients. Four studies were included in the meta-analysis involving 5,168 HIV negative hemophilics (52,925 person-years) and 2,979 HIV positive hemophilics (38584.5 person-years). We obtained a pooled mortality risk of 6.24 for HIV coinfected patients, which we used in our 2007 and 2010 models (Table 4.3.4.2).

4.3.5. ALT level and genotype

Liver biopsy is usually recommended for patients who have persistent or intermittent abnormalities in ALT levels for > 6 months.[93] Published data suggest that patients with normal or near-normal ALT levels have a favorable prognosis, although these patients may have histologically and clinically progressive disease. For example, Mathurin *et al*.[45] compared 102 patients with persistently normal ALT and 102 patients with higher ALT, and found a progression rate of 0.07 fibrosis units per year in patients with near-normal ALT levels (ALT <45 units), in comparison with a rate of 0.15 fibrosis units per year in patients with an elevated ALT level ($\geq$50 units). Hui *et. al*.[94] also found that individuals with persistently normal ALT levels with an initial fibrosis of F0 or F1 were less likely to develop progression of fibrosis than those with elevated ALT. Kyrlagkitsis *et al*.[95] compared 91 patients with persistently normal ALT levels and 94 patients with abnormal ALT, and found that overall necroinflammatory score and fibrosis were significantly lower in those with normal ALT, although none had normal liver histology. The authors concluded that one in six patients with HCV infection and persistently

normal ALT will have evidence of significant progressive liver disease that can only be identified on liver biopsy. Similarly, Shiffman *et al*.[96] found that patients with normal ALT levels had significantly lower inflammation and fibrosis scores on liver biopsy than patients with elevated ALT levels, but almost two-thirds had portal fibrosis and 10% had bridging fibrosis. Despite these findings, no correlation between baseline ALT activity and liver histology was observed in patients with normal ALT levels in many of these studies. This may relate to the different definitions of persistently normal ALT levels used in these studies.

Genotype and its effect on HCV progression has been the subject of a number of reports.[25,40,97] Although the literature generally does not support the hypothesis that genotype is an independent prognostic factor, conflicting reports exist. For example, in a study of 140 patients with chronic hepatitis C, Kobayashi *et al*.[98] reported that unfavourable progression was more likely to occur in patients with genotype 1b than genotype 2. By contrast, genotype has been shown to be critically important in predicting treatment duration and probability of response to antiviral therapy.[99,100] (see section 4.3.1 above).

4.3.6. Hemophilia (Tables 4.3.4.1 and 4.3.4.2)

Hemophilia is a group of hereditary bleeding disorders characterized by a deficiency of one of the factors necessary for coagulation of the blood. The two most common forms of the disorder are hemophilia A and hemophilia B. Hemophilia A is the result of a deficiency of antihemophilic factor VIII and hemophilia B represents a deficiency of the plasma thromboplastin component, factor IX. The last half-century has witnessed important advances in the treatment of hemophilia. Studies from Europe showed that mortality among persons with hemophilia has declined

substantially.[101,102] For example, the mean age at death of patients with severe hemophilia increased from less than 10 in the 1930s to around 25 years in the 1970s.[101,102] The primary reason for this decline was the increased wide application of clotting factor replacement products for treating life-threatening bleeding episodes.[103]

Several studies after the 1980s consistently indicate that bleeding or hemorrhage account for only a small proportion of the increased overall mortality observed among individuals with hemophilia. In a 3-year follow-up of 2,950 hemophilics, Soucie *et al*.[103] reported that only 20 (9%) of 236 patients died from hemorrhage (including 6 intracerebral hemorrhage) and the Standardized Mortality Ratio (SMR) was not significantly different from 1. In contrast, 53% of deaths were HIV-related, and 8% were caused by liver disease.[103] These findings were corroborated by other studies. Based on a survey study of 919 male hemophilics, Triemstra and colleagues[104] reported that the overall SMR for the individuals with hemophilia was 2.0. Much of the increased SMR could be accounted for by HIV infection since they found that infection with HIV was the strongest independent predictor of death, with a RR of 27.5 (95% CI, 5.7 to 132.8). They further concluded that: "*in the absence of viral infections, the life expectancy of patients with hemophilia would almost equal that of the general male population.*"

As reported above in the section on HIV coinfection, the literature has consistently shown that hemophilic patients with both HCV and HIV were more likely to develop ESLD in comparison with people with HCV alone. Ragni *et al*.[82] studied ESLD in 157 HCV-infected individuals with hemophilia for an average of 24 years. Eighteen developed ESLD, 11 (12.9%) of 85 HIV positive and 7 (9.7%) of 72 HIV negative. Telfer *et al*.[90] followed a cohort of 183 patients with

hemophilia and HCV (with/out HIV) and 11 of them developed hepatic decompensation. Kaplan Meier estimates of progression rates are 1.7% at 10 years and 10.8% at 20 years after infection of HCV. A large cohort study of mortality in 4,865 hemophilic men and boys by Darby *et al.*[105] in the UK showed that the cumulative risk of death from chronic or unspecified liver disease or liver cancer in the 25 years was 6.5 % for HIV positive patients compared to 1.4% for HIV negative patients. A recent Canadian study[106] of mortality among 1,134 HCV-infected individuals with hemophilia using the Canadian Hemophilia Registry showed that the liver-related death in HIV positive patients was 8.8% compared with 1.1% in HIV-negative patients.

Thus, a review of the published literature suggests that the effect of HIV coinfection on outcomes is at least partially understood, but there are no published reports in which the independent effect of hemophilia on liver-related outcomes or liver-related excess mortality is described. It has been suggested that hemophilia may even play a protective role, as intrahepatic thrombosis, which accounts for "hepatic extinction" may be less common in this group (personal communication, Dr. Ian Wanless). Nonetheless, the independent role of hemophilia itself on HCV progression is unclear. In order to explore potential differences in fibrosis progression rates between patients with and without hemophilia, we compared liver-related outcomes reported in the studies described above with the predictions of the natural history of HCV disease generated by the previous Markov model developed by our group for the entire PTCC cohort. A comparison of these data is also provided in Table 4.3.4.1 (the columns without HIV).[9] HIV negative hemophilics develop ESLD at a rate between 0.0041-0.0088 in comparison with our 2002 projections for the entire cohort of 0.005 per year. HIV negative hemophilics die from liver-related causes at a rate of 0.0009-0.0023 per year, in comparison with our 2002 projections of 0.005 for the entire cohort. These data suggest that hemophilic HCV patients without HIV

develop liver-related outcomes at a similar rate to that used in our 2002 model. Though this comparison is crude, it suggests that hemophilia does not appear to have a powerful independent prognostic effect on the rate of progression to liver-related death or ESLD.

In our model, therefore, we do not assign higher rates of fibrosis progression to hemophilic patients. They are assumed to have the same annual rate of developing fibrosis as non-hemophilic patients. We also assume that there are no independent effects of hemophilia on mortality, except those mediated through HIV infection. Thus, hemophilics are assumed to have the same prognosis as non-hemophilics, apart from much higher rates of HIV coinfection.

4.3.7. Obesity

It is well known that obesity is a risk factor for hepatic steatosis.[107] Recent studies have shown that visceral obesity may also play a role in accelerating fibrosis in people with hepatitis C. This effect may be mediated by steatosis.[107,108] Obesity is also likely to be associated with poorer response to IFN treatment.[109] However, the link between HCV progression and obesity is not consistent. In a study of 148 clinical patients, Fiore and co-workers[110] suggested that the association between hepatitis C and steatosis may be caused by some confounding factors. Because steatosis and BMI data are infrequently reported in published prognostic studies, these variables were not explicitly represented in our prognostic model. However, each of the prognostic studies from which our progression rates are drawn will include some overweight and obese individuals. Thus, not explicitly representing obesity only introduces bias to the extent to which the distribution of BMI differs between the studies from which our transition rates are derived, and the population whose prognosis we are estimating (i.e., the PTCC cohort).

4.3.8. Acquiring HCV infection through transfusion

Some studies in the literature suggest that community-acquired hepatitis C tends to be more benign than transfusion-acquired infection. Because age is known to be associated with histologic severity, it may be that differences between routes of HCV acquisition reflect the younger age of most community-acquired cohorts such as injecting drug users. In a large cross-sectional study of 6,664 individuals, Roudot-Thoraval *et al*.[78] examined the association between the onset of cirrhosis and the route of transmission of hepatitis C. The results suggest that the occurrence of cirrhosis was more frequent in blood or blood product recipients than in drug users after controlling for duration of infection. In a study of 626 consecutively evaluated nonalcoholic patients with chronic hepatitis C patients, Gordon and colleagues[111] reported that patients with post-transfusion hepatitis C were more likely to develop decompensation than individuals who were not transfusion recipients with a relative risk of 3.92.

Based on stored sera, Rodger *et al*.[112] conducted a quasi-cohort study and followed 98 patients with community-acquired HCV infection (i.e., injecting drug uses as presumed route of infection) for a period of 25 years. They reported that 54% of the anti-HCV positive group had evidence of chronic HCV infection, 69% had elevated ALT levels, but only 8% had progressed to overt cirrhosis. There were no cases of HCC. The authors concluded that the natural history of community-acquired HCV may be more benign than previously thought.[112]

However, the role of disease transmission on HCV outcomes is still a matter of debate. In his 1999 editorial published in JGH, Seeff articulated his view of the evidence.

"... while others have suggested that community acquired hepatitis C has a better prognosis than hepatitis C that follows transfusion, I believe it is premature for the authors to reach this conclusion, based on their current data. The number of subjects studied thus far are too few, the duration of study is too short and historical comparison is less than ideal. We must await ... the passing of more time before comfortably accepting this conclusion."

With the aim of better understanding of the course of disease and its covariates in chronic HCV infection, a systematic review was conducted in Australia[75] involving 57 reported studies of HCV natural history. Their analysis of the data indicated that after 20 years of HCV infection, cirrhosis had developed in: 24% (95% CI, 11% -37%) of the post-transfusion cohort, whose mean age was 42 years at acquisition of infection; 22% (95% CI, 18% -26%) of the liver clinic series, with a mean age of 29 years; 7% (95% CI, 4%-10%) of the community-based cohort, with a mean age of 26 years; and 4% (95% CI, 1%-7%) of the blood donor series, whose mean age was 22 years. Thus, their results confirm previous reports that community-acquired hepatitis C tends to have a more benign course than transfusion-acquired infection.

4.3.9. Determining the impact of covariates on fibrosis progression

In order to investigate the effect of covariates on fibrosis progression, we performed a meta-regression on our literature-derived stage-specific transition probabilities (Table 4.2.4). Our meta-regression model included study design, setting and population, publication year, proportion of males, age at HCV infection, duration of infection, proportion of injecting drug use, blood or blood product transfusion, excess alcohol consumption, HIV positivity, HCV RNA

positivity and genotype as explanatory factors and natural log of stage-specific transition probabilities as dependent variables. The regression was weighted by the use of a multiplicative variance adjustment factor, taking into account both within-study variances of transition probabilities and the residual between-study heterogeneity.[113] Statistical analysis was performed with SAS version 9.1 and Proc Mixed ML procedure[114] was employed for meta-regression.

We found that study setting, study population, age at HCV infection, duration of HCV infection, mode of HCV acquisition, excess alcohol use, and HCV RNA positivity were independently associated with fibrosis progression (Table 4.2.4). Studies conducted in non-clinical settings had a slower rate of progression from F0→F1 than those conducted in clinical settings. More rapid progression was observed in community-based population, post-transfusion cohorts, and pediatric population compared to liver clinic patients. A higher proportion of male gender was marginally associated with more rapid progression from F0→F1. Higher proportion of blood transfusion as a risk of HCV acquisition (F3→F4) and excess alcohol consumption (F1→F2) were significantly associated with higher rate of progression.

4.4. Development of hepatocellular carcinoma

4.4.1. Risk of hepatocellular carcinoma in HCV-infected individuals with cirrhosis

Published studies have consistently demonstrated a strong association between hepatitis C infection and HCC (Table 4.4.1). Almost all HCV-infected patients who develop HCC have had liver disease that has progressed to liver cirrhosis prior to developing cancer. A synthesis of the literature on the HCV and HCC suggests that 0.4%-2.5% of people with chronic HCV infection eventually develop HCC.[115] In our 1998 model, the weighted annual probability of progression

to HCC given cirrhosis was 1.7% per year.[116-118] Additional references were included in the 2002 study. In a cohort study of 252 patients with HCV-related cirrhosis, Kato *et al*.[119] found that 151 (90%) of 161 deaths were due to HCC-related complications. This fact implies that the incidence rate of HCC among HCV cirrhosis patients is high, perhaps because these were Japanese patients. In a prospective study of 416 patients with HCV-related cirrhosis, Degos *et al*.[20] reported that 13.4% (9.0%-17.8%) of the initial cohort developed HCC in 5 years with an annual rate of 2.9%, which is much higher than the earlier reported 5-year risk of 7%[120] and 5%[121]. del Olmo *et al*.[122] performed a longitudinal/retrospective study in which patients with liver cirrhosis were followed for a mean period of 5 years. Among 967 cirrhotics, 64 patients developed HCC, for an annual incidence rate of 2.1%. The weighted mean annual rate of all reported studies was 2.1%.

In the 2007 model, 13 additional studies among HCV-infected individuals with cirrhosis were included. The estimated annual rate in these 13 studies, range from 1.0% to 6.9%. The weighted mean (95% CI) annual rate for all 18 studies included in the meta-analysis is 3.1% (2.4%-3.8%). This rate is similar to the transition rate (0.035, 95% CI, 0.024-0.046) used in the prediction study of the burden of hepatitis C in England by Sweeting *et al*.[123] Therefore, we used our new weighted mean annual HCC rate of 3.1%.

In the current model, 12 additional studies among HCV-infected individuals with cirrhosis were included. The overall (n=30) pooled transition rate was 0.033 (95% CI, 0.027-0.038) which remained similar to the transition rate (0.035, 95% CI, 0.024-0.046) used in the prediction study

of the burden of hepatitis C in England by Sweeting *et al*. [123] Therefore, we used our new weighted mean annual HCC rate of 3.3%.

4.4.2. Risk of HCC in HCV-infected individuals without cirrhosis

Although most HCC patients have cirrhosis, there are some who have no fibrosis or very minimal fibrosis. Bralet *et al*.[124] retrospectively analyzed 330 HCC biopsy samples, and found 80 cases (approximately 1/4) in which the non-tumoral liver showed no or minimal portal fibrosis. If patients with cirrhosis represent 10% of the sample of all patients with hepatitis who are at risk for HCC, then the transition rate to HCC for patients without cirrhosis is approximately 1/40 times the rate of cirrhosis to HCC. Another study[125] from Asia-Pacific region reported results by fibrosis stage. Patients with F0 disease developed HCC at an annual rate of 1.2%, and the patients with more severe fibrosis in F1, F2, and F3 developed HCC with annual rates of 1.3%, 3.4% and 5.7 %, respectively. The pooled annual rate is 2.1%. However, at the time of diagnosis of HCC, cirrhosis was found in all the patients except two patients, implying that most patients developed HCC after cirrhosis. Since residents of Japan have the highest incidence rate in HCC on the world, these patients may not be directly comparable to our cohort. In the previous models, we did not use these rates, but adopted the transition rates from the 1998 model.[9] The annual rate to HCC used in 1998 is 0.0001 in moderate chronic hepatitis C, and zero in mild chronic hepatitis C. We assumed that F0 is similar to the mild chronic hepatitis and that the transition probability was 0. We believed that F1 and F2 stages were more similar to moderate chronic hepatitis and were assigned to be 0.0001. We believed that the risk in F3 patients was higher. We therefore chose a value (0.001) between the values for F1/F2 (0.0001) and the value

for F4 (0.021 in 2004 model). In the current model, we adopted the same transition rates from HCV without cirrhosis to HCC.

4.5. Excess mortality

Patients who acquire hepatitis C infection through blood transfusion may be at higher risk of death from non–liver causes than the patients who are infected through other routes, and also much higher than the general population. The excess mortality risk in this group is most likely attributable to the diseases for which transfusion is indicated. Indications for transfusions are often recent trauma or severe medical illness.

The BC lookback program[4] evaluated the mortality experience of all individuals transfused within BC between the periods of January 1985 and June 1990. This study reported an overall mortality rate of 39.8% at 9.75 years among 106,401 individuals who received a transfusion during this period. As indicated in Remis *et al*.,[4] approximately 5% of short-term deaths may not have been captured in the lookback program, so the actual mortality rate may be as high as 45% at 10 years.

To account for excess mortality in our cohort, we followed the strategy used in the previous models, and utilized the survival experience of the cohort reported by Vamvakas.[16] By comparing the survival rates after transfusion for each age group to the survival rate in Canadian population, we estimated the excess mortality ratio according to years elapsed from transfusion. Since the highest likelihood of death occurs within the first 2 years after transfusion, we divided the post transfusion period into four time periods, 0-1,1-2, 2-10, >10 years (Table 4.5.1). As we

can see, for the groups of age <40 years, rate ratios for the first two years are similar, but the rate ratio drops sharply thereafter. Table 4.5.2 provides age- and sex-specific mortality (reported by Statistics Canada in 1997) as well as the estimated baseline distributions for age, sex, and year of first infection, which are only utilized for the simulations that begin at the time of infection (e.g. Table 7.1). For the baseline analyses (defined as future projections using our best estimate for each model variable) (Tables 8.1.1 to 8.1.20), observed age, gender, and stage distributions in the compensation cohort are utilized (5.4.1 through 5.4.6). In our baseline analyses we assumed that there was no excess mortality attributable to transfusion, as all patients received blood transfusion more than 10 years ago, and rate ratios after this time period decrease to 1.0.

4.6. Transition rates post-cirrhosis

A comprehensive literature review of outcomes for late stage liver disease (post-cirrhosis) was performed in constructing the 1998 and 2002 models.[1] We adopted transition probabilities from the 2002 model as well as updated estimates described in section 3.1.2.

5. Analysis of Clinical and Demographic Data Characterizing Claimants for Compensation

5.1. Data sources

In order to be compensated, a claimant or his/her immediate kin is obliged to provide information to validate the claim. All patients included in this study were required to show that they had received blood transfusion or other blood products between January 1, 1986 and July 1, 1990 and to demonstrate that they had one or more of the following serological or clinical

manifestations stipulated in the ***Hepatitis C January 1, 1986 – July 1, 1990 Class Actions Settlement*** agreement:

- Level 1: HCV antibody positivity
- Level 2: HCV-RNA positivity
- Level 3: Non-bridging fibrosis
- Level 4: Bridging fibrosis
- Level 5: Cirrhosis of liver, unresponsive porphyria cutanea tarda, unresponsive thrombocytopenia
- Level 6: liver transplant, decompensation of the liver, hepatocellular cancer (HCC), B-cell lymphoma, symptomatic mixed cryoglobulinema, glomerulonephritis, renal failure.

Individuals with any known HCV infection or consequences were included. By August 2010, Crawford Adjusters, the administrators of the compensation agreement, had provided the research team with all claim records that had been processed by that date and were deemed to be legitimate (i.e., met the criteria for compensation). At that time 5,225 individuals had been accepted as legitimate claimants for compensation, and had been assigned to one of the compensation classes. According to the claims received up to August 31, 2010, 1,419 (27.2%) of the 5,225 legitimate claimants were deceased.

All data describing the clinical and demographic characteristics of the successful claimants were forwarded to our research team. Information in the database provided by individual claimants or their proxies was cross-checked against the physician reports, and compiled into several data files, which were fully accessible by the research team. The relevant information contained in these files includes:

- Demographic variables: year of birth, sex, place of residence, date of death for deceased people
- Hemophilic history and/or the underlying medical condition necessitating blood transfusion
- Blood transfusion history (for non-hemophilic patients only): date of first transfusion, number of transfusions
- Serological testing results and dates for HCV-antibody and HCV-RNA status at time of claim being made
- Severity of HCV infection and supporting diagnostic information. Disease severity was based on a 6 level compensation scale which can be (almost directly) converted into the corresponding METAVIR stages
- Coinfection with HIV for hemophilic patients
- Treatment information: starting time, type of drug, serological testing information

5.2. Data management

Considerable efforts were expended to check and manage the original data files, in order to address problems of missing data and data entry errors. Each data file was separately reviewed to identify missing data for each variable. The range of values for each variable was reviewed to identify outliers, especially date variables. Logical checks were performed within data files to identify conflicting information. Logical checks were performed between data files to ensure consistency. For example, we reviewed the transfusion file and the claim file to ensure that the dates of reported transfusion were identical. A permanent data set was created for the study,

based on the revised and corrected data submitted to the investigators by Crawford Adjusters. The quality of the data had improved considerably since the past revisions. No data entry errors were identified.

5.3. Descriptive analysis of post-transfusion claimant cohort

5.3.1. Patient characteristics

All 5,225 patients with valid claims for compensation were included in this study. Tables 5.3.1 and 5.3.2 and Figures 5.1 to 5.2 provide baseline demographic, clinical, and serological characteristics of the study cohort. The mean±SD age (current) of the living PTCC cohort was 56.3±18.2 years and the duration of HCV infection was 23.6±4.5 years. There were 3,230 (61.8%) males and 1,994 (38.2%) females (Table 5.3.1). Among living patients, males were younger, on average, than females (54.8 vs. 58.3 years). Overall, males were more likely to be in a higher compensation category (i.e., level 5/6, 21.5% vs. 14.4%). The observed differences between males and females in terms of age and stage distributions can be largely explained by hemophilia that occurs predominantly (as defined in the compensation agreement) in males. At the time the study started, 1,419 (27.2%) claimants were deceased. The number of patients from each province is roughly proportional to its population size, with the exception of British Columbia, which was the home of a disproportionate number of claimants.

Of the 5,225 claimants, 3,964 were positive for serum antibody to HCV based on the last available testing results, 203 had negative HCV antibody test, and 1,058 had missing information. Of those 1,058 with missing HCV antibody test information, 158 were deceased hemophilics and 900 were others; of which 808 were RNA positive (including 106 with RNA

testing date, i.e., confirmed PCR positive tests). Of the rest with missing HCV antibody test information (n=92), 50 patients had died, and of the 42 alive patients, 41 had Compensation Level 3 and above.

Among 3,428 with HCV RNA testing records, 96.9% were HCV RNA positive. History of blood transfusion was available for 3,812 non-hemophilic patients, of whom 567 (14.9%) indicated that they received a blood transfusion before 1986. Among those with blood transfusion records, 63.2% were multiple blood transfusion recipients. A total of 2,472 (64.9%) patients received their first transfusion before the age of 50 years.

Distributions of disease severity (METAVIR stage as well as compensation level) are reported in Table 5.4.1 and Figures 5.3-5.4. Perhaps the most important fact about the observed stage distribution is that biopsy information is missing for 74.5% of the living patients. Although most of these patients will probably have early stage disease, this fact is not known with certainty. Cirrhosis was present in 7.2% of claimants, and decompensated cirrhosis, liver transplant, and HCC in 1.9%, 0.7%, and 0.8% of claimants, respectively. The proportion of patients in F4 stage of disease was much higher in individuals who had a liver biopsy than those who did not have a liver biopsy (21.2% vs. 2.4%), but appear not substantially different in the more advanced disease stages.

5.3.2. Hemophilia and other underlying conditions for blood transfusion

There were 1,335 (25.6%) hemophilic patients, of which 1,183 (88.6%) were males (Table 5.3.2). Few (11.4%) female patients with Von Willebrand's disease and inherited Factor 8 and 9

deficiencies were included in the analysis as "hemophilics" based on the compensation agreement. In comparison with non-hemophilics, hemophilic patients were significantly younger (47.0 vs. 59.1 years, $P<0.0001$). Although the two groups had similar distributions of serologic status (anti-HCV positivity), non-hemophilics had higher HCV RNA positivity (95.9% vs. 93.4%, $P=0.010$)). In contrast, hemophilics had higher compensation levels ($\geq$level 3: 64.6% vs. 47.5%, $P<0.0001$) and higher proportion of previous HCV treatment (27.1% vs. 22.7%, $P=0.001$). A higher proportion of claims came from estates of deceased patients among hemophilics than non-hemophilics (33.0% vs. 25.2%, $P<0.0001$). Forty-one percent of hemophilic patients were HIV positive compared to only 0.4% of non-hemophilic individuals ($P<0.0001$).

5.4. Estimating the true fibrosis stage distribution from post-transfusion claimant cohort data

We initially used the PTCC data to estimate fibrosis stage distribution using the following system:

Level 1: HCV antibody positive: unknown fibrosis stage

Level 2: HCV-RNA positive: unknown fibrosis stage

Level 3: Non-bridging fibrosis: F1

Level 4: Bridging fibrosis: F2-F3

Level 5: Cirrhosis: F4

In the 2007 analysis, we revised the link between compensation level and fibrosis stage as follows to correct the previous misclassification for level 4:

Level 1: HCV antibody positive: unknown fibrosis stage

Level 2: HCV-RNA positive: unknown fibrosis stage

Level 3: Non-bridging fibrosis: F1-F2 (F1=portal fibrosis without septa; F2=portal fibrosis with rare septa)[38]

Level 4: Bridging fibrosis: F3 (numerous septa without cirrhosis)[38]

Level 5: Cirrhosis: F4

We used the 2007 compensation level and fibrosis stage classifications in the current model. However, the PTCC data, as reported, are difficult to use directly for the purposes of estimating the true stage distribution among claimants. As indicated above, 75% of cases do not have liver biopsy data (Tables 5.4.1-5.4.3). These cases could represent benign liver disease with minimal or no fibrosis, as one of the indications for liver biopsy is elevated liver enzymes. Patients with normal or minimally elevated liver enzymes are often not candidates for therapy, and therefore may not be offered a biopsy. On the other hand, patients may not be biopsied for a variety of other reasons: i) ineligibility for treatment due to advanced age or co-morbidity; ii) refusal; iii) never being offered a biopsy. Thus, some patients without a liver biopsy almost certainly have more advanced liver disease. Relying exclusively on claim information therefore runs the risk of underestimating true severity of stage distribution in those without biopsy information.

We approached this problem in the following way. The Markov states in our natural history model include both pathologic (e.g. fibrosis stage) and clinical (e.g. decompensation, liver transplant) stages. Thus, we have clinical information regarding end-stage disease (decompensated cirrhosis) for the non-biopsy group as well as for the biopsy group. We believed that the completeness and validity of the clinical information was likely to be similar in both (biopsy and no-biopsy) groups. If we assume that progression rates from mild fibrosis to

cirrhosis among those without a biopsy are the same as for those with a biopsy, it is possible to retrospectively allocate those without a biopsy to a variety of intermediate stages (F0 to F4).

In the 2002 revision, patients' characteristics (e.g. age, gender, treatment, hemophilic status, compensation level/stage), which are associated with biopsy, were not taken into account in the stage adjustment for those without biopsy information. To address this limitation, in this report the working group utilized a propensity score approach[126,127] to estimate true stage distribution. The propensity approach is a means of adjusting for differences in multiple prognostic covariates by collapsing all covariates into a single variable, which in this case is the "propensity" or probability of having received a liver biopsy. Biopsy and non-biopsy patients with similar propensity scores should have a similar distribution of all covariates, including stage distribution. We accomplished this by using the following steps:

- A propensity score for biopsy was derived by fitting a logistic regression model with biopsy status (yes/no) as dependent variable, and age, gender, compensation level (4 categories: level 1, level 2, level 3 and level 4-6), previous HCV treatment (yes/no), survival status – (deceased at 2007 – yes/no), and hemophilic status (yes/no) as independent variables (Table 5.3.3). In the current revision, we excluded compensation level from the logistic regression model since it is highly correlated with biopsy status, the outcome variable.
- Based on the propensity score (predicted probability of having biopsy), patients were then classified into two groups: propensity score <0.4 and $\underline{\geq}\ 0.4$).
- We assumed that patients at late stages (such as decompensated cirrhosis and HCC) could be diagnosed using clinical information only, and that there were no "subclinical" or occult

cases of decompensated disease in either group. Thus, no further adjustments were made for these stages. We further assumed that HCV RNA negative hepatitis patients did not have liver fibrosis, and therefore no adjustments were made for this group.

- In each group, the stage distributions were compared between patients with and without biopsy records. The patients without biopsy but with the same propensity score as those with biopsy in the following stages: F1; F2; and F3 were adjusted according to the distribution of patients with biopsy records. Note that stage F0 was not distributed to later stages nor were later stages (i.e., F4, decompensated cirrhosis, and liver transplant) assigned to earlier stages.

Tables 5.4.1 – 5.4.3 show the observed and adjusted stage distribution for all living patients, and non-hemophilic and hemophilic patients. We believe that the adjusted stage distribution is necessary for the purpose of estimating fibrosis transition probabilities directly from the reported PTCC cohort data.

The propensity score model was used to generate tables of estimated true (as opposed to observed) stage distributions, stratified by age and sex, as of August 31, 2010. See Tables 5.4.4 through 5.4.7.

5.5. Using the estimated stage distribution of the post-transfusion claimant cohort to calculate stage-specific transition probabilities

Given the fact that we know the approximate time at which HCV infection was acquired and have estimated the stage distribution at the time of the claim, it is possible to use data from the PTCC to estimate transition rates between fibrosis stages. We used adjusted stage distribution

data from the non-hemophilic patients without HIV infection and who received first blood transfusion between 1986 and 1990 to derive these rates. We chose this group because the time of infection for hemophilic patients is uncertain, and therefore calculation of stage transition rates is also uncertain. We used adjusted data because, as argued above, the unadjusted data assigns all patients without liver biopsy to the F0 stage (i.e., HCV RNA+), an assumption that is certainly incorrect.

Using the MMLE method,[18] we derived the fibrosis progression rates from stage distributions in our adjusted non-hemophilic PTCC data. The derived rates are 0.029, 0.118, 0.137 and 0.103 for transitions from F0→F1, F1→F2, F2→F3, and F3→F4 (cirrhosis), respectively (Table 4.2.5). Note that these rates are lower than in previous estimates except for transition from F3→F4 (slightly higher than in 2007). These transition probabilities were then calibrated to match with the observed data (Table 4.2.5). The corresponding rates used in the 2007 revision are 0.032, 0.137, 0.150, and 0.097, respectively and in the 2004 revision are 0.041, 0.088, 0.327, and 0.384, respectively. The rates used in the 2002 revision are F0→F1: 0.061; F1→F2: 0.146; F2→F3: 0.407; and F3→F4: 0.501. Transition rates are lower for recent models than 2002 model largely because the adjusted stage distribution was different. Using the larger, more complete patient sample and better estimation methods (propensity score method), fewer patients appear to have advanced disease, and derived transition rates are correspondingly lower. Additionally, the difference in rates between previous models and recent models (2007 and 2010) is due to the revision of the link between compensation level and fibrosis stage distribution as described in section 5.4 (i.e., level 3, non-bridging fibrosis has been distributed to F1/F2 and level 4, bridging fibrosis to F3 instead of F1 and F2/F3, respectfully).

Compared to literature-derived rates, PTCC-derived rates are much lower for F0→F1 and F3→F4, but higher for F1→F2 (Table 4.2.5). In addition, the estimated number of years (60 years=1/0.029+1/0.118+1/0.137+1/0.103) required to progress from infection (F0) to cirrhosis are somewhat longer than our previous estimates (41.5 years in 2004 and 55.5 years in 2007) and the 30 years (4/0.133) reported by Poynard *et al*.[25]

It is instructive to compare these transition rates with those derived from the literature using the same methods (i.e., "Markov maximum likelihood" method). In the 2004 report, both cohort and the PTCC data showed the same pattern: a slower transition from F0 to F2, and a more rapid transition from F2 to F4. This differs quite dramatically from the single fibrosis progression rate between all stages reported in the literature by many studies, and suggests that the assumption that transition rates are constant across stages is probably incorrect. In the recent reports, the PTCC data showed a different pattern: increased rates from F0→F1 to F2→F3, and a slower rate from F3→F4. This change in pattern can be explained by the revised fibrosis stage distribution as described above.

6. Final Parameters for the New Model: Combining Data From the Literature and From the Post-Transfusion Claimant Cohort

We incorporated data from a wide variety of sources into the final prognostic model. Table 6 is a summary of the final parameters used in the model. Data from the PTCC cohort were used to estimate the age, gender, and clinical stage distribution (e.g. HCV RNA- F0, HCV RNA+ F0,

F1-F4, decompensated cirrhosis, liver transplant and HCC) at the beginning of the simulation. We also used data from the PTCC cohort to estimate the proportion of claimants with hemophilia and HIV infection. Data from the literature and the PTCC cohort data were used to estimate transition probabilities, and HCV treatment (PEG-IFN and ribavirin) efficacy data, general population and post-transfusion mortality rates, and the effect of HIV and hemophilia on long-term prognosis were derived from the literature. Annual HCV treatment rates by age and disease stage were derived from the PTCC cohort. Finally, we used our previous models as well as literature as the source of transition probabilities for health states more advanced than liver cirrhosis.

However, a number of key judgments were required in order to integrate the available information in the most valid, defensible, and evidence-based manner possible. These are described below.

6.1. Choosing fibrosis transition rates

Choosing the best transition probabilities between fibrosis stages is both the single most important, as well as methodologically the most challenging aspect of estimating prognosis accurately. In the 2004 model, we had three sets of data to choose from: 1) non-cohort studies reported in the literature; 2) true cohort studies; and 3) estimates derived from the 1986-1990 transfusion cohort. In addition, we had several methods of deriving transition probabilities: the MMLE method, and the direct and indirect estimation methods.

With respect to the issue of estimation method, our group believed that the MMLE method[18] is able to best represent stage-specific transition rates, as it does not require the assumption that transition between stages was constant. The evidence would seem to strongly suggest that transition rates increase with increasing age (Table 4.2.6).[1] We therefore adopted this approach wherever possible to calculate transition rates, and pooled rates derived from individual studies in order to estimate transition rates.

With respect to the choice of transition probabilities, although we would have preferred to use our own data directly, based on the 2002 and 2004 models, our group believed that the transition probabilities derived directly from the PTCC cohort (as described in section 5.5), especially for late stage disease (F2→F4) were too dissimilar to those observed in other published studies to be relied upon exclusively, particularly for the transition rates F2→F3 and F3→F4. We believed that the observed stage distribution in the post-transfusion data most likely demonstrated some degree of selection bias, as patients with more advanced disease were simply more likely to come to medical attention and/or claim for compensation. In 2002 and 2004, we compared the observed stage distribution of PTCC cohort to the predicted distribution, using transition rates derived from the literature. The observed stage distribution was somewhat different from the predicted stage distribution. There was both more advanced disease and more early stage disease among claimants than one would expect. Because we were concerned about the possibility of selection bias, particularly for disproportionate selection of later stage cases, we were reluctant to rely exclusively on transition probabilities derived from the PTCC cohort.

Among prognostic studies reported in the literature, we believed that the prospective cohort studies were the least subject to bias, but probably underestimated the fibrosis transition rates because the population in these studies was much younger and more often female than in other studies, and certainly in comparison to our PTCC cohort. Non-prospective studies usually had a population whose age and gender profile was more similar, but was more subject to bias.

Two approaches were possible. First, we could simply have used the adjusted (for age and gender) prospective cohort data to correct the age and gender problem. However, this would mean building the entire prognostic model on two somewhat unusual studies that described the prognosis of HCV in young women infected in point source outbreaks. This approach would exclude much of the published prognostic data, albeit with the advantage of relying on the least biased data.

Alternatively, we could have pooled all of the literature-derived data, recognizing that demographic factors and selection bias might introduce potentially offsetting errors. Our group discussed the relative advantages of each approach, bearing in mind the considerations outlined in section 7. Validating the stage-based prognostic model, as described below. We also recognized that if errors were to be made, errors overestimating the rapidity of progression might be preferred, as ensuring the sufficiency of the compensation fund is an important goal of this exercise.

Thus, for the current model and the 2007 model, our group ultimately decided to pool literature-derived and PTCC-derived transition rates. Since we have been closely following this PTCC

cohort for several years, we treated the PTCC cohort as another study, and considered its study design as a retrospective-prospective being conducted in a non-clinical setting. We then calculated the expected fibrosis progression rates based on the significant stage-specific coefficient of covariates ($P<0.1$) derived from the literature (see section 4.3.9 and Table 4.2.4). The effects of various transition rates on the outcomes are explored through sensitivity analyses.

6.2. Modeling the prognosis of hemophilics

The PTCC cohort data indicate that 26% of claimants are hemophilics, who are about 12 years younger than non-hemophilics and more often male (89% vs. 53%) (Table 5.3.2). The literature also suggests that the general age-related mortality (i.e., non-liver mortality) for hemophilics tends to be lower than non-hemophilics (see section 4.3.6). Thus, we modeled prognosis for hemophilics and non-hemophilics separately, though we also report projections for the entire cohort.

For the prediction for hemophilics and non-hemophilics, most of the parameters are the same except age and sex distributions and excess mortality. The age, sex, and stage distributions were taken from PTCC cohort data for hemophilics and non-hemophilics separately. According to Vamvakas,[16] the mortality rate more than10 years after blood transfusion would be the same as that of the general population. Although hemophilia per se is not associated with a significant increase of excess mortality, when taking HIV infection into account, the modeled excess mortality for hemophilics was approximately twice that of the general population for the entire life span.

7. Validating the Revised Stage-based Prognostic Model

How is it possible to know whether the predictions of our prognostic model are accurate? One obvious answer might be to compare the predictions of the model with published studies, but this is clearly a circular argument, since it is published prognostic studies that serve as the source of transition probabilities for the model. Hence, the model will predict whatever the studies from which transition probabilities are drawn predict.

Another approach might be to compare the observed stage distribution in our post transfusion cohort to that predicted by the model. If the prognostic features of the model are correctly specified, we should be able to run the model starting at the time at which infection was acquired (time of transfusion) and predict the stage distribution at the present time. The extent to which the predicted distribution matches the observed distribution is one check on the validity of the predictive model.

Table 7.1 compares the adjusted observed stage distribution (i.e., adjusted using propensity score) in the PTCC cohort to the stage distribution predicted (i.e., assuming starting distribution of F0 for all patients in 1986 and projected up to 2010 by using both literature- and PTCC-derived transition rates) by the model. The model predicts the present stage distribution by assuming that the age and gender distribution of those infected with HCV at the start of the simulation is predicted by the demographic characteristics of transfusion recipients, as reported in Remis *et al*.[4] The transition probabilities for the model are our best estimates, as described above, hereafter referred to as our ***baseline*** estimates. We compare stage distributions only for non-hemophilics, as hemophilics for the most part acquired their infections much earlier.

As shown in Table 7.1, our current model predicts the adjusted observed distribution in non-hemophilics with a moderate degree of fidelity after calibrating model input, including transition probabilities and annual treatment rates against the observed disease distribution.

Both the 2004 and 2007 models fit the data considerably better than the 2002 model. Our current model fits the data better than the previous models. For the purpose of comparison, the results from the first revision are also provided in Table 7.2. It is evident that the observed and predicted are much closer for the third and fourth revisions than those in the earlier revisions.

However, this method of establishing the validity of the predictive model has limitations. The observed and predicted stage distributions will match only under certain assumptions: i) all members of the transfusion-acquired HCV cohort did in fact acquire their HCV infections between 1986-1990, and not before; ii) the observed stage distribution at present among those claiming compensation is representative of the PTCC cohort as a whole (i.e., no selection biases are operating); iii) our method of predicting true stage distribution among transfusion recipients who did not receive a liver biopsy is approximately correct; iv) our prediction of the age and gender distribution of HCV-infected patients from 1986-1990 is approximately correct.

In comparison to the 2002 report, there have been no changes for assumptions 1 and 4. The significantly improved agreement between the observed and retrospectively predicted stage distribution may be due to changes in factors 2 and 3. The stage distribution in our more complete 2007 and 2010 PTCC cohort may be a more accurate reflection of the stage distribution

among all patients with transfusion-acquired HCV, and/or our method of predicting true stage distribution may be more accurate for those without liver biopsy data.

Another approach to validation is to compare the predictions of our current model to the predictions of other models. Our 1998 model used mainly studies of post-transfusion hepatitis. Although many of these studies were older and did not confirm that the source of hepatitis was HCV, all of these studies were prospective studies with a true inception cohort. We believe that the 2002 model is a reliable reference in attempting to ascertain the predictive accuracy of the 2004 and current models. Our 2002 model used a wider selection of studies. Table 7.3 documents differences between the projections among non-hemophilics of all five models. The 2007 and 2010 model projections generally fall between those of the 2002 model and the 2004 model.

The 2004, 2007 and 2010 predictions are lower than 2002 for several reasons: i) transition rates between fibrosis stages are lower; ii) the starting distribution of patients with cirrhosis is considerably lower (7-8% vs. 15.5%); iii) life table mortality rates have fallen slightly (Note that the 2000-2002 age- and gender-specific mortality used in the current model has slightly fallen further from the 1997 data used in the 2004 model); iv) HCV treatment is now more effective and the proportion who had received treatment has increased (14% in 2002 to 17% in 2004 to 22% in 2007 and 24% in 2010).

In the previous models, Figures 7.1 and 7.2 compare the cumulative probabilities of cirrhosis and liver-related death based on the pooled stage-specific transition rates used in the current

projection and the stage-constant transition rates (age- and gender-specific) reported by Salomon *et al*.[1] Salomon *et al*. presented a comprehensive epidemiological model of hepatitis C in the United States. Their approach was to fit transition rates to their prognostic model empirically. They attempted to derive model parameters that best fit data derived from both a literature survey and epidemiologic data, including seroprevalence data derived from the Third National Health and Nutrition Examination Survey (NHANES III) to project long-term consequences of HCV. Salomon *et al's*[1] model represents a very high level effort to derive transition probabilities. It differs from ours in the following way: i) they attempt to estimate age- and gender-specific transition parameters; ii) they did not estimate stage-specific transition parameters; iii) they use epidemiologic data whereas our data are derived only from the literature and from our own PTCC cohort. As a means of checking the validity of our prognostic projections, we used Salomon *et al's* published transition rate estimates in our model and compared those projections with our baseline results.

For both approaches, cohorts with the same starting age and gender distribution (given by the distribution of transfusion recipients) were used. Both models assume that all patients begin in the HCV RNA+ F0 health state (for comparability with the old model). As shown in Figure 7.1, both approaches produced very similar cumulative risk of cirrhosis for the first 13 years. However, the results from the two approaches begin to diverge after years 2020. By 2060 the differences are greatest, with the cumulative proportion of cirrhosis reaching 39% in our model, relative to 45% in Salomon *et al's* model. As for liver-related death, results from the two approaches begin to diverge only after 2040, and the cumulative proportion reaching 24% in our model, relative to 27% in their model. Given the overall level of uncertainty associated with

predicting prognosis in the very long-term, and the fact that both modeling efforts used different data, methods of synthesizing data, and projecting long term outcomes, we believe that these predictions are sufficiently similar to lend support to the validity of both models. Therefore, we did not repeat this validation in our current model.

8. Prognosis of Post-transfusion Hepatitis C Patients Based on Projections of the Markov Model

The following section consists of two parts: i) our baseline projections for all living patients, and living non-hemophilics and hemophilics, using our best estimates for all model parameters; ii) sensitivity analyses exploring the effects of different transition probabilities, starting distributions, and all other variables. All projections were based on Markov models programmed in TREEAGE PRO.[15] The anchor date for the simulation is August 31, 2007.

8.1. Long-term projection based on pooled transition rates derived from literature and post-transfusion claimant cohort

Tables 8.1.1 to 8.1.3 display the results of projections for the entire transfusion cohort, the entire hemophilic cohort, and the entire non-hemophilic cohort, respectively. Tables 8.1.4 through 8.1.20 report age-stratified outputs for hemophilic and non-hemophilic patients. Note that Tables 8.1.4. and 8.1.5. for hepatitis C prognosis of age group 10-19 years among hemophilic and non-hemophilic patients are not created as there are very few patients in this group.

Each table displays the cumulative incidence rate of cirrhosis, decompensated cirrhosis, HCC, liver transplantation, non-liver and liver-related death, and all cause death. Tables 8.1.1 through 8.1.3 also list the distribution of gender, age, and stage of the patients alive in future years. The predicted results for non-hemophilics and hemophilics differ in death rates and gender distribution.

For the overall population, our model predicts that the cumulative lifetime incidence of cirrhosis in living patients is 38.5%, starting from a point prevalence rate of 10.0% in August 2010. Thus, about 30% of this cohort who are currently living but do not yet have cirrhosis, are predicted to develop it over the course of their lifetime. Approximately one in ten (10.5%) will develop liver cancer, and about one in four (24.0%) will ultimately die of their liver disease.

Comparison between hemophilics and non-hemophilics shows that more non-hemophilics will die in the next 10, 20, and 30 years, even though cumulative all cause mortality will be similar by the year 2060. Hemophilics are more commonly co-infected with HIV, but the non-hemophilic population is older. In the medium term, the effect of age on mortality is greater than the effect of HIV infection. However the relative proportion of patients who die from liver-related disease is higher in hemophilics than non-hemophilics (35.6% vs. 20.4%), and all other cirrhosis-related events are relatively higher than non-hemophilics (HCC: 15.0% vs. 9.1%; liver transplant: 5.6% vs. 3.8%). Hemophilics are younger with more years to develop liver disease, and HIV-HCV co-infection increases the rate of fibrosis progression.

8.2. Sensitivity analysis

The effects of uncertainty in our prognostic model were explored using a number of scenarios. We ran analyses using second order Monte Carlo simulation in order to take account of all sources of uncertainty in the model (Table 8.2.1). This includes variables such as treatment efficacy, as well as choosing the source of fibrosis transition parameters. In this approach, probability estimates for the model are represented by probability distributions rather than by fixed point estimates. For each simulation, a set of parameters is randomly drawn from each distribution. This set is used to run a series of simulations using a large number of patients.

Table 6 lists the plausible range for each transition probability and other prediction parameters. Most of the probabilities were assumed to follow a beta distribution, though some of them were modeled using a triangular distribution. The "baseline" value was assumed to represent the mean of the distribution. For each randomly sampled set of transition probabilities, 50,000 repeated patients with different age, gender, or treatment were simulated. Overall, 500 sets of transition rates were sampled, with 10,000 simulations per set. The mean and 95% CI of the predicted event rates from the year 2020 to 2060 are reported in Table 8.2.1.

Table 8.2.1 suggests that the credible interval in lifetime cirrhosis incidence rate (38.5%) is about +/- 6.3% in absolute terms (32.2%-44.8% and about +/- 16.4% in relative terms. The credible interval in lifetime HCC incidence rate (10.5%) is about +/- 3.7% in absolute terms and ~35.2% in relative terms and +/- ~4.5% in absolute terms and ~18.8% in relative terms in the lifetime incidence of liver-related death (24.0%). These values reflect the overall uncertainty in our prediction model which are smaller than in the 2007 model. These estimates exclude uncertainty

attributable to the size and stage distribution among HCV-infected transfusion recipients who have not yet come forward to claim compensation.

In the 2002 and 2004 reports, we explored the effects of using transition probabilities directly from the PTCC cohort. Use of PTCC cohort data in 2004 resulted in a 20% higher estimate for the lifetime risk of cirrhosis, and a 21% increase in the risk of liver death. In contrast, using the estimated starting distribution at the time of infection, rather than that observed in the PTCC cohort, resulted in a 13% increase in the risk of cirrhosis, but virtually no change in the life-time risk of liver death. We did not perform this sensitivity analysis in the current report. We expect that results would not be substantially different from 2004 estimates.

9. Estimating the Stage Distribution of Post-transfusion HCV-infected Individuals Who Have Not Yet Presented to Claim Compensation

The compensation agreement is intended to be sufficient to compensate all individuals who claim for compensation within a specified time period. Because the number who have claimed to date is short of the estimated total of potential claimants (up to 9,000), it is useful to estimate the number of future claimants, a topic which is beyond the scope of this report. Equally, important, however, is estimating the stage distribution of the unknown cohort. The prognosis of these individuals, and the total potential claims upon the fund are likely to differ quite substantially depending on whether they all have advanced liver disease at the present time, or whether they have, in general, mild, asymptomatic liver disease.

Hereafter, the group of individuals who were infected with HCV through the blood supply, and who may eventually come forward to claim for compensation, are described as the "unknown" cohort.

Despite the significance of the HCV stage distribution information for the unknown cohort, we have limited direct data upon which to base a reliable estimate of current stage distribution. Following the method used in the first model revision (2002), we have used two complementary approaches to derive a plausible estimate.

9.1. Approach 1: Regression method

In this approach, we estimate future stage distribution by analyzing temporal trends of those who have claimed already, and projecting these trends forward into the future. We have assumed that the time sequence of a claim is influenced by a person's age, sex, hemophilic status, and HCV disease severity. Thus, we are able to estimate the HCV stage distributions for the "unknown cohort" from the "known cohort". In the 2004 model, we assigned all 4,530 patients in known cohort into 10 groups, and hemophilic individuals into 8 groups (waves) according to their time sequence of claims. The distributions of age (less than 40 and 40+), sex, hemophilic status, and compensation levels were calculated. Six level-specific regression models were fitted using the proportion of claimants within a given level as a dependent variable and the proportions of age, sex, and hemophilia as independent variables. These models were further weighted by the numbers of patients in each wave. We subsequently estimate that all remaining patients would come forward in a seventh wave. Table 9.1.1 in 2005 report[10] displays the estimated level distributions using this approach. Using a similar method, adjusted fibrosis distributions were

also calculated for non-hemophilic and hemophilic groups, respectively (Tables 9.1.2 and 9.1.3 in 2005 report).[10]

The results showed that most prospective claimants would be in compensation levels 1 to 3, and that 2/3 of patients would be in stages prior to F2 as of August 2004. Different HCV stage distributions are expected between people with and without hemophilia. In general, hemophilic patients are more likely to have advanced fibrosis, though, paradoxically, decompensated liver disease, HCC, and liver transplant are slightly less common among hemophilics. Since the 2004 projection was based on a much larger sample size than that in 2002, the results are expected to be somewhat more accurate.

For the current revision, we were not able to estimate future stage distribution of the unknown cohort using this method due to lack of relevant information. However, we estimated the future stage distribution of the prospective claimants using the second approach as described below.

9.2. Approach 2: True target population distribution method

This method assumes that the ***predicted*** HCV stage distributions (text section 7 and Table 7.1) reflect the true distributions for the overall infected cohort (known + unknown). The ***predicted*** stage distributions, as indicated in section 7, are the distributions, as of August 2010, that our prognostic model predicts under the following assumptions: i) the number and timing of HCV infections between 1986-1990 are correctly predicted using the estimates of Remis *et al.*,[4] which were based on the number of transfusions during that period, and the estimated per-unit risk of

transfusion; b) our stage-transition probabilities, derived from the literature, are approximately correct.

The discrepancies between the ***predicted*** distribution and the ***observed*** distribution among compensation claimants for the known cohort are assumed to be entirely accounted for by the fact that the known cohort is a biased sample of the overall cohort. Thus, theoretically, the true HCV stage distributions could be restored when the "known cohort" and "unknown cohort" are combined. Similarly, given the distributions for the overall HCV victims and known cohort, the HCV stage distributions for the unknown cohort can be derived.

Using this method, the following steps are used to estimate the HCV stage distributions for the unknown cohort.

(1) Estimate the total number of patients (known + unknown) in each stage as of August 2010 by multiplying the predicted stage distribution by the total number of HCV infected patients who are currently alive. This yields the total number of patients within each stage.
(2) Calculate the difference between the predicted numbers of the alive patients and the observed numbers of the alive patients by stage. The residual for each stage is the number of unknown patients in that stage. The sum of the differences over the stages is the total number of patients in the unknown cohort.
(3) Repeat these calculations for a variety of estimates of the total number of unknown patients.

In our current model, the predicted number of patients with HCC closely matches with the observed number of patients. As the observed number of patients with liver transplant is much higher than predicted, we adjusted the observed number downward to the predicted level. Based on the natural history of HCV, we believe this adjustment is necessary to reflect the fact that some patients became infected by HCV before 1986.

Table 9.1.4 is adapted from the 2002 report of Remis *et al*. According to Remis's report, approximately 9,000 HCV patients who were infected by HCV through blood products during 1986-1990 were still alive in 2002. Table 9.1.4 also provides our estimates for the unknown cohort in terms of HCV stage distribution. In comparison with 2004 model, these 2010 results suggest that many more individuals would be in stages F0-F2 and F4, and few in F3 and HCC stages.

9.3. Comment

Which of these approaches is more likely to yield a reliable estimate? First, it should be noted that the second approach cannot be used to estimate the stage distribution of hemophilics who are yet to come forward. We do not know when hemophilic patients became initially infected, but for most, infection likely predated the 1986-1990 period during which non-hemophilics were infected. Thus, predictions based on transfusion practice during that period (approach 2) are not useful as a guide to hemophilic patients. The first approach generates our only usable estimate for hemophilics.

With respect to non-hemophilic patients, the situation is less straightforward. On the one hand, we strongly suspect that patients who have presented for compensation to date are an unrepresentative sample of the entire PTCC. Thus, simply extrapolating from current trends may lead us astray in attempting to discern the true disease status of those who have not yet come forward.

On the other hand, approach 1 is based on ***real*** data from compensation claimants, whereas the estimates of total numbers of patients infected and their current stage distribution (approach 2) are somewhat more ***speculative***, based on theoretical numbers of infected patients and literature-derived estimates of the rate of disease progression. Further, estimates of stage distribution appear to be quite stable across waves (Tables 9.1.2 to 9.1.3 in 2005 report).[10]

It is our belief that the stage distribution of claimants who have already presented (approach 1) is likely to be quite similar to those who will present in the future. We also believe that it is quite likely that not all claimants will come forward. Thus, the most realistic estimate of the stage distribution of those who will ultimately come forward is probably given by approach 1. However, a "conservative" approach would be to run the actuarial model using both sets of estimates for stage distribution and use the estimate that results in the greatest fund liability.

10. Discussion

This study reports updated and revised estimates of the natural history of transfusion-acquired HCV infection. Building on our previous work, this revision incorporates a more contemporary biological understanding of HCV prognosis. Fibrosis stage and transition rates between fibrosis

stages are the key elements of the prognostic Markov model, as implemented in the Markov health states that represent fibrosis stages (F0, F1, F2, F3, F4). The literature expressing HCV prognosis by fibrosis stage, both longitudinal and cross-sectional, study setting (i.e., clinical/non-clinical), and covariates was systematically reviewed and the data abstracted in order to estimate revised and updated transition probabilities between fibrosis stages.

Another key element of this fourth revision of the post-transfusion HCV prognostic model is the incorporation of virtually complete clinical and demographic data describing characteristics and outcomes of PTCC. In this report, we describe characteristics of 5,225 individuals whose claims for compensation had been approved as of August 2010. Close to two-thirds (62%) of claimants were male, and 27% of claims were from the estates of deceased individuals. More than a quarter of claimants (26%) were hemophilics, of whom 41% were HIV positive. More than three-quarters (76%) of claimants were compensated at level 3 or below. Nearly a quarter (24%) had received prior HCV therapy. Approximately a quarter (25%, no substantial change from 2002 and 2004 revisions) of living patients had received a liver biopsy, which made the estimation of true clinical stage distribution very difficult.

Data from the new literature review and from the previous models were used to estimate most prognostic variables, including fibrosis transition rates, treatment efficacy, and the effect of hemophilia and HIV status on prognosis. Stage-specific transition probabilities were also developed from the PTTC data, and were incorporated into the literature-derived pooled data from which the baseline model's state transition probabilities were estimated. Data from the

PTCC was used to estimate age, gender, and stage distribution of claimants, as well as the proportions of individuals with hemophilia and HIV.

Although this model offers a variety of projections, we believe that the most reliable predictions of long-term prognosis are represented in Tables 8.1.1 through 8.1.20. The model predicts that 35% of non-hemophilic patients alive in 2010 will ultimately develop cirrhosis, and 20% will ultimately die of liver disease. Because hemophilic patients are younger, and are frequently co-infected with HIV, they will have higher cumulative rates of cirrhosis and liver-related death (52% and 36%, respectively). Compared with the results in the 2002 and 2004 revisions, recent (2007 and 2010) long-term projections for cumulative proportions of cirrhosis fall between the two. Since the recent projections were based on a more complete claim cohort and updated parameters, they are likely to be somewhat more valid than previous projections.

Why do the projections of the 2010, 2007, 2004, 2002, and 1998 models differ? Although both the structure and many of the parameters have changed with each iteration of the model, the major differences have to do with the transition probabilities estimating the rate of developing liver cirrhosis. In our first model (1998), we decided to exclude all non-cohort studies, i.e., all studies in which an inception cohort was not identified. In addition, we could not use any studies in which outcomes were represented as fibrosis stages. The first revision of the model (2002) included these studies. Also, by consensus of the members of the study team, all available HCV prognostic studies were pooled. This resulted in a substantial worsening of the predicted prognosis of HCV-infected individuals. This judgment was reached because of the concern that the very small number of true prognostic studies were unrepresentative by age and gender, and

we were unable to easily adjust for those factors in estimation of stage-specific transition probabilities using the MMLE method. In addition, we reasoned that an error in the direction of overestimating progression rates was likely to have less serious consequences for the purpose of this project, as ensuring the viability of the compensation fund was a high priority. The second revision of the model maintains the same rationale and pooled all cohort and non-cohort data. In addition, we pooled the data from the PTCC cohort, as we believed that the sample now included a more complete representation of the entire cohort, and the derived transition rates between stages were more similar to those derived from published studies, decreasing our concern about the possibility of serious selection bias.

The third revision of the model maintains the same rationale, and pooled literature-derived and PTCC-derived stage-specific transition probabilities. In addition, we adjusted for the effect of study design and clinical factors on disease progression, as we were informed from the literature and from our previous experience. Moreover, we revised the link between compensation level and fibrosis stage distribution, as we became aware that compensation level 3 (non-bridging fibrosis) equates with F1/F2, and level4 (bridging fibrosis) equates with F3. This does not appear to change the overall results substantially in the short-term, but may differ in the very long-term.

Finally, estimates of this fourth revision reflect closely to the observed data, particularly the advanced disease stage through the addition of transition from HCC to liver transplant and updating transition probabilities (e.g., HCC to liver-related death). Moreover, we used the annual HCV treatment rates of the cohort instead of expert estimates.

This version of the model has unique strengths, and may represent the state-of-the-art in estimating HCV prognosis. Key strengths are more comprehensive literature review on HCV natural history studies and treatment efficacy, incorporation of actual data to estimate stage distribution and transition probabilities, adjustment for study design, study setting, and relevant prognostic factors, thus reducing several potential sources of bias, separate estimates for hemophilic and non-hemophilic patients, estimates of overall model uncertainty generated by Monte Carlo simulation, the use of annual treatment rates derived from the cohort, and the use of complementary prognostic data to qualitatively estimate the overall model uncertainty attributable to study selection.

However, this model also has a number of potential biases and limitations.

Bias 1: We include non-cohort studies in estimation of stage-specific transition rates.
Net Effect: Potential (small-moderate) upward bias in fibrosis transition rates, and possible overestimation of the rate at which cirrhosis develops.

Bias 2: We include compensation cohort data in estimation of stage-specific transition rates.
Net Effect: Potential (small) upward bias in fibrosis transition rates, and possible overestimation of the rate at which cirrhosis develops.

Bias 3: We use a single transition rate between fibrosis stages. Because more rapidly progressing individuals exit disease states at a more rapid rate, state transition rates may fall in the very long term.

Net Effect: Potential (very small) upward bias in fibrosis transition rates, and possible overestimation of the rate at which cirrhosis develops.

Bias 4: We assume that no regression between stages occurs, and that progression continues at 10% of the baseline rate in treated individuals who achieve a sustained virological response.
Net Effect: Potential (small) upward bias in fibrosis transition rates, and possible overestimation of the rate at which cirrhosis develops.

Limitation 1: One key limitation, is that the size of the compensation cohort remains unknown. We believe that, as of August 2010, most claimants have come forward, but some uncertainty remains regarding the final size of the claimant cohort.

Limitation 2: Another key limitation is the lack of liver biopsy data for many compensation recipients. A number of fairly strong assumptions were required in order to derive reasonably plausible estimates of the true stage distribution. We assumed, for example, that the stage distribution with the same propensity score among biopsied and non-biopsied patients is the same, even though this is unlikely to be true, as patients who were biopsied are more likely to have advanced liver disease. However, we believe that incorporating this assumption to estimate the "adjusted" stage distribution results in less bias than using the unadjusted data, which would incorporate the implicit assumption that all patients without a liver biopsy have no liver fibrosis.

Future studies will be useful in updating and revising model projections. Analysis of the full dataset will make it possible to more accurately estimate the stage distribution of compensation

claimants. Comparison of accepted and rejected claims will be useful in estimating the clinical and demographic characteristics of transfusion-acquired and non-transfusion-acquired HCV infection, and provide some information on the generalizability of our model's projections to HCV infected patients as a whole. Finally, this cohort provides an invaluable resource to study the natural history and resource utilization of HCV infected patients in future studies.

Acknowledgements

The authors thank Ms. Sharon Matthews for her assistance in dealing with the legal aspects of this work.

11. Tables

Table 4.1. Spontaneous clearance of hepatitis C virus infection:* Literature review

Author	Population	Risk	Sample size	Years of follow-up	Total viral clearance	Chronic HCV†	Clearance in chronic stage	Clearance rate in chronic stage	Est. person-yr	Clearance rate/yr
Mattsson,1993[30]	Acute	Non-A, Non-B	24	13	8 (33%)	20	4	0.216	265	0.017
Barrera,1995[29]	Acute	Transfusion	41	6	5 at 6 wks 5 at 6 yrs (24%)	36	5	0.139	216	0.023
Kenny-Walsh,1999[27]	Acute	Contaminated anti-D	704	17	314 (45%)	563	173	0.308	9574	0.018
Villano,1999[33]	Acute	IDU	34	6	6 (18%)	29	1	0.031	173	0.005
Vogt,1999[128]	Acute	Pediatric, surgical	67	19.8	30 (45%)	57	20	0.350	1128	0.018
Wiese,2000[36]	Acute	Contaminated anti-D	917	20	412 (45%)	734	229	0.312	14672	0.016
Barrett,2001[129]	Acute	Contaminated anti-D	155	22	68 (44%)	124	37	0.298	2728	0.014
Lehmann,2004[130]	Acute	IDU	84	0.5-1	19 (23%)	71	6	0.090	71	0.090
Spada,2004[131]	Acute	IDU, surgical	34	0.5-1	10 (29%)	29	5	0.170	29	0.170
Wiese,2005[37]	Acute	Contaminated anti-D	1811	25	836 (46%)	1449	362	0.327	36220	0.013
Micallef,2005[34]	Acute	Pooled	675	~3	173 (26%)	574	72	0.125	1721	0.042
		Transfusion	231	~3.5	42 (18%)	196	7	0.037	687	0.011
Santantonio,2006[132]	Acute	Community-acquired	203	1.2	73 (36%)	173	43	0.247	207	0.205
Alter,1992[133]	Chronic	Community-acquired		3.75		25	1	0.040	94	0.011
Seeff,1997[39]	Chronic			25		129		0.23	3225	0.009
Thomas,2000[32]	Chronic	IDU		8.8		919	90	0.098	8087	0.011
Messick,2001[134]	Chronic	Hemophilics		24		49	12	0.245	1176	0.010
Mazzeo,2003[121]	Chronic	General population		10		63	7	0.111	630	0.011
Bortolotti,2005[135]	Chronic	Pediatric, transfusion, maternal infection		8		522	24	0.046	4176	0.006
Grebely,2006[136]	Chronic	IDU		5.2		658	152	0.231	3422	0.044
Posthouwer,2006[137]	Chronic	Pediatric, transfusion		15		68	24	0.353	1020	0.024
Scott,2006[138]	Chronic	IDU, transfusion, sporadic		7		139	11	0.079	943	0.012
Harris,2007[139]	Chronic	Transfusion (90%)		15.7		508	86	0.169	7976	0.011

Table 4.1. Spontaneous clearance of hepatitis C virus infection:* Literature review (continued)

Author	Population	Risk	Sample size	Years of follow-up	Total viral clearance	Chronic HCV[†]	Clearance in chronic stage	Clearance rate in chronic stage	Est. person-yr	Clearance rate/yr
Yeung,2007[140]	Chronic	Pediatric, transfusion		11.9		55	11	0.200	655	0.017
Yeung,2007[140]	Chronic	Pediatric, nontransfusion		7.4		20	6	0.300	148	0.041
Krahn,2005[141§]	Chronic	Transfusion		17		1935	138	0.071	32895	0.004
Pooled rate[±]										
Fixed effects model										0.014 (0.011-0.017)
Random effects model										0.020 (0.013-0.027)

*Seroconversion from HCV RNA+ to HCV RNA-.

[†]Assuming that virus was cleared in 15% of patients during the acute stage and the further clearance will happen during the chronic stage (with an exception of women cohorts, where spontaneous clearance rate during the acute stage was assumed 20% viral clearance during the acute stage).[27,36,37]

[§]Based on 1,935 claims with both transfusion date and RNA test available.

[±] Weighted by sample size; excluding Villano *et al*., Barrera *et al*. (included in Micallef *et al's* review), Krahn *et al*., and Wiese *et al*. (2000).

HCV, hepatitis C virus; IDU, injecting drug use; RNA, ribonucleic acid.

Table 4.2.1. Natural history of hepatitis C: Study characteristics – Literature review

Study	Study period	Country	Population	Setting	Study design
Alter, 1997[142]	1991-1994	USA	Blood donors	Non-clinical	R-P
Silva, 2004[143]	1997-2001	Brazil	Blood donors	Non-clinical	C-S/R
Dalgard, 2003[144]	2000-2001	Norway	Community	Non-clinical	C-S/R
Saadoun, 2006[145]		France	Community	Non-clinical	C-S/R
Serra, 2003[146]		Spain	Community	Non-clinical	C-S/R
Verma, 2006[147]	1994-2004	USA	Community	Non-clinical	C-S/R
Hu, 2005[148]	1999-2003	USA	Dialysis patients	Clinical	C-S/R
Martin, 2000[149]	1992-1997	USA	Dialysis patients	Clinical	C-S/R
Sezer, 2001[150]		Turkey	Dialysis patients	Clinical	C-S/R
Sterling, 1999[151]		USA	Dialysis patients	Clinical	C-S/R
Toz, 2002[152]	1996-2000	Turkey	Dialysis patients	Clinical	C-S/R
Varaut, 2005[153]	1999-2003	France	Dialysis patients	Clinical	C-S/R
Di Martino, 2004[154]	1993-2001	France	Females	Clinical	C-S/R
Kenny-Walsh,1999[27]	1970-1994	Ireland	Females	Non-clinical	R-P
Levine, 2006[155]	1977-2004	Ireland	Females	Non-clinical	R-P
Wiese, 2005[37,156]	1978-2003	Germany	Females	Non-clinical	R-P
Benhamou, 1999[74]		France	Injecting drug users	Clinical	C-S/R
Cournot, 2004[157]	1990-2000	France	Injecting drug users	Clinical	C-S/R
Grando-Lemaire, 2001[158]	1997-2000	France	Injecting drug users	Non-clinical	C-S/R
Puoti, 2001[159]	1988-1996; 1993-1996	Italy+USA	Injecting drug users	Clinical	C-S/R
Rai, 2002[160]	1996-1998	USA	Injecting drug users	Non-clinical	C-S/R
Wilson, 2006[161]	2001-2003	USA	Injecting drug users	Non-clinical	R-P
Allory, 2000[162]		France	Liver clinic	Clinical	C-S/R
Asselah, 2003[163]	2000-2001	France	Liver clinic	Clinical	C-S/R
Bedossa, 2007[164]	2005-2006	France	Liver clinic	Clinical	C-S/R
Cheung, 2005[165]	1999-2000	USA	Liver clinic	Clinical	C-S/R
Cholet, 2004[166]	1992-2001	France	Liver clinic	Clinical	C-S/R
Costa, 2002[167]	1994-2000	Brazil	Liver clinic	Clinical	C-S/R
Cournot, 2004[157]	1990-2000	France	Liver clinic	Clinical	C-S/R
Erhardt, 2003[168]		Germany	Liver clinic	Clinical	C-S/R
Fernandez-Rodriguez, 2004[169]	1998-2003	Spain	Liver clinic	Clinical	C-S/R
Fernandez-Salazar, 2004[170]	2000-2002	Spain	Liver clinic	Clinical	C-S/R
Fontaine, 2001[171]		France	Liver clinic	Clinical	C-S/R
Fontana, 2006[172]		USA	Liver clinic	Clinical	C-S/R
Forrest, 2005[173]		UK	Liver clinic	Clinical	C-S/R
Freeman, 2003[174]		UK	Liver clinic	Clinical	C-S/R
Gaslightwala & Bini, 2006[175]		USA	Liver clinic	Clinical	C-S/R
Geier, 2004[176]	1994-2001	Germany	Liver clinic	Clinical	C-S/R

Table 4.2.1. Natural history of hepatitis C: Study characteristics – Literature review (continued)

Study	Study period	Country	Population	Setting	Study design
Ghany, 2003[44]	1980-2000	USA	Liver clinic	Clinical	R-P
Gonzalez, 2006[177]		USA	Liver clinic	Clinical	C-S/R
Haber, 1995[178]	1990-1992	USA	Liver clinic	Clinical	C-S/R
Hezode, 2005[179]	2003-2005	France	Liver clinic	Clinical	C-S/R
Hofer, 2005[180]		Austria	Liver clinic	Clinical	C-S/R
Hollander, 2004[181]	1997-1998; 1999-2000	Sweden	Liver clinic	Clinical	C-S/R
Hu, 2005[148]	1999-2003	USA	Liver clinic	Clinical	C-S/R
Huang, 2006[182]		USA	Liver clinic	Clinical	C-S/R
Huang, 2006[182]		USA	Liver clinic	Clinical	C-S/R
Hui, 2003[94]	1991-1998	USA	Liver clinic	Clinical	R-P
Imazeki, 2005[183]	1986-1998	Japan	Liver clinic	Clinical	C-S/R
Khan, 2000[184]	1982-1996	Australia	Liver clinic	Clinical	R-P
Kryczka, 2003[185]		Poland	Liver clinic	Clinical	C-S/R
Lagging, 2002[186]	1971-1996	Sweden	Liver clinic	Clinical	C-S/R
Leroy, 2004[187]	1999-2000	France	Liver clinic	Clinical	C-S/R
Macias, 2005[188]		Spain	Liver clinic	Clinical	C-S/R
Marine-Barjoan, 2002[189]	1997-1998	France	Liver clinic	Non-clinical	C-S/R
Martinez-Sierra, 2003[190]		Spain	Liver clinic	Clinical	C-S/R
Metwally, 2004[191]	1998-1999	USA	Liver clinic	Clinical	C-S/R
Mohsen, 2003[192]		UK	Liver clinic	Clinical	C-S/R
Monto, 2002[193]	1997-2000	USA	Liver clinic	Clinical	C-S/R
Monto, 2004[194]	1997-2002	USA	Liver clinic	Clinical	C-S/R
Monto, 2004[194]	1997-2002	USA	Liver clinic	Clinical	C-S/R
Monto, 2004[194]	1997-2002	USA	Liver clinic	Clinical	C-S/R
Monto, 2005[195]		USA	Liver clinic	Clinical	C-S/R
Muller, 2003[196]	2001-2002	France	Liver clinic	Clinical	C-S/R
Myers, 2001[197]	1995-1999	Canada	Liver clinic	Clinical	C-S/R
Myers, 2002[198]	1997-2000	France	Liver clinic	Clinical	C-S/R
Myers, 2003[199]		France	Liver clinic	Clinical	C-S/R
Nguyen, 2002[200]	1992-2000	USA	Liver clinic	Clinical	C-S/R
Ong, 2001[201]	1997-1999	USA	Liver clinic	Clinical	C-S/R
Oritz, 2002[202]	2000-2001	Spain	Liver clinic	Clinical	C-S/R
Patel, 2006[203]	1992-2001	USA+UK	Liver clinic	Clinical	C-S/R
Patton, 2004[204]	1992	USA	Liver clinic	Clinical	C-S/R
Pohl, 2001[205]		USA	Liver clinic	Clinical	C-S/R
Poujol-Robert, 2006[206]	2000-2003	France	Liver clinic	Clinical	C-S/R
Poynard, 1997 DOSVIRC[25]		France	Liver clinic	Clinical	C-S/R
Poynard, 1997 METAVIR[25]		France	Liver clinic	Clinical	C-S/R

Table 4.2.1. Natural history of hepatitis C: Study characteristics – Literature review (continued)

Study	Study period	Country	Population	Setting	Study design
Poynard, 1997 OBSVIRC[25]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 DOSVIRC-1[99]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 DOSVIRC-2[99]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 HITG[99]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 IHIT[99]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 OBSVIRC[99]		France	Liver clinic	Clinical	C-S/R
Poynard, 2002[52,54,64,207,208]	1996; 1997	France+USA	Liver clinic	Clinical	C-S/R
Poynard, 2002[52,54,64,207,208]	1996; 1997	USA	Liver clinic	Clinical	C-S/R
Poynard, 2002[52,54,64,207,208]	1996; 1997	USA	Liver clinic	Clinical	C-S/R
Poynard, 2002[52,54,64,207,208]	1996; 1997	Germany	Liver clinic	Clinical	C-S/R
Ratziu, 2003[209]	1993-2000	France	Liver clinic	Clinical	C-S/R
Renou, 2002[210]	1999-2000	France	Liver clinic	Clinical	C-S/R
Reynolds, 2002[211]	1994-1999	USA	Liver clinic	Clinical	C-S/R
Roger, 2005[212]		France	Liver clinic	Clinical	C-S/R
Romero-Gomez, 2003[213]		Spain	Liver clinic	Clinical	C-S/R
Ryder, 2004[46]	2000	UK	Liver clinic	Non-clinical	C-S/R
Sud, 2004[214]	1999-2002	Australia	Liver clinic	Clinical	C-S/R
Toccaceli, 2003[215]	1990-1997	Italy	Liver clinic	Clinical	C-S/R
Watt, 2004[216]		Canada	Liver clinic	Clinical	C-S/R
Wietzke-Braun, 2003[217]		Germany	Liver clinic	Clinical	C-S/R
Wilfredo Canchis, 2004[218]		USA	Liver clinic	Clinical	C-S/R
Wong, 1997[219]		UK	Liver clinic	Clinical	C-S/R
Wright, 2003[220]	1990-2001	Europe	Liver clinic	Clinical	C-S/R
Zarski, 2003[47]		France+USA	Liver clinic	Clinical	C-S/R
de Le'dinghen, 2002[221]	1998-2000	France	Liver clinic	Clinical	C-S/R
Castellino, 2004[222]	1995-2002	USA	Pediatric population	Clinical	R-P
Guido, 1998[223]	1990-1996	Italy	Pediatric population	Clinical	C-S/R
Guido, 2003[224]		Europe	Pediatric population	Clinical	C-S/R
Mohan, 2007[225]	1982-1992	USA	Pediatric population	Clinical	R-P
Hamada, 2002[226]	1980-2000	Japan	Post-transfusion	Clinical	R-P
Shin, 2005[227]	1992-2003	Canada	Post-transfusion	Clinical	C-S/R
Giordano, 2003[228]	1993-1995	Brazil	Renal transplant recipients	Clinical	C-S/R
Kamar, 2005[229]		France	Renal transplant recipients	Clinical	C-S/R
Toz, 2002[152]	1996-2000	Turkey	Renal transplant recipients	Clinical	C-S/R
Varaut, 2005[153]	1999-2003	France	Renal transplant recipients	Clinical	C-S/R

C-S/R, cross-sectional/retrospective study; R-P, retrospective-prospective.
Studies among females consisted of females infected after exposure to contaminated immunoglobulin except a study by Di Martino *et al.*,[154] which examined the influence of estrogen on liver fibrosis progression in HCV-infected females.

Table 4.2.2. Study and clinical characteristics of individuals with chronic hepatitis C virus infection: Literature review

Study	Sample size	Biopsy sample	Age (yr)	Age at HCV (yr)	Duration of infection (yr)	Histological classification	F0	F1	F2	F3	F4	Person-Years
Alter, 1997[142]	81	74	37.0	19.0	18.0	Conventional/unspecified	32	33	2	3	4†	1332.0
Silva, 2004[143]	142	142	38.7	19.9	18.8	METAVIR	9	66	32	25	10	2669.6
Dalgard, 2003[144]	72	38	42.5	20.5	22.0	Knodell	10	11	6	8	3†	836.0
Saadoun, 2006[145]	437	437	50.9	31.0	19.9	METAVIR	17	204	106	46	64	8696.3
Serra, 2003[146]	375	298	46.0	29.3	16.7	Batts-Ludwig	11	116	61	43	67	4976.6
Verma, 2006[147]	232	232	45.4	22.7	24.2	Ishak	16	51	51	41	73	5614.4
Hu, 2005[148]	91	91	46.4	25.7	20.7	Knodell	33	27	6	15	10	1883.7
Martin, 2000[149]	37	37	47.5	33.1	14.4	Scheuer	7	10	8	3	9	532.8
Sezer, 2001[150]	68	68	39.8	36.1	3.7	Scheuer/Desmet/Batts-Ludwig	8	13	27	16	4	250.2
Sterling, 1999[151]	50	50	42.3	26.7	15.6	Knodell	17	22	3	3	5	780.0
Toz, 2002[152]	40	40	42.0	38.2	3.8	Scheuer	7	14	14	4	1	153.2
Varaut, 2005[153]	50	50	48.0	29.0	17.0	METAVIR	1	28	11	7	3	850.0
Di Martino, 2004[154]	157	157	48.0	29.0	18.0	METAVIR	20	68	38	20	11	2826.0
Kenny-Walsh,1999[27]	376	363	45.0	28.0	17.0	Desmet	177	124	36	19	7	6171
Levine, 2006[155]	184	167	56.0	27.0	27.0	Ishak	50	53	34	26	4	4509.0
Wiese, 2005[37,156]	683	490	49.0	24.0	25.0	Ishak	164	173	97	43	13†	12250.0
Benhamou, 1999[74]	122	122	35.6	22.1	13.5	METAVIR	15	50	36	8	13	1647.0
Cournot, 2004[157]	225	122	31.9	20.6	11.3	METAVIR	36	36	20	21	9	1378.6
Grando-Lemaire, 2001[158]	225	88	33.0	19.5	13.4	METAVIR	3	38	27	6	14	1183.6
Puoti, 2001[159]	204	204	32.0	20.0	12.0	METAVIR	13	111	56	14	10	2448.0
Rai, 2002[160]	207	207	40.4	20.7	19.7	Ishak	74	65	47	18	3	4077.9
Wilson, 2006[161]	119	119	46.0	20.0	26.0	Ishak	32	30	34	15	8	3094.0
Allory, 2000[162]	58	58	35.0	20.0	12.0	METAVIR	6	27	14	5	6	696.0
Asselah, 2003[163]	290	290	46.0	25.0	21.0	METAVIR	4	177	73	21	15	6090.0
Bedossa, 2007[164]	278	278	47.0	24.0	23.0	METAVIR	54	54	101	40	29	6394.0
Cheung, 2005[165]	2931	866	50.3	24.0	26.2	Conventional/unspecified	108	226	230	172	130	22689.2

Table 4.2.2. Study and clinical characteristics of individuals with chronic hepatitis C virus infection: Literature review (continued)

Study	Sample size	Biopsy sample	Age (yr)	Age at HCV (yr)	Duration of infection (yr)	Histological classification	F0	F1	F2	F3	F4	Person-Years
Cholet, 2004[166]	314	314	40.8	26.8	13.7	METAVIR	72	72	82	42	46	4301.8
Costa, 2002[167]	59	59	43.0	29.0	14.0	Ludwig/Desmet	7	21	8	10	13	826.0
Cournot, 2004[157]	210	84	53.3	38.9	14.4	METAVIR	21	22	11	11	19	1209.6
Erhardt, 2003[168]	401	217	47.7	35.3	12.4	Knodell	42	93	27	27	28	2690.8
Fernandez-Rodriguez, 2004[169]	133	133	43.5	24.5	19.0	METAVIR	5	66	38	12	12	2527.0
Fernandez-Salazar, 2004[170]	50	50	40.7	21.0	19.8	Scheuer	1	17	18	10	4	987.5
Fontaine, 2001[171]	76	76	41.0	30.0	11.0	Knodell/METAVIR	9	46	8	7	6	836.0
Fontana, 2006[172]	399	399	48.5	22.5	26.0	Ishak	42	100	111	117	29	10374.0
Forrest, 2005[173]	195	195	38.6	24.1	14.5	Ishak	27	70	42	38	18	2827.5
Freeman, 2003[174]	87	87	44.9	35.4	9.5	Wong	8	13	27	24	15	826.5
Gaslightwala & Bini, 2006[175]	554	554	51.1	31.1	20.0	Scheuer	87	143	158	90	76	11080.0
Geier, 2004[176]	166	166	41.8	33.5	8.3	Batts-Ludwig	45	44	47	22	8	1377.8
Ghany, 2003[44]	123	123	44.7	27.0	17.7	Ishak	15	28	22	41	17	2177.1
Gonzalez, 2006[177]	117	117	48.6	27.7	20.9	Scheuer	13	38	37	22	7	2445.3
Haber, 1995[178]	90	90	40.9	26.4	14.5	Knodell	7	34	11	12	26	1305.0
Hezode, 2005[179]	270	270	43.2	24.4	18.8	METAVIR	13	154	46	21	36	5076.0
Hofer, 2005[180]	212	212	44.7	25.6	19.1	Ludwig	11	11	108	27	55	4051.3
Hollander, 2004[181]	323	323	45.0	24.0	21.0	METAVIR	51	52	98	76	46	6783.0
Hu, 2005[148]	159	159	46.3	24.9	21.4	Knodell	27	44	20	39	29	3402.6
Huang, 2006[182]	433	433	52.7	25.4	27.3	Knodell	93	109	110	73	48	11820.9
Huang, 2006[182]	483	483	50.8	28.9	21.9	Knodell	84	82	83	114	120	10577.7
Hui, 2003[94]	81	81	54.9	25.8	29.1	METAVIR	22	27	20	7	5	2357.1
Imazeki, 2005[183]	459	459	50.1	26.5	23.6	Desmet	19	238	76	58	68	10832.4
Khan, 2000[184]	455	432	37.0	25.0	12.0	Scheuer	29	96	143	73	91[†]	5184.0
Kryczka, 2003[185]	337	337	43.0	30.0	13.0	Ishak	132	82	28	56	39	4381.0
Lagging, 2002[186]	98	98	44.3	33.2	13.0	Ishak	1	14	34	35	14	1274.0

Table 4.2.2. Study and clinical characteristics of individuals with chronic hepatitis C virus infection: Literature review (continued)

Study	Sample size	Biopsy sample	Age (yr)	Age at HCV (yr)	Duration of infection (yr)	Histological classification	F0	F1	F2	F3	F4	Person-Years
Leroy, 2004[187]	194	188	43.0	25.0	18.0	METAVIR	32	72	48	22	14	3384.0
Macias, 2005[188]	100	100	42.0	21.0	21.0	Scheuer	22	17	21	24	16	2100.0
Marine-Barjoan, 2002[189]	924	924	44.9	30.9	14.0	METAVIR	100	496	147	136	45	12936.0
Martinez-Sierra, 2003[190]	147	147	38.1	21.7	17.9	Scheuer/Desmet	51	51	18	18	9	2631.3
Metwally, 2004[191]	100	100	45.5	22.5	22.6	METAVIR	21	13	31	10	25	2260.0
Mohsen, 2003[192]	153	153	39.8	23.0	15.0	METAVIR/Ishak	13	53	41	23	23	2295.0
Monto, 2002[193]	297	297	49.0	24.9	24.1	Batts-Ludwig	63	83	83	40	28	7157.7
Monto, 2004[194]	324	324	47.0	22.0	22.0	METAVIR	70	114	69	32	39	7128.0
Monto, 2004[194]	199	199	47.0	24.0	24.0	METAVIR	56	57	56	18	12	4776.0
Monto, 2004[194]	277	277	50.0	24.0	25.0	METAVIR	51	75	82	36	33	6925.0
Monto, 2005[195]	372	372	49.0	25.0	24.0	Batts-Ludwig	100	89	100	49	34	8928.0
Muller, 2003[196]	90	90	44.0	24.1	19.9	Knodell/METAVIR	14	27	18	13	18	1791.0
Myers, 2001[197]	106	106	42.0	23.0	19.0	METAVIR	26	36	16	12	16	2014.0
Myers, 2002[198]	211	211	42.0	28.0	17.0	METAVIR	34	93	49	15	20	3587.0
Myers, 2003[199]	132	132	45.9	28.5	15.4	METAVIR	2	46	42	21	21	2031.5
Nguyen, 2002[200]	206	206	46.5	22.5	24.0	METAVIR	17	61	62	35	31	4944.0
Ong, 2001[201]	170	170	48.7	30.9	17.8	Ishak	16	28	33	31	62	3026.0
Oritz, 2002[202]	114	114	41.0	23.0	18.0	Desmet	31	57	5	18	3	2052.0
Patel, 2006[203]	515	515	43.4	23.2	20.2	METAVIR	87	183	114	69	62	10403.0
Patton, 2004[204]	574	560	44.9	23.2	21.7	METAVIR	167	168	114	46	65	12152.0
Pohl, 2001[205]	211	153	45.0	24.1	20.9	METAVIR	61	38	18	13	23	3197.7
Poujol-Robert, 2006[206]	346	346	46.8	23.7	20.9	METAVIR	10	177	76	35	48	7231.4
Poynard, 1997 DOSVIRC[25]	607	607	46.2	32.0	14.2	METAVIR	36	229	159	79	104	8619.4
Poynard, 1997 METAVIR[25]	490	490	49.1	36.7	12.4	METAVIR	13	136	87	100	154	6076.0
Poynard, 1997 OBSVIRC[25]	1138	1138	43.8	32.5	11.3	METAVIR	178	441	216	161	142	12859.4
Poynard, 2001 DOSVIRC-1[99]	320	320	45.0	31.0	14.0	METAVIR	18	116	103	37	46	4480.0
Poynard, 2001 DOSVIRC-2[99]	355	355	47.0	29.0	18.0	METAVIR	50	122	103	33	47	6390.0

Table 4.2.2. Study and clinical characteristics of individuals with chronic hepatitis C virus infection: Literature review (continued)

Study	Sample size	Biopsy sample	Age (yr)	Age at HCV (yr)	Duration of infection (yr)	Histological classification	F0	F1	F2	F3	F4	Person-Years
Poynard, 2001 HITG[99]	597	597	44.0	24.0	20.0	METAVIR	14	397	86	63	37	11940.0
Poynard, 2001 IHIT[99]	495	495	40.0	24.0	16.0	METAVIR	11	399	40	26	19	7920.0
Poynard, 2001 OBSVIRC[99]	546	546	43.0	31.0	12.0	METAVIR	94	213	99	84	56	6552.0
Poynard, 2002[52,54,64,207,208]	832	832	41.0	26.0	15.0	METAVIR	16	657	75	50	34	12480.0
Poynard, 2002[52,54,64,207,208]	912	912	44.0	25.0	19.0	METAVIR	18	627	127	91	49	17328.0
Poynard, 2002[52,54,64,207,208]	1219	1219	43.0	24.4	18.6	METAVIR	49	938	110	73	49	22673.4
Poynard, 2002[52,54,64,207,208]	1530	1530	43.0	23.7	19.3	METAVIR	15	1071	260	92	92	29529.0
Ratziu, 2003[209]	710	710	41.0	23.9	15.7	METAVIR	98	291	175	50	96	11147.0
Renou, 2002[210]	316	316	46.6	32.2	14.4	METAVIR	78	109	64	39	26	4550.4
Reynolds, 2002[211]	166	166	48.0	27.0	21.0	Knodell/METAVIR	30	86	14	15	21	3486.0
Roger, 2005[212]	28	28	46.5	28.5	18.0	METAVIR	1	9	12	4	2	504.0
Romero-Gomez, 2003[213]	131	131	38.0	22.0	16.0	Scheuer	4	58	47	12	10	2096.0
Ryder, 2004[46]	214	214	36.0	19.6	18.9	Knodell/Ishak	128	55	10	16	5	4044.6
Sud, 2004[214]	176	176	40.9	21.5	18.9	Scheuer	46	46	37	37	10	3326.4
Toccaceli, 2003[215]	112	112	46.4	36.4	10.0	Knodell	25	61	11	12	3	1120.0
Watt, 2004[216]	116	116	46.0	27.0	18.0	Desmet	45	32	21	3	15	2088.0
Wietzke-Braun, 2003[217]	72	72	46.8	31.4	15.4	Knodell/Desmet/Ishak	33	10	10	11	8	1108.8
Wilfredo Canchis, 2004[218]	156	156	49.0	26.0	23.0	METAVIR	14	44	32	45	21	3588.0
Wong, 1997[219]	140	140	36.0	24.0	12.0	Wong	14	15	58	43	10	1680.0
Wright, 2003[220]	352	352	41.8	27.1	14.7	Ishak	26	70	101	94	61	5174.4
Zarski, 2003[47]	180	180	45.3	26.2	18.0	METAVIR	48	69	28	26	9	3240.0
de Le'dinghen, 2002[221]	321	317	41.0	26.8	14.2	METAVIR	12	95	123	68	19	4501.4
Castellino, 2004[222]	122	60	29.0	5.0	19.5	Desmet	13	17	10	11	9†	1170.0
Guido, 1998[223]	80	80	9.1	5.7	3.5	Ishak	22	22	22	13	1	276.8
Guido, 2003[224]	112	112	8.6	0.6	8.0	METAVIR	25	57	24	5	1	900.5
Mohan, 2007[225]	60	45	15.2	0.6	13.4	Batts-Ludwig/Knodell	17	10	10	5	3†	600.8

Table 4.2.2. Study and clinical characteristics of individuals with chronic hepatitis C virus infection: Literature review (continued)

Study	Sample size	Biopsy sample	Age (yr)	Age at HCV (yr)	Duration of infection (yr)	Histological classification	F0	F1	F2	F3	F4	Person-Years
Hamada, 2002[226]	469	436	54.7	30.0	28.1	Desmet	72	72	87	69	136	12251.6
Shin, 2005[227]	65	63	33.0	15.6	26.9	METAVIR	4	17	17	11	14	1694.7
Giordano, 2003[228]	45	26	41.1	31.1	10.0	Knodell	9	11	2	3	1	260.0
Kamar, 2005[229]	51	42	38.0	27.8	10.2	METAVIR	6	16	9	8	3	428.4
Toz, 2002[152]	46	46	36.0	32.7	4.9	Scheuer	5	14	15	9	3	222.2
Varaut, 2005[153]	60	60	44.0	29.0	17.0	METAVIR	10	21	17	9	3	1020.0

HCV, hepatitis C virus. Hepatic fibrosis stage based on METAVIR fibrosis scoring system:[38] F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with numerous septa without cirrhosis; F4, cirrhosis.
[†]Includes clinical cirrhosis and/or hepatocellular carcinoma.

Table 4.2.3. Literature-derived annual stage-specific transition probabilities in hepatitis C – Markov maximum likelihood estimation

Study	F0→F1†			P	F1→F2†			P	F2→F3†			P	F3→F4†			P
	Mean	LB	UB		Mean	LB	UB		Mean	LB	UB		Mean	LB	UB	
Alter, 1997[142]	0.047	0.034	0.063	0.000	0.025	0.011	0.053	0.000	0.865	0.071	10.554	0.887	0.110	0.025	0.490	0.013
Silva, 2004[143]	0.147	0.110	0.196	0.000	0.055	0.042	0.073	0.000	0.103	0.064	0.166	0.000	0.059	0.025	0.137	0.000
Dalgard, 2003[144]	0.061	0.039	0.095	0.000	0.079	0.041	0.151	0.000	0.141	0.053	0.377	0.004	0.046	0.010	0.211	0.003
Saadoun, 2006[145]	0.163	0.136	0.196	0.000	0.052	0.044	0.060	0.000	0.091	0.070	0.118	0.000	0.167	0.112	0.251	0.000
Serra, 2003[146]	0.198	0.158	0.247	0.000	0.078	0.064	0.094	0.000	0.163	0.122	0.218	0.000	0.203	0.137	0.299	0.000
Verma, 2006[147]	0.111	0.089	0.138	0.000	0.096	0.076	0.122	0.000	0.123	0.092	0.165	0.000	0.147	0.101	0.213	0.000
Hu, 2005[148]	0.049	0.037	0.066	0.000	0.071	0.044	0.113	0.000	0.318	0.122	0.823	0.027	0.079	0.033	0.190	0.001
Martin, 2000[149]	0.116	0.072	0.185	0.000	0.137	0.074	0.257	0.000	0.173	0.074	0.406	0.003	0.435	0.108	1.749	0.184
Sezer, 2001[150]	0.582	0.402	0.842	0.013	0.739	0.458	1.190	0.164	0.341	0.199	0.584	0.004	0.190	0.052	0.688	0.021
Sterling, 1999[151]	0.069	0.047	0.101	0.000	0.046	0.023	0.095	0.000	0.315	0.075	1.318	0.093	0.256	0.053	1.244	0.078
Toz, 2002[152]	0.455	0.290	0.715	0.007	0.385	0.218	0.679	0.008	0.196	0.064	0.597	0.013	0.203	0.014	2.955	0.187
Varaut, 2005[153]	0.230	0.121	0.436	0.002	0.044	0.027	0.071	0.000	0.096	0.040	0.228	0.001	0.069	0.015	0.332	0.007
Di Martino, 2004[154]	0.114	0.090	0.145	0.000	0.063	0.047	0.083	0.000	0.088	0.054	0.142	0.000	0.086	0.037	0.200	0.001
Kenny-Walsh,1999[27]	0.042	0.036	0.049	0.000	0.045	0.033	0.062	0.000	0.097	0.055	0.171	0.000	0.069	0.024	0.198	0.001
Levine, 2006[155]	0.045	0.036	0.055	0.000	0.054	0.039	0.075	0.000	0.065	0.039	0.108	0.000	0.018	0.005	0.065	0.001
Wiese, 2005[37,156]	0.044	0.039	0.050	0.000	0.047	0.038	0.057	0.000	0.050	0.035	0.072	0.000	0.038	0.018	0.081	0.000
Benhamou, 1999[74]	0.155	0.118	0.204	0.000	0.091	0.067	0.125	0.000	0.086	0.049	0.151	0.000	0.307	0.116	0.813	0.026
Cournot, 2004[157]	0.108	0.084	0.139	0.000	0.145	0.099	0.210	0.000	0.239	0.136	0.421	0.001	0.105	0.043	0.257	0.001
Grando-Lemaire,2001[158]	0.251	0.165	0.383	0.000	0.085	0.060	0.119	0.000	0.099	0.056	0.176	0.000	0.394	0.140	1.112	0.069
Puoti, 2001[159]	0.229	0.181	0.291	0.000	0.067	0.052	0.085	0.000	0.074	0.044	0.125	0.000	0.170	0.067	0.433	0.005
Rai, 2002[160]	0.052	0.043	0.063	0.000	0.069	0.050	0.093	0.000	0.050	0.028	0.089	0.000	0.028	0.006	0.127	0.002
Wilson, 2006[161]	0.051	0.039	0.065	0.000	0.078	0.054	0.114	0.000	0.051	0.029	0.087	0.000	0.058	0.022	0.156	0.001
Allory, 2000[162]	0.189	0.126	0.284	0.000	0.085	0.054	0.135	0.000	0.127	0.056	0.286	0.001	0.260	0.070	0.960	0.045
Asselah, 2003[163]	0.204	0.152	0.274	0.000	0.030	0.024	0.036	0.000	0.046	0.030	0.071	0.000	0.093	0.044	0.199	0.000
Bedossa, 2007[164]	0.071	0.060	0.085	0.000	0.118	0.092	0.152	0.000	0.053	0.039	0.072	0.000	0.083	0.049	0.141	0.000

Table 4.2.3. Literature-derived annual stage-specific transition probabilities in hepatitis C – Markov maximum likelihood estimation (continued)

Study	F0→F1†			P	F1→F2†			P	F2→F3†			P	F3→F4†			P
	Mean	LB	UB		Mean	LB	UB		Mean	LB	UB		Mean	LB	UB	
Cheung, 2005[165]	0.079	0.072	0.088	0.000	0.079	0.070	0.089	0.000	0.081	0.069	0.095	0.000	0.072	0.057	0.092	0.000
Cholet, 2004[166]	0.107	0.092	0.126	0.000	0.168	0.134	0.212	0.000	0.137	0.102	0.184	0.000	0.199	0.127	0.310	0.000
Costa, 2002[167]	0.152	0.102	0.227	0.000	0.106	0.067	0.167	0.000	0.301	0.138	0.656	0.011	0.204	0.088	0.470	0.005
Cournot, 2004[157]	0.096	0.071	0.131	0.000	0.137	0.088	0.213	0.000	0.289	0.146	0.569	0.005	0.257	0.120	0.551	0.006
Erhardt, 2003[168]	0.132	0.109	0.161	0.000	0.086	0.067	0.112	0.000	0.285	0.179	0.454	0.001	0.207	0.117	0.367	0.001
Fernandez-Rodriguez, 2004[169]	0.173	0.124	0.241	0.000	0.049	0.037	0.065	0.000	0.063	0.037	0.107	0.000	0.138	0.057	0.334	0.002
Fernandez-Salazar, 2004[170]	0.198	0.104	0.376	0.001	0.074	0.047	0.116	0.000	0.066	0.034	0.129	0.000	0.054	0.015	0.203	0.002
Fontaine, 2001[171]	0.194	0.138	0.273	0.000	0.053	0.033	0.085	0.000	0.272	0.109	0.681	0.015	0.204	0.060	0.691	0.020
Fontana, 2006[172]	0.087	0.074	0.101	0.000	0.082	0.069	0.099	0.000	0.080	0.064	0.101	0.000	0.026	0.016	0.041	0.000
Forrest, 2005[173]	0.136	0.110	0.169	0.000	0.101	0.078	0.129	0.000	0.160	0.108	0.235	0.000	0.088	0.047	0.166	0.000
Freeman, 2003[174]	0.251	0.178	0.354	0.000	0.338	0.214	0.533	0.002	0.214	0.139	0.330	0.000	0.157	0.081	0.305	0.001
Gaslightwala & Bini, 2006[175]	0.093	0.082	0.105	0.000	0.105	0.089	0.123	0.000	0.090	0.073	0.112	0.000	0.107	0.077	0.149	0.000
Geier, 2004[176]	0.157	0.127	0.195	0.000	0.231	0.168	0.316	0.000	0.152	0.095	0.245	0.000	0.130	0.050	0.336	0.003
Ghany, 2003[44]	0.119	0.090	0.156	0.000	0.133	0.095	0.186	0.000	0.202	0.129	0.316	0.000	0.057	0.031	0.104	0.000
Gonzalez, 2006[177]	0.105	0.079	0.140	0.000	0.079	0.057	0.109	0.000	0.068	0.043	0.110	0.000	0.044	0.016	0.118	0.000
Haber, 1995[178]	0.176	0.124	0.249	0.000	0.095	0.067	0.135	0.000	0.327	0.171	0.625	0.007	0.290	0.146	0.576	0.006
Hezode, 2005[179]	0.161	0.129	0.201	0.000	0.039	0.032	0.048	0.000	0.117	0.079	0.174	0.000	0.215	0.120	0.384	0.001
Hofer, 2005[180]	0.155	0.121	0.198	0.000	0.300	0.187	0.480	0.001	0.053	0.042	0.069	0.000	0.205	0.130	0.326	0.000
Hollander, 2004[181]	0.088	0.075	0.103	0.000	0.151	0.119	0.193	0.000	0.091	0.071	0.116	0.000	0.072	0.049	0.106	0.000
Hu, 2005[148]	0.083	0.066	0.104	0.000	0.091	0.068	0.122	0.000	0.221	0.136	0.359	0.000	0.080	0.049	0.131	0.000
Huang, 2006[182]	0.056	0.049	0.065	0.000	0.077	0.064	0.093	0.000	0.071	0.055	0.091	0.000	0.064	0.043	0.095	0.000
Huang, 2006[182]	0.080	0.070	0.091	0.000	0.140	0.115	0.170	0.000	0.168	0.133	0.212	0.000	0.103	0.080	0.133	0.000

Table 4.2.3. Literature-derived annual stage-specific transition probabilities in hepatitis C – Markov maximum likelihood estimation (continued)

Study	F0→F1†			P	F1→F2†			P	F2→F3†			P	F3→F4†			P
	Mean	LB	UB		Mean	LB	UB		Mean	LB	UB		Mean	LB	UB	
Hui, 2003[94]	0.045	0.033	0.061	0.000	0.049	0.031	0.077	0.000	0.043	0.020	0.092	0.000	0.071	0.019	0.262	0.003
Imazeki, 2005[183]	0.135	0.113	0.161	0.000	0.037	0.032	0.043	0.000	0.115	0.087	0.152	0.000	0.117	0.081	0.170	0.000
Khan, 2000[184]	0.225	0.191	0.265	0.000	0.192	0.161	0.229	0.000	0.148	0.121	0.181	0.000	0.237	0.173	0.324	0.000
Kryczka, 2003[185]	0.072	0.062	0.084	0.000	0.140	0.109	0.181	0.000	0.413	0.267	0.641	0.004	0.132	0.085	0.206	0.000
Lagging, 2002[186]	0.353	0.203	0.614	0.005	0.204	0.138	0.303	0.000	0.140	0.097	0.202	0.000	0.073	0.038	0.140	0.000
Leroy, 2004[187]	0.098	0.080	0.121	0.000	0.073	0.056	0.095	0.000	0.082	0.052	0.128	0.000	0.099	0.047	0.213	0.001
Macias, 2005[188]	0.072	0.054	0.096	0.000	0.145	0.093	0.227	0.000	0.134	0.082	0.219	0.000	0.077	0.040	0.149	0.000
Marine-Barjoan, 2002[189]	0.159	0.144	0.176	0.000	0.056	0.050	0.064	0.000	0.164	0.131	0.205	0.000	0.068	0.046	0.101	0.000
Martinez-Sierra, 2003[190]	0.059	0.047	0.074	0.000	0.066	0.045	0.095	0.000	0.161	0.086	0.299	0.001	0.079	0.031	0.199	0.001
Metwally, 2004[191]	0.069	0.052	0.092	0.000	0.169	0.103	0.277	0.000	0.078	0.050	0.122	0.000	0.227	0.106	0.486	0.004
Mohsen, 2003[192]	0.164	0.126	0.214	0.000	0.102	0.078	0.134	0.000	0.128	0.085	0.191	0.000	0.165	0.089	0.305	0.001
Monto, 2002[193]	0.064	0.055	0.076	0.000	0.078	0.063	0.098	0.000	0.064	0.046	0.088	0.000	0.079	0.046	0.135	0.000
Monto, 2004[194]	0.070	0.060	0.081	0.000	0.064	0.052	0.079	0.000	0.089	0.063	0.124	0.000	0.142	0.085	0.237	0.000
Monto, 2004[194]	0.053	0.043	0.064	0.000	0.072	0.054	0.096	0.000	0.046	0.029	0.074	0.000	0.080	0.035	0.185	0.001
Monto, 2004[194]	0.068	0.057	0.080	0.000	0.079	0.063	0.099	0.000	0.062	0.045	0.085	0.000	0.095	0.057	0.160	0.000
Monto, 2005[195]	0.055	0.047	0.063	0.000	0.090	0.072	0.111	0.000	0.065	0.048	0.087	0.000	0.079	0.048	0.128	0.000
Muller, 2003[196]	0.094	0.069	0.127	0.000	0.090	0.061	0.132	0.000	0.140	0.080	0.243	0.000	0.160	0.077	0.335	0.001
Myers, 2001[197]	0.074	0.056	0.097	0.000	0.076	0.051	0.111	0.000	0.161	0.087	0.298	0.001	0.170	0.076	0.377	0.002
Myers, 2002[198]	0.107	0.088	0.131	0.000	0.063	0.049	0.081	0.000	0.085	0.054	0.134	0.000	0.207	0.098	0.435	0.003
Myers, 2003[199]	0.272	0.178	0.417	0.001	0.091	0.068	0.120	0.000	0.104	0.069	0.155	0.000	0.155	0.082	0.292	0.001
Nguyen, 2002[200]	0.104	0.083	0.130	0.000	0.075	0.059	0.096	0.000	0.074	0.053	0.103	0.000	0.092	0.055	0.153	0.000
Ong, 2001[201]	0.133	0.104	0.169	0.000	0.168	0.123	0.230	0.000	0.192	0.135	0.273	0.000	0.209	0.138	0.315	0.000
Oritz, 2002[202]	0.072	0.056	0.093	0.000	0.036	0.023	0.056	0.000	0.397	0.135	1.161	0.078	0.026	0.006	0.117	0.002

Table 4.2.3. Literature-derived annual stage-specific transition probabilities in hepatitis C – Markov maximum likelihood estimation (continued)

Study	F0→F1†			P	F1→F2†			P	F2→F3†			P	F3→F4†			P
	Mean	LB	UB		Mean	LB	UB		Mean	LB	UB		Mean	LB	UB	
Patel, 2006[203]	0.088	0.077	0.100	0.000	0.072	0.061	0.084	0.000	0.103	0.080	0.132	0.000	0.116	0.080	0.168	0.000
Patton, 2004[204]	0.056	0.050	0.063	0.000	0.073	0.062	0.087	0.000	0.087	0.067	0.114	0.000	0.166	0.110	0.252	0.000
Pohl, 2001[205]	0.044	0.035	0.055	0.000	0.084	0.058	0.123	0.000	0.168	0.094	0.299	0.001	0.197	0.095	0.409	0.002
Poujol-Robert, 2006[206]	0.170	0.136	0.212	0.000	0.042	0.035	0.051	0.000	0.091	0.067	0.123	0.000	0.157	0.098	0.250	0.000
Poynard, 1997 DOSVIRC[25]	0.199	0.173	0.229	0.000	0.097	0.085	0.111	0.000	0.137	0.111	0.167	0.000	0.220	0.162	0.299	0.000
Poynard, 1997 METAVIR[25]	0.293	0.242	0.354	0.000	0.144	0.124	0.168	0.000	0.290	0.233	0.361	0.000	0.243	0.191	0.309	0.000
Poynard, 1997 OBSVIRC[25]	0.164	0.151	0.179	0.000	0.115	0.104	0.128	0.000	0.220	0.185	0.261	0.000	0.200	0.157	0.256	0.000
Poynard, 2001 DOSVIRC-1[99]	0.206	0.169	0.250	0.000	0.103	0.085	0.123	0.000	0.102	0.077	0.135	0.000	0.218	0.137	0.346	0.000
Poynard, 2001 DOSVIRC-2[99]	0.109	0.093	0.127	0.000	0.085	0.071	0.103	0.000	0.081	0.061	0.109	0.000	0.198	0.122	0.321	0.000
Poynard, 2001 HITG[99]	0.188	0.157	0.224	0.000	0.026	0.022	0.030	0.000	0.104	0.077	0.140	0.000	0.079	0.049	0.125	0.000
Poynard, 2001 IHIT[99]	0.238	0.196	0.289	0.000	0.016	0.013	0.020	0.000	0.132	0.083	0.208	0.000	0.122	0.062	0.242	0.001
Poynard, 2001 OBSVIRC[99]	0.147	0.130	0.166	0.000	0.106	0.091	0.124	0.000	0.211	0.163	0.272	0.000	0.148	0.102	0.215	0.000
Poynard, 2002[52,54,64,207,208]	0.263	0.225	0.308	0.000	0.019	0.016	0.022	0.000	0.138	0.099	0.193	0.000	0.121	0.074	0.201	0.000
Poynard, 2002[52,54,64,207,208]	0.207	0.178	0.240	0.000	0.025	0.022	0.028	0.000	0.105	0.082	0.134	0.000	0.077	0.051	0.115	0.000
Poynard, 2002[52,54,64,207,208]	0.173	0.155	0.192	0.000	0.016	0.014	0.019	0.000	0.114	0.086	0.150	0.000	0.099	0.065	0.150	0.000
Poynard, 2002[52,54,64,207,208]	0.240	0.208	0.276	0.000	0.023	0.021	0.025	0.000	0.069	0.056	0.085	0.000	0.134	0.097	0.186	0.000
Ratziu, 2003[209]	0.126	0.113	0.141	0.000	0.078	0.068	0.089	0.000	0.102	0.082	0.128	0.000	0.298	0.205	0.434	0.000
Renou, 2002[210]	0.097	0.083	0.114	0.000	0.097	0.078	0.122	0.000	0.136	0.095	0.193	0.000	0.128	0.073	0.224	0.000
Reynolds, 2002[211]	0.081	0.065	0.101	0.000	0.036	0.026	0.049	0.000	0.211	0.111	0.402	0.002	0.158	0.077	0.323	0.001

Table 4.2.3. Literature-derived annual stage-specific transition probabilities in hepatitis C – Markov maximum likelihood estimation (continued)

Study	F0→F1†			P	F1→F2†			P	F2→F3†			P	F3→F4†			P
	Mean	LB	UB		Mean	LB	UB		Mean	LB	UB		Mean	LB	UB	
Roger, 2005[212]	0.185	0.088	0.387	0.002	0.088	0.048	0.164	0.000	0.050	0.019	0.134	0.001	0.076	0.011	0.527	0.019
Romero-Gomez, 2003[213]	0.218	0.153	0.311	0.000	0.069	0.052	0.091	0.000	0.056	0.033	0.095	0.000	0.140	0.055	0.358	0.003
Ryder, 2004[46]	0.027	0.022	0.034	0.000	0.047	0.029	0.074	0.000	0.223	0.097	0.509	0.005	0.049	0.015	0.166	0.001
Sud, 2004[214]	0.071	0.058	0.088	0.000	0.104	0.076	0.141	0.000	0.119	0.078	0.182	0.000	0.041	0.018	0.093	0.000
Toccaceli, 2003[215]	0.150	0.116	0.194	0.000	0.059	0.038	0.092	0.000	0.272	0.119	0.621	0.010	0.075	0.016	0.353	0.008
Watt, 2004[216]	0.053	0.041	0.068	0.000	0.086	0.056	0.132	0.000	0.097	0.050	0.188	0.000	0.634	0.148	2.709	0.457
Wietzke-Braun, 2003[217]	0.051	0.036	0.071	0.000	0.201	0.105	0.388	0.001	0.201	0.094	0.432	0.003	0.118	0.044	0.319	0.003
Wilfredo Canchis, 2004[218]	0.105	0.081	0.136	0.000	0.083	0.063	0.109	0.000	0.131	0.089	0.193	0.000	0.051	0.029	0.088	0.000
Wong, 1997[219]	0.192	0.147	0.250	0.000	0.341	0.224	0.519	0.001	0.113	0.081	0.156	0.000	0.051	0.023	0.113	0.000
Wright, 2003[220]	0.177	0.148	0.212	0.000	0.173	0.141	0.211	0.000	0.150	0.120	0.187	0.000	0.106	0.076	0.148	0.000
Zarski, 2003[47]	0.073	0.060	0.090	0.000	0.064	0.047	0.087	0.000	0.134	0.080	0.223	0.000	0.056	0.023	0.137	0.000
de Le'dinghen, 2002[221]	0.231	0.186	0.286	0.000	0.120	0.100	0.145	0.000	0.085	0.066	0.111	0.000	0.055	0.030	0.100	0.000
Castellino, 2004[222]	0.078	0.054	0.113	0.000	0.095	0.058	0.157	0.000	0.166	0.079	0.346	0.002	0.103	0.041	0.263	0.002
Guido, 1998[223]	0.373	0.274	0.508	0.000	0.528	0.336	0.829	0.015	0.368	0.185	0.732	0.013	0.070	0.005	0.931	0.046
Guido, 2003[224]	0.187	0.144	0.241	0.000	0.089	0.059	0.133	0.000	0.073	0.025	0.211	0.001	0.083	0.006	1.223	0.063
Mohan, 2007[225]	0.073	0.048	0.111	0.000	0.156	0.079	0.310	0.001	0.118	0.045	0.310	0.002	0.127	0.025	0.652	0.023
Hamada, 2002[226]	0.064	0.056	0.074	0.000	0.111	0.090	0.137	0.000	0.113	0.090	0.142	0.000	0.138	0.104	0.183	0.000
Shin, 2005[227]	0.102	0.066	0.158	0.000	0.072	0.047	0.112	0.000	0.083	0.047	0.145	0.000	0.106	0.048	0.237	0.001
Giordano, 2003[228]	0.106	0.062	0.181	0.000	0.078	0.030	0.208	0.001	0.383	0.063	2.331	0.230	0.097	0.007	1.437	0.077
Kamar, 2005[229]	0.191	0.121	0.301	0.000	0.132	0.076	0.228	0.000	0.214	0.090	0.509	0.006	0.103	0.022	0.473	0.012
Toz, 2002[152]	0.666	0.422	1.052	0.071	0.532	0.318	0.888	0.025	0.431	0.207	0.900	0.032	0.283	0.062	1.289	0.085
Varaut, 2005[153]	0.105	0.073	0.153	0.000	0.087	0.055	0.139	0.000	0.081	0.038	0.171	0.000	0.058	0.012	0.270	0.005

†F0→F1, F1→F2, F2→F3, F3→F4: stage-specific transition probabilities.
LB, lower bound estimates; UB, upper bound estimates.

Table 4.2.4. Meta-regression* of covariates associated with liver fibrosis progression in chronic hepatitis C virus infection

	F0→F1†				F1→F2†				F2→F3†				F3→F4†			
Covariates	β	SE	P-value	RR	β	SE	P-value	RR	β	SE	P-value	RR	β	SE	P-value	RR
Intercept	-1.531	0.655	0.022		-2.281	0.819	0.007		-1.137	0.592	0.058		-2.218	0.762	0.005	
Study design																
Cross-sectional (ref)	---	---	---	1.00	---	---	---	1.00	---	---	---	1.00	---	---	---	1.00
Retrospective-Prospective	-0.192	0.174	0.272	0.83	0.246	0.219	0.263	1.28	0.139	0.159	0.386	1.15	0.201	0.201	0.319	1.22
Setting																
Clinical (ref)	---	---	---	1.00	---	---	---	1.00	---	---	---	1.00	---	---	---	1.00
Non-clinical	-0.421	0.208	0.046	0.66	-0.231	0.261	0.380	0.79	0.088	0.188	0.643	1.09	-0.433	0.241	0.077	0.65
Study population																
Liver clinic (ref)	---	---	---	1.00	---	---	---	1.00	---	---	---	1.00	---	---	---	1.00
Blood donors	0.299	0.370	0.422	1.35	-0.457	0.476	0.339	0.63	-0.124	0.382	0.747	0.88	0.044	0.473	0.927	1.04
Community	0.751	0.297	0.013	2.12	0.340	0.372	0.362	1.40	0.129	0.261	0.622	1.14	0.809	0.322	0.014	2.25
Dialysis patients	-0.081	0.194	0.676	0.92	-0.150	0.242	0.539	0.86	0.076	0.214	0.723	1.08	0.186	0.280	0.509	1.20
Females	0.311	0.371	0.403	1.36	0.132	0.460	0.775	1.14	-0.385	0.332	0.249	0.68	-0.163	0.428	0.703	0.85
Injecting drug users	0.040	0.324	0.902	1.04	-0.039	0.404	0.923	0.96	-0.164	0.295	0.581	0.85	0.404	0.381	0.293	1.50
Pediatric population	-0.175	0.504	0.728	0.84	1.787	0.626	0.005	5.97	0.111	0.461	0.811	1.12	-0.746	0.619	0.232	0.47
Post-transfusion	0.395	0.421	0.351	1.48	1.116	0.523	0.036	3.05	0.117	0.363	0.748	1.12	-0.471	0.442	0.290	0.62
Renal transplant recipients	-0.312	0.232	0.182	0.73	0.238	0.293	0.420	1.27	0.111	0.247	0.654	1.12	-0.395	0.383	0.305	0.67
Publication year																
Before 2000 (ref)	---	---	---	1.00	---	---	---	1.00	---	---	---	1.00	---	---	---	1.00
2000 and after	0.076	0.145	0.599	1.08	0.033	0.182	0.857	1.03	-0.109	0.133	0.413	0.90	-0.257	0.160	0.113	0.77
Gender – male‡	0.810	0.470	0.088	2.25	0.359	0.579	0.537	1.43	0.052	0.425	0.903	1.05	0.278	0.544	0.611	1.32
Age at HCV infection	0.003	0.013	0.817	1.00	0.053	0.016	0.002	1.05	0.016	0.012	0.183	1.02	0.001	0.014	0.940	1.00
Duration of infection	-0.083	0.011	<0.0001	0.92	-0.039	0.014	0.006	0.96	-0.051	0.010	<0.0001	0.95	-0.037	0.013	0.004	0.96
Injecting drug use‡	-0.077	0.281	0.785	0.93	0.093	0.349	0.790	1.10	-0.389	0.252	0.127	0.68	0.164	0.315	0.603	1.18
Blood transfusion‡	0.060	0.335	0.859	1.06	-0.622	0.418	0.140	0.54	0.113	0.298	0.704	1.12	1.171	0.369	0.002	3.23
Excess alcohol use‡	-0.241	0.315	0.447	0.79	1.075	0.390	0.007	2.93	0.447	0.280	0.114	1.56	-0.316	0.349	0.367	0.73
HIV positive‡	0.378	1.154	0.744	1.46	-0.131	1.434	0.972	0.88	-0.641	1.049	0.542	0.53	0.040	1.391	0.977	1.04
HCV RNA positive‡	0.037	0.406	0.928	1.04	-1.238	0.509	0.017	0.29	-0.228	0.383	0.554	0.80	0.718	0.516	0.168	2.05
Genotype – 1‡	0.455	0.273	0.098	1.58	-0.101	0.340	0.768	0.90	-0.303	0.233	0.198	0.74	-0.538	0.285	0.063	0.58

β, coefficient; SE, standard error; RR, relative risk; HCV, hepatitis C virus; RNA, ribonucleic acid.

*Linear mixed model – maximum likelihood method.

†Log stage-specific transition probabilities. ‡Proportion.

Table 4.2.5. Summary annual stage-specific transition probabilities – random effects model: Literature- and post-transfusion claimant cohort-derived for use in 2010 model

Data source	F0→F1	F1→F2	F2→F3	F3→F4
PTCC only*	0.029 (0.025-0.032)	0.118 (0.080-0.145)	0.137 (0.079-0.175)	0.103 (0.042-0.130)
Literature and PTCC†	0.059 (0.046-0.076)	0.096 (0.074-0.125)	0.147 (0.118-0.184)	0.167 (0.121-0.228)
Calibrated according to PTCC validation (observed and projected)	0.057(0.044,0.073)	0.145(0.112,0.189)	0.150(0.120,0.188)	0.120(0.087,0.164)

*Estimated based on data in Table 5.4.2, a non-hemophilic cohort without HIV and had first transfusion between 1986 and 1990; Fibrosis stage 1cases (Compensation Level 3) distributed to F1 and F2.
†Literature and PTCC cohort transition probabilities combined.
PTCC, post-transfusion claimant cohort.

Table 4.2.6. Annual progression rates for chronic hepatitis C virus infection by age and gender (Salomon *et al.*[1])

Age (years)	Male	Female
<20	0.00-0.05	0.00-0.04
20-29	0.00-0.10	0.00-0.08
30-49	0.03-0.15	0.01-0.12
50-59	0.05-0.20	0.01-0.16
60-69	0.10-0.40	0.02-0.32
≥70	0.20-0.50	0.04-0.40

Table 4.3.1.1. Effectiveness of pegylated interferon and ribavirin therapy

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Modality	Treatment duration	Sustained virological response rate
North American-based studies: HCV monoinfection							
Heathcote, 2000[62]	RCT	271	F3-F4; treatment naive	1=56% Non-1=44%	PEG-IFN alfa-2a 180 μg No ribavirin (n=87)	48 wks	At 72 wks: Overall 30% Genotype-1: 12% Genotype non-1: 51% Bridging fibrosis: 22% Cirrhosis: 32%
Lindsay, 2001[51]	RCT	1219	F1-F4; treatment naive	1=70% 2/3=27%	PEG-IFN alfa-2b 1.0 μg/kg No ribavirin (n=297)	48 wks	At 72 wks: 25%
					PEG-IFN alfa-2b 1.5 μg/kg No ribavirin (n=304)	48 wks	At 72 wks: 23%
Reddy, 2001[230]	RCT	159	F0-F3; treatment naive	1=74% Non-1=24%	PEG-IFN alfa-2a 180 μg No ribavirin (n=45)	48 wks	At 72 wks: 36%
Fried, 2002[65]	RCT	1121	F0-F4; treatment naive	1=65% Non-1=34%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=453)	48 wks	At 72 wks: Overall 56% Genoypte-1: 46% Genotype-2/3: 76% Genotype-4: 77% Cirrhosis: 43%
Sulkowski, 2002[231]	RCT	20	F1-F4		PEG-IFN alfa-2a 180 μg plus ribavirin (n=20)	24 wks	At 48 wks: 50%
Jeffers, 2004[232]	Non-RCT	106	F0-F4; 78 Blacks	1-100%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=106)	48 wks	African-Americans: 26% Caucasians: 39%
Krawitt, 2006[233]	RCT	314	F0-F4; treatment naive	1=73% 2/3=27%	PEG-IFN alfa-2b 50 μg plus ribavirin (n=152)	48 wks	At 72 wks: Low dose: Overall: 33% Genotype-1: 24% Genotype-2/3: 56% F0 37%; Fibrosis 34%; Cirrhosis: 23%
					PEG-IFN alfa-2b 100/150 μg plus ribavirin (n=162)	48 wks	Overall: 45% Genotype-1: 38% Genotype-2/3: 65% F0: 55%; Fibrosis: 42%; Cirrhosis: 29%

Table 4.3.1.1. Effectiveness of pegylated interferon and ribavirin therapy (continued)

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Modality	Treatment duration	Sustained virological response rate
Gish, 2007[234]	RCT	191	Compensated chronic HCV; treatment naive	1/4/indeterm =74% 2/3=26%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=45)	24/48 wks	Overall: 44% Genotype-1/4/indet: 35% Genotype-2/3: 73%
					PEG-IFN alfa-2a 180 μg plus taribavirin (n=135)	24/48 wks	Overall: 30% Genotype-1/4/indet: 21% Genotype-2/3: 56%
Jacobson, 2007[235]	RCT	387	F0-F4; treatment naïve; African Americans; community-based	1=100%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin: flat dose 800mg/d (n=188)	48 wks	At 72 wks: Overall: 10% <65kg: 11%; ≥65 kg: 10% F0-F2: 9%; F3-F4: 13%
					PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin: weight-based dose 800-1400 mg/d (n=174)	48 wks	Overall: 21% <65 kg: 19%; ≥65 kg: 21% F0-F2: 21%; F3-F4: 20%
North American-based studies: HCV monoinfection – non-responders/relapsers							
Shiffman, 2004[236]	RCT	604	F3-F4; non-responder to PEG-IFN+RBV	1=89% Non-1=10%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=604)	48 wks	At 72 wks: 18%
Jacobson, 2005[237]	RCT	321	Non-responders to IFN+RBV or IFN Relapsers to IFN+RBV	1=89% 2/3=8% Other=3%	PEG-IFN alfa-2b 1.0 μg/kg plus ribavirin (n=161)	48 wks	At 72 wks: Overall 16%
					PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=160)		At 72 wks: Overall: 18% Genotype-1: 14% Genotype-2/3: 31%
Mathew, 2006[238]	RCT	152	Non-responders/ relapsers	1=84% Non-1=9%	PEG-IFN alfa-2b 0.5 μg/kg plus ribavirin (n=80)	24/48 wks	Overall: 17%; Genotype-1 15%; Genotype non-1 35% Low dose: Overall: 12% Genotype-1: 12%; Genotype non-1: 33%
					PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=72)	24/48 wks	Overall: 21% Genotype-1: 19% Genotype non-1: 38%
North American-based studies: HIV/HCV coinfection							
Chung , 2004[68]	RCT	133	HIV/HCV coinfection; F0-F4; treatment naive	1=78%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=66)	48 wks	At 72 wks: Overall 27% Genotype-1: 14% Genotype non-1: 73%

Table 4.3.1.1. Effectiveness of pegylated interferon and ribavirin therapy (continued)

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Modality	Treatment duration	Sustained virological response rate
Torriani, 2004[70]	RCT	860	HIV/HCV co-infection	1=61% Non-1=38%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=289)	48 wks	At 72 wks: 40% Genotype-1: 29% Genotype-2/3: 62%
Khalili, 2005[239]	RCT	154	HIV/HCV coinfection; HCV treatment naive	1=76% 1=10% 3=12% 4=2%	PEG-IFN alfa-2a 180 μg no ribavirin (early virological response [EVR], n=55)	48 wks	At 72 wks: 35%
					PEG-IFN alfa-2a 180 μg plus ribavirin (no EVR, n=37)	48 wks	At 72 wks: 5%
International studies: HCV monoinfection							
Zeuzem, 2000[240]	RCT	531	F1-F4	1=63% 2/3=34%	PEG-IFN alfa-2a 180 μg No ribavirin (n=223)	48 wks	At 72 wks: 39%
Manns, 2001[52]	RCT	1530	F0-F4; treatment naive	1=68% 2/3=29%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=511)	48 wks	At 72 wks: Overall 54% Genotype-1: 42% Genotype-2/3: 82% Genotype-4/5/6: 50% F0-F1: 57% F3-F4: 44%
Bosques-Padilla, 2003[241]	RCT	32	F1-F4		PEG-IFN alfa-2a 180 μg plus ribavirin (n=14)	48 wks	At 72 wks: 50%
Alfaleh, 2004[242]	RCT	96	F1-F4; treatment naive	1=19% 2/3=5% 4=61%	PEG-IFN alfa-2b 100 μg plus ribavirin (n=48)	48 wks	At 72 wks: Overall: 44% Genotype 4: 43%
Dalgard, 2004[243]	Non-RCT	122	F0-F4; treatment naive	2=24% 3=76%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin	14 w=95 24 w=27	Overall: 82% At 36 weeks: 90% At 48 weeks: 56%
Hadziyannis, 2004 [66]	RCT	1311	F1-F4; treatment naïve	1=58% Non-1=42%	PEG-IFN alfa-2a 180 μg plus ribavirin	24 w=502 48 w=809	At 72 wks: Overall 63%; Genotype-1 52% ; F1-F2 57%; F3-F4 41% At 48 wks: Genotype-2/3 84%; F1-F2 84%; F3-F4 74%
Pockros, 2004[244]	RCT	639	F1-F4	1=67% 2/3=32%	PEG-IFN alfa-2a 180 μg No ribavirin (n=210)	48 wks	At 2 wks: 28%

Table 4.3.1.1. Effectiveness of pegylated interferon and ribavirin therapy (continued)

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Modality	Treatment duration	Sustained virological response rate
Zeuzem, 2004[245]	Non-RCT	224	F0-F4; treatment naive	2=19% 3=81%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=224)	24 wks	At 48 wks: Overall: 81% Genotype-2: 93% Genotype-3: 79% F0-F1: 84% F3-F4: 78%
Zeuzem, 2004[246]	RCT	440	Ishak F0-F1 (66%); F2 (21%); F3-F4 (12%); >F4 (0%); treatment naïve; persistently normal ALT levels	1=68% Non-1=32%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=212)	24 wks	At 72 wks: Overall: 30% Genotype-1: 13% Genotype-2/3: 72% Genotype-4: 13%
			Ishak F0-F1 (69%); F2 (20%); F3-F4 (9%); >F4 (<1%); treatment naïve; persistently normal ALT levels	1=67% Non-1=33%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=210)	48 wks	At 72 wks: Overall: 52% Genotype-1: 40% Genotype-2/3: 78% Genotype-4: 56%
Derbala, 2005[247]	Non-RCT	70	F1-F4	4=100%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=30)	48 wks	At 72 wks: 33%
Lee, 2005[248]	RCT	153	F0-F4	1=50% 2=50%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=76)	24 wks	At 48 wks: Overall: 67% Genotype-1: 66% Genotype non-1: 68%
Legrand-Abravanel, 2005[249]	Non-RCT	84		1=33% 2/3=33% 4=33%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=28)	24/48 wks	At 72 wks: Genotype-1: 33% Genotype-4: 32% At 48 weeks: Genotype-2/3: 62%
Mangia, 2005[250]	RCT	362	F0-F4; treatment naive	1=55% 2=30% 3=15%	PEG-IFN alfa-2a 180 μg No ribavirin (n=121)	48 wks	At 72 wks: Overall: 65% Genotype-1/4: 55% Genotype-2/3: 78% F0/F1: 67% F2-F4: 64%

Table 4.3.1.1. Effectiveness of pegylated interferon and ribavirin therapy (continued)

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Modality	Treatment duration	Sustained virological response rate
von Wagner, 2005[251]	RCT	153	F0-F4; treatment naive	2=26% 3=74%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=82)	24 wks	At 48 wks: With rapid virological response: 81% Without rapid virological response: 36%
Berg, 2006[252]	RCT	455	F0-F4; treatment naive	1=100%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=455)	48 w=230 72 w=225	At 72 wks: 53% At 96 wks: 54%
Bronowicki, 2006[253]	RCT	516	F1-F4; treatment naive	1-100%	PEG-IFN alfa-2a 180 μg only continued at 24 weeks (n=176)	48 wks	At 72 wks: 53%
					PEG-IFN alfa-2a 180 μg plus ribavirin continued (n=173)	48 wks	At 72 wks: 68%
Derbala, 2006[254]	RCT	73	F0-F4; treatment naive	4=100%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=38)	48 wks	At 72 wks: 66%
Helbling, 2006[255]	RCT	124	Ishak F4-F6; treatment naive	1=44% 2=15% 3=34% 4=6%	PEG-IFN alfa-2a 180 μg plus ribavirin: low dose (n=60)	48 wks	At 72 wks: Genotype-1/4: Overall 32% Low dose RBV 32% Genotype-2/3: Overall 58% Low dose RBV 45% Ishak F4: 33% Ishak F5-F6: 41%
					PEG-IFN alfa-2a 180 μg plus ribavirin: standard dose (n=64)	48 wks	Genotype-1/4: 32% Genotype-2/3: 72% Ishak F4: 58% Ishak F5-F6: 42%
Meyer-Wyss, 2006[256]	RCT	227	F0-F2; treatment naive	1=51% 2=11% 3=31% 4=7%	PEG-IFN alfa-2b 1.0 μg/kg plus ribavirin (n=113)	24/48 wks	At 72 wks: Genotype-1/4: 38% Genotype-2/3: 72%
					PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=106)	24/48 wks	At 72 wks: Genotype-1/4: 39% Genotype-2/3: 81%
Mimidis, 2006[257]	RCT	176	Treatment naive	1=43% 2=9% 3=43% 4=6%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=176)	48 wks	At 72 wks: Overall: 71% Genotype-1: 47% Genotype-2/3: 94% Genotype-4: 91%

Table 4.3.1.1. Effectiveness of pegylated interferon and ribavirin therapy (continued)

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Modality	Treatment duration	Sustained virological response rate
Zeuzem, 2006[258]	Non-RCT	235	F1-F4; treatment naïve; low pre-treatment viremia ≤600,000 IU/mL	1=100%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=235)	24 wks	At 48 wks: 50%
Di Marco, 2007[259]	RCT	102	F4	1=86% Non-1=14%	PEG-IFN alfa-2b 1.0 μg/kg only (n=102)	52 wks	At 76 wks: Overall:10% Genotype-1/4: 10% Genotype-2/3: 33%
Yu, 2007[260]	RCT	150	F0-F4; treatment naive	2=100%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=50)	16 wks	At 40 wks: 94%
					PEG-IFN alfa-2a 180 μg plus ribavirin (n=100)	24 wks	At 48 wks: 95%
Mangia, 2008[261]	RCT	694	F0-F4, treatment naive	1=100%	PEG-IFN alfa-2a 180 μg plus ribavirin OR PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin	24/48 wks	At 72 weeks: 45% EVR wk 4: 87% EVR wk 8: 70% EVR wk 12: 38%
					Individualized duration based on the time when HCV RNA first became negative		At 72 weeks: 49% EVR wk 4: 77% EVR wk 8: 72% EVR wk 12: 64%
International studies: HCV monoinfection – non-responders/relapsers							
August-Jorg, 2003[262]	RCT	37	F1-F4; monotherapy relapsers	1=24% Non-1=76%	Interferon alfa-2b 3x3MIU plus ribavirin	24 w=19 48 w=18	At 48 wks: 53% At 72 wks: 72%
Taliani, 2006[263]	Non-RCT	141	Non-responders to IFN+RBV	1/4=85% 2/3=14%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=141)	48 wks	At 72 wks: Overall: 20% Genotype-1: 19% Genotype-2: 57% Genotype-3: 15% Genotype-4: 10%
Basso, 2007[264]	Non-RCT	242	78 combination therapy relapsers	1/4=64% 2/3=28%	PEG-IFN alfa-2b 1.0 μg/kg plus ribavirin (n=78)	24/48 wks	At 72 wks: Overall: 41% Genotype-1/4: 20% Genotype-2/3: 79%
Fernandez-Rodriguez, 2010[71]	Multicenter retrospective cohort study	568	F4; 22.2% non-responders 77.8% treatment naive	1=70.1% Non-1=29%	PEG- IFN alfa-2a or 2b combined with bodyweight-adjusted dose of RBV	Genotype 2/3: 24 wks Genotype 1: 48 wks	All: 30.6% Genotype 1: 24.4% Genotype non-1: 54.9% Non-responders: 4.9% Naïve: 25.7%

Table 4.3.1.1. Effectiveness of pegylated interferon and ribavirin therapy (continued)

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Modality	Treatment duration	Sustained virological response rate
International studies: HIV/HCV coinfection							
Carrat, 2004[67]	RCT	412	HIV/HCV coinfection; F1-F4	1=48% 2/3=38% 4=13%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=205)	48 wks	At 72 wks: Overall: 27% Genotype-1/4: 17% Genotype-2/3/5: 44%
Crespo, 2007[265]	RCT	121	HIV/HCV coinfection	1=48% 2=2% 3=33% 4=17%	PEG-IFN plus ribavirin (n=60)	48 wks	At 72 weeks: 55%
Laguno, 2004[69]	RCT	95	HIV/HCV coinfection; F0-F4; HCV treatment naive	1=49% 2/3=36% 4=21%	PEG-IFN alfa-2b 100/150 μg plus ribavirin (n=52)	24/48 wks	At 72 wks: Overall: 44% Genotype-1/4: 38% Genotype-2/3: 53% F0-F2: 49% F3-F4: 33%
Cargnel, 2005[266]	RCT	135	HIV/HCV coinfection	1=47% 2=5% 3=44% 4=5%	PEG-IFN alfa-2b 1.5 μg/kg No ribavirin (n=66)	48 wks	At 72 wks: Overall: 9% Genotype-1/4: 9% Genotype-2/3: 9%
				1=41% 2=4% 3=42% 4=13%	PEG-IFN alfa-2b 1.5 μg/kg plus ribavirin (n=69)		Overall: 22% Genotype-1/4: 11% Genotype-2/3: 34%;
Fuster, 2006[267]	RCT	110	HIV/HCV coinfection; no early virological response	1=46% 2/3=40% 4=14%	PEG-IFN alfa-2a 180 μg plus ribavirin (n=110)	24/48 wks	At 72 wks: Overall: 42% Genotype-1: 37% Genotype-2/3: 55% Genotype-4: 20%
Santin, 2006[268]	Non-RCT	60	HIV/HCV coinfection	NA	PEG-IFN alfa-2a 80-150 μg plus ribavirin (n=60)	24/48 wks	Overall: 27%

Table 4.3.1.1. Effectiveness of pegylated interferon and ribavirin therapy (continued)

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Modality	Treatment duration	Sustained virological response rate
Voigt, 2006[269]	Non-RCT	122	HIV/HCV coinfection; HCV treatment naive	1=56% 2=2% 3=30% 4=8%	PEG-IFN alfa-2b 1.5 µg/kg plus ribavirin	24/48 wks	Overall: 25% Genotype-1/4: 18% Genotype-2/3: 44%
					PEG-IFN alfa-2b 1.0 µg/kg plus ribavirin	52 wks	Overall: 22% Genotype-1/4: 13% Genotype-2/3: 83%
Nunez, 2007[270]	Non-RCT	389	HIV/HCV coinfection	1/4=61%	PEG-IFN plus ribavirin (weight-based)	24/48 wks 48/72 wks	Overall: 50% Genotype-1/4: 35% Genotype-2/3: 72%

RCT, randomized controlled trial; PEG-IFN, pegylated interferon; HCV, hepatitis C virus.

Table 4.3.1.2. Effectiveness of pegylated interferon and ribavirin therapy in treatment naïve HCV-infected individuals – studies included in the meta-analysis

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Treatment modality	Sample size of modality group	Treatment duration	Sustained virological response rate
Manns, 2001[52]	RCT	1530	F0-F4; treatment naive	1=68% 2/3=29%	PEG-IFN alfa-2b 1.5 µg/kg plus ribavirin	511	48 wks	At 72 wks: Overall 54% Genotype-1: 42% Genotype-2/3: 82% Genotype-4/5/6: 50% F0-F1: 57% F3-F4: 44%
Fried, 2002[65]	RCT	1121	F0-F4; treatment naive	1=65% Non-1=34%	PEG-IFN alfa-2a 180 µg plus ribavirin	453	48 wks	At 72 wks: Overall 56% Genoypte-1: 46% Genotype-2/3: 76% Genotype-4: 77% Cirrhosis: 43%
Bosques-Padilla, 2003[241]	RCT	32	F1-F4		Peginterferon alfa-2a 180 µg plus ribavirin	14	48 wks	At 72 wks: 50%
Alfaleh, 2004[242]	RCT	96	F1-F4; treatment naive	1=19% 2/3=5% 4=61%	PEG-IFN alfa-2b 100 µg plus ribavirin	48	48 wks	At 72 wks: Overall: 44% Genotype 4: 43%
Hadziyannis, 2004 [66]	RCT	1311	F1-F4; treatment naïve	1=58% Non-1=42%	PEG-IFN alfa-2a 180 µg plus ribavirin (both low and standard dose combined)	1311	24 w=502 48 w=809	At 72 wks: Overall 63%; Genotype-1: 52% ; F1-F2: 57%; F3-F4: 41% At 48 wks: Genotype-2/3 84%; F1-F2 84%; F3-F4 74%
Lee, 2005[248]	RCT	153	F0-F4	1=50% 2=50%	PEG-IFN alfa-2b 1.5 µg/kg plus ribavirin	76	24 wks	At 48 wks: Overall: 67% Genotype-1: 66% Genotype non-1: 68%
Helbling, 2006[255]	RCT	124	Ishak F4-F6; treatment naive	1=44% 2=15% 3=34% 4=6%	PEG-IFN alfa-2a 180 µg plus ribavirin: standard dose	64	48 wks	Genotype-1/4: 32% Genotype-2/3: 72% Ishak F4: 58% Ishak F5-F6: 42%
Krawitt, 2006[233]	RCT	314	F0-F4; treatment naive	1=73% 2/3=27%	PEG-IFN alfa-2b 100/150 µg plus ribavirin	162	48 wks	Overall: 45% Genotype-1: 38% Genotype-2/3: 65% F0: 55%; F1-F3: 42%; Cirrhosis: 29%

Table 4.3.1.2. Effectiveness of pegylated interferon and ribavirin therapy in treatment naïve HCV-infected individuals – studies included in the meta-analysis (continued)

Author and Year	Study design	Sample size	Patient characteristics	Genotype	Treatment modality	Sample size of modality group	Treatment duration	Sustained virological response rate
Mimidis, 2006[257]	RCT	176	Treatment naive	1=43% 2=9% 3=43% 4=6%	PEG-IFN alfa-2b 3.0 µg/kg x 12 wks followed by PEG-IFN alfa-2b 1.5 µg/kg x 36 wks OR PEG-IFN alfa-2b 1.5 µg/kg plus ribavirin	176	48 wks	At 72 wks: Overall: 71% Genotype-1: 47% Genotype-2/3: 94% Genotype-4: 91%
Gish, 2007[234]	RCT	191	Compensated chronic HCV; treatment naive	1/4/indeterm=74% 2/3=26%	PEG-IFN alfa-2a 180 µg plus ribavirin	45	24/48 wks	Overall: 44% Genotype-1/4/indet: 35% Genotype-2/3: 73%
Carrat, 2004[67]	RCT	412	HIV/HCV coinfection; F1-F4	1=48% 2/3=38% 4=13%	PEG-IFN alfa-2b 1.5 µg/kg plus ribavirin	205	48 wks	At 72 wks: Overall: 27% Genotype-1/4: 17% Genotype-2/3/5: 44%
Chung , 2004[68]	RCT	133	HIV/HCV coinfection; F0-F4; treatment naive	1=78%	PEG-IFN alfa-2a 180 µg plus ribavirin	66	48 wks	At 72 wks: Overall 27% Genotype-1: 14% Genotype non-1: 73%
Laguno, 2004[69]	RCT	95	HIV/HCV coinfection; F0-F4; HCV treatment naive	1=49% 2/3=36% 4=21%	PEG-IFN alfa-2b 100/150 µg plus ribavirin	52	24/48 wks	At 72 wks: Overall: 44% Genotype-1/4: 38% Genotype-2/3: 53% F0-F2: 49% F3-F4: 33%
Torriani, 2004[70]	RCT	860	HIV/HCV co-infection	1=61% Non-1=38%	PEG-IFN alfa-2a 180 µg plus ribavirin	289	48 wks	At 72 wks: 40% Genotype-1: 29% Genotype-2/3: 62%
Crespo, 2007[265]	RCT	121	HIV/HCV coinfection	1=48% 2=2% 3=33% 4=17%	PEG-IFN alfa-2b 1.5 µg/kg plus ribavirin	60	48 wks	At 72 weeks: 55% Genotype-1/4: 46% Genotype-2/3: 71%

Table 4.3.1.3. Effectiveness of pegylated interferon and ribavirin therapy in treatment naïve HCV-infected individuals by stage of liver disease – meta-analysis

				Sustained virological response rate	
Reference	Number of RCTs	Patient population	Fibrosis stage	Fixed effects model	Random effects model
[52,65,66,233,234,241,242,248,257]	9	HCV monoinfection	F1-F4	0.57 (0.54-0.59)	0.56 (0.50-0.61)
[52,65-68,70,233,234,241,242,248,257,265]	14	HCV monoinfection + HIV/HCV coinfection	F1-F4	0.51 (0.49-0.54)	0.49 (0.42-0.56)
[52,66,233]	3	HCV monoinfection	F0-F1	0.61 (0.57-0.65)	0.60 (0.52-0.68
[52,65,66,69,233,255]	6	HCV monoinfection + HIV/HCV coinfection	F3-F4	0.452 (0.403-0.501)	0.451 (0.403-0.501)

RCT, randomized controlled trial; PEG-IFN, pegylated interferon; HCV, hepatitis C virus.

Table 4.3.2. Hepatologists reported proportion of patients with hepatitis C receiving antiviral therapy in their clinical practice: findings from the 2001 Canadian hepatologists survey

	Median (95% CI)	Mean (95% CI)	Min	Max
1. What % of all patients are not eligible because of co-existing conditions (eg. depression, heart disease, continuing alcohol and drug abuse).	25.0 (20.0, 32.5)	30.1 (24.3, 35.9)	5	75
2. Overall, what % of **all patients** with hepatitis C do you treat?	40.0 (33.0, 50.2)	43.6 (37.5, 49.7)	10	85
3. What % of patients **with normal enzymes** do you treat?	1.5 (0.0, 5.0)	6.0 (2.9, 9.1)	0	45
4.What % of patients with **mild hepatitis/ nonfibrosis** do you treat?	13.8 (10.0, 30.0)	28.7 (19.2, 38.2)	0	100
5. What % of patients with **moderate-severe hepatitis** with fibrosis do you treat?	80.0 (75.0, 95.0)	76.7 (68.6, 84.8)	12.5	100
6.What % of patients with **well compensated cirrhosis** do you treat?	75.0 (50.0, 90.0)	62.0 (49.9, 74.1)	0	100
7. What % of patients with **decompensated cirrhosis** do you treat?	0.0 (0.0, 0.0)	3.8 (0.4, 7.2)	0	50

Source: Wang *et al*. (2003)[271]. Number of survey participants=38

Table 4.3.3. Risk factors for progression of liver fibrosis

Variable	Category	Sample size	Transition path	Relative risk of progression	Reference
Age	≥40/<40		All paths	1.5	[25]
	>30/≤30	2313		2.3-27.1[†]	[99]
Sex	Male/Female		All paths	1.39	[25]
		2313		1.0-2.0	[99]
				1.08	[76]
Alcohol	<50g/none			1.14	[25]
	≥50g/none			1.34	[25]
	>50g/≤50 g/d			1.3-4.5	[99]
	>50g/≤50 g/d	2313		1.61	[76]
HIV co-infection	Yes/No	157	F4 to ESLD	3.74	[25]
	Yes/No	244	F0 to F4	1.44	[74]
	Yes/No	310	F0 to liver-related death	7.0	[92]
	Yes/No	1816	HIV seroconversion to ESLD/death	7.9 (4.2-15.2)	[272]
		183	HIV seroconversion to liver failure	21.4 (2.6-174.5)	[90]
		157	F0 to ESLD	3.7 (1.3-11.1)	[82]
ALT	≥45/<45	204	All paths	2.10	[45]
				1.23	[76]
HAI	>6			1.22	[76]

ESLD, end-stage liver disease; ALT, alanine aminotransferase; HAI, histological activity index.
[†]Depending on stage of fibrosis.

Table 4.3.4.1. Hemophilia and HIV: Effects on progression of liver disease in HCV-infected patients

	HIV negative hemophilics			HIV positive hemophilics		
Author and Year	Liver-related death/yr (cumulative rate)	ESLD/Liver decompensation. & death/yr (cum rate)	FPR (METAVIR units/yr)	Liver-related death/yr (cumulative rate)	ESLD/Liver decompensation. & death/yr (cum rate)	FPR (METAVIR units/yr)
Telfer, 1994[90]		0.0054 (20 yr: 10.8%)*				
Darby, 1997[105§]	0.0009 (25 yr: 2.2%)			0.0068 (25 yr: 17.1%)		
Benhamou,1999[74†]			0.106			0.153
Yee, 2000[92]	0.0023 (13.3 yr: 3.0%)			0.0158 (13.3 yr: 21.0%)		
Ragni, 2001[82]		0.0041 (24 yr: 9.7%)			0.0054 (24year: 12.9%)	
Goedert, 2002[273]		0.0088 (16 yr: 14.0%)				
Arnold, 2007[106]	0.0005 (21 yr: 1.1%)			0.0042 (21 yr: 8.8%)		
Krahn, 1999[274]	0.0021 (20 yr: 4.2%)	0.0050 (20 yr: 9.6%)				

*May include some patients with HIV; HIV+ in 40% in the cohort.

[§]HIV negative hemophilics: all ages, 1.4%; <25 yr first recorded exposure to HCV-risk products, 0.1%; 25-44 yr, 2.2%; 45+ yr, 14.3%; HIV positive hemophilics:all ages, 6.5%, <25 yr, 3.8%; 25-44 yr, 17.1%; 45+ yr, 18.7%.

[†]Rate ratio of fibrosis progression (HIV+/HIV-) =1.44

HCV, hepatitis C virus; ESLD, end-stage liver disease; FPR, fibrosis progression rate.

Table 4.3.4.2. Relative risk of death in hemophilic patients with and without HIV infection

Author and Year	HIV negative hemophilics					HIVpositive hemophilics			Relative risk	
	Sample size	Person years	Event	Death (%)	Mean follow-up (years)	Sample size	Person-years	Death (%)	RR (95% CI)	Adj RR (95% CI)
Darby, 1997[105‡]	3647	25529.0	All cause	200 (5.5)	7.0	1218	8526.0	401 (32.9)	6.0 (5.1-7.1)	
Darby, 1997[105‡]	3647	25529.0	Non-liver	170 (4.7)	7.0	1218	8526.0	351 (28.8)	6.2 (5.1-7.4)	
Soucie, 2000[103]	1366	3551.6	All cause	25 (1.8)	2.6	781	2030.6	186 (23.8)	13.0 (8.6-19.8)	4.7 (3.0-7.2)[§]
Yee, 2000[92]	185	2460.5	All cause	16 (8.6)	13.3	125	1662.5	71 (56.8)	6.6 (3.8-11.3)	19.5 (9.2-41.1)*
Yee, 2000[92]	185	2460.5	Non-liver	10 (5.4)	13.3	125	1662.5	51 (40.8)	7.5 (3.8-14.9)	
Ragni, 2001[82]	72	1728.0	All cause	21 (29.2)	24.0	85	2040.0	62 (72.9)		3.8 (1.2-12.2)[†]
Arnold, 2007[106]	712	14952.0	All cause	58 (8.1)	21.0	444	9324.0	207 (46.6)	5.7 (4.3-7.7)	
Arnold, 2007[106]	712	14952.0	Non-liver	50 (7.0)	21.0	444	9324.0	168 (37.8)	5.4 (3.9-7.4)	
Darby, 2004[275]	6004	126084.0	All cause	848 (14.1)	21.0	1246	26166	802 (64.4)	4.6 (4.1-5.0)	
Goedert, 2002[273]	624	9984.0	Non-liver	39 (6.2)	16.0	1192	19072.0	536 (45.0)	7.2 (5.2-10.0)	
Pooled RR – All cause										
Fixed effects model									5.14 (4.75-5.56)	5.64 (5.60-5.68)
Random effects model									6.38 (4.81-8.47)	9.33 (2.85-15.82)
Pooled RR – Non-liver										
Fixed/random effects model									6.24 (5.43-7.18)	

[‡]Based on 1985-1992 data, combined mild/moderate and severe hemophilia.
[†]Adjusted for age at HCV infection, HBsAg status, and excess alcohol consumption.
*Adjusted for age at HCV infection, genotype-1.
[§]Adjusted for age, race, state of residence, hemophilia type, disease severity, insurance type, presence of inhibitor, liver disease, AIDS, hemophilia care source.

Table 4.4.1. Development of hepatocellular carcinoma in HCV-infected patients with cirrhosis

Study	Sample size	Mean follow-up (years)	Event	Person-years	Event rate (%)	Annual rate
Ikeda, 1993[276]	349	5.8	95	2024.2	27.3	0.047
Imberti, 1993[277§]	228	3.7	43	843.6	18.9	0.051
Mandelli, 1994[278§]	396	4.2	57	1663.2	14.3	0.034
Nishiguchi, 1995[279]	45	5.5	17	247.5	38.0	0.069
Takano, 1995[280]	124	6.1	5	756.4	4.0	0.007
Mazello, 1996[281]	92	2.8	9	260.7	9.8	0.035
Bruno, 1997[282‡]	163	5.3	22	863.9	13.3	0.025
Fattovich, 1997[120‡]	384	5.1	29	1958.4	7.6	0.015
Gentilini, 1997[283§]	405	8.0	32	3240.0	7.9	0.010
Tsai, 1997[284§]	400	3.0	80	1185.0	20.0	0.068
Benvegnu, 1998[285]	77	6.0	20	458.2	26.0	0.044
del Olmo, 1998[122]	967	5.0	64	3048.0	6.6	0.021
Gordon, 1998[111]	189	4.0	16	756.0	8.5	0.021
Niederau, 1998[286]	141	4.0	13	588.0	9.2	0.022
Serfaty, 1998[118]	103	3.0	11	343.0	10.7	0.032
Chairamonte, 1999[287]	166	5.5	42	913.0	25.3	0.046
Gramenzi, 1999[288]	72	4.8	19	348.0	26.4	0.055
Hu, 1999[97‡]	112	4.5	11	504.0	9.5	0.021
Valla, 1999[289‡]	49	3.1	9	150.8	18.4	0.060
Degos, 2000 [20‡]	416	5.0	60	2080.0	14.7	0.029
Fattovich, 2002[290]	136	6.8	23	924.8	16.9	0.025
Mazziotti, 2002[291]	104	4.7	20	488.8	19.2	0.041
Planas, 2004[292†]	200	2.8	33	560.0	16.5	0.059
Sangiovanni, 2006[22‡]	171	9.5	60	1624.5	35.1	0.037
Bruno, 2007[293±]	69	6.0	9	414.0	13.0	0.022
Bruno, 2007[‡]	163	10.7	55	1744.1	33.7	0.032
Mallet, 2008[‡]	96	9.8[¶]	17	944.0	17.7	0.018

Bruno, 2009[‡]	352	14.4	109	5068.8	0.310	0.022
Asahina, 2010[‡]	102	7.5	35	765.0	34.5	0.046
Cardoso, 2010[‡][‖]	307	3.8	46	1164.7	15.0	0.039
Pooled annual rate*						
Fixed effects model						0.022 (0.020-0.024)
Random effects model						0.033 (0.027-0.038)
Pooled annual rate* (excluding studies[‡] where individuals received antiviral therapy)						
Fixed effects model						0.021 (0.019-0.023)
Random effects model						0.035 (0.027-0.043)

[§]Includes HCV antibody negative individuals.
[‡]Includes individuals who had received antiviral therapy.
[†]Patients with HCV-related decompensated cirrhosis.
[±]HIV/HCV coinfected patients; 3 positive for both HCV and HBV.
[‖]Includes HCV-infected individuals with bridging fibrosis or cirrhosis.
[¶]Median follow-up.
*Weighted by sample size.
HCV, hepatitis C virus.

Table 4.5.1. Excess mortality: Comparing rate ratios of post-transfusion all-cause mortality to general population mortality, by age group and years elapsed since blood transfusion

	Age-specific mortality ratio					
	Male			Female		
Years after transfusion	<40	40-64	65-	<40	40-64	65-
Proportion	0.0971	0.1372	0.2116	0.1044	0.1891	0.2607
--1	46.178	25.890	5.694	108.267	46.995	9.754
1--2	46.699	3.771	2.464	106.371	6.866	4.138
2--10	1.018	1.920	1.620	2.072	3.481	2.527
10--	1.000	1.000	1.000	1.000	1.000	1.000

Note: excess mortality estimates derived from Vamvakas *et. al.* [16,17]

Table 4.5.2. Other parameters used in the prediction model

Age and sex-related mortality, 1992 (used only for validation, not projection)

Age	Female	Male	Age	Female	Male
0	0.00593	0.00707	50	0.0027	0.00452
1	0.00041	0.00054	51	0.00294	0.00497
2	0.00029	0.00041	52	0.0032	0.00555
3	0.00022	0.00032	53	0.00353	0.00621
4	0.0002	0.00027	54	0.00391	0.00686
5	0.0002	0.00025	55	0.00432	0.00753
6	0.00019	0.00022	56	0.00478	0.00835
7	0.00016	0.00018	57	0.00526	0.0093
8	0.00014	0.00017	58	0.00578	0.01038
9	0.00013	0.00017	59	0.00634	0.01152
10	0.00013	0.00018	60	0.00692	0.01276
11	0.00014	0.0002	61	0.00756	0.01422
12	0.00015	0.00024	62	0.00826	0.01581
13	0.00018	0.0003	63	0.00902	0.01747
14	0.00023	0.00038	64	0.00988	0.0192
15	0.0003	0.00053	65	0.01089	0.02105
16	0.00038	0.00074	66	0.01204	0.023
17	0.00041	0.00098	67	0.01328	0.02511
18	0.00041	0.0012	68	0.01456	0.02735
19	0.00039	0.00135	69	0.01592	0.02975
20	0.00038	0.00139	70	0.01737	0.03225
21	0.00037	0.00132	71	0.01895	0.03514
22	0.00036	0.00125	72	0.02082	0.03876
23	0.00037	0.00121	73	0.02305	0.04307
24	0.00038	0.0012	74	0.0256	0.04776
25	0.0004	0.00122	75	0.02848	0.05248
26	0.00042	0.00126	76	0.03166	0.05723
27	0.00046	0.00128	77	0.03515	0.06224
28	0.0005	0.00128	78	0.03901	0.06756
29	0.00052	0.00129	79	0.04323	0.07343
30	0.00053	0.0013	80	0.04779	0.08016
31	0.00054	0.00132	81	0.05299	0.088
32	0.00054	0.00136	82	0.05908	0.09693
33	0.00055	0.00141	83	0.06608	0.10659
34	0.00061	0.00148	84	0.07383	0.11657
35	0.00069	0.00152	85	0.08224	0.12679
36	0.00074	0.00152	86	0.09134	0.13748
37	0.00078	0.00158	87	0.1014	0.14883
38	0.00086	0.0017	88	0.11285	0.16078
39	0.00098	0.0018	89	0.12603	0.17305
40	0.0011	0.00189	90	0.14078	0.18513
41	0.00119	0.00199	91	0.15625	0.1967
42	0.00126	0.00214	92	0.17164	0.20775
43	0.00136	0.00231	93	0.18639	0.21843
44	0.00147	0.00254	94	0.20015	0.22877
45	0.0016	0.00284	95	0.21287	0.23869
46	0.00179	0.00315	96	0.2246	0.24783
47	0.00204	0.00348	97	0.23545	0.2558
48	0.00229	0.00385	98	0.24561	0.26246
49	0.00251	0.00419	99	0.2551	0.26783

Age distribution of the infected, as estimated from the per-unit transfusion risk

Age	%
0-	0.0176
5-	0.0107
10-	0.0192
15-	0.0254
20-	0.0322
25-	0.0403
30-	0.0268
35-	0.0292
40-	0.0391
45-	0.0481
50-	0.0644
55-	0.0754
60-	0.0993
65-	0.176
70-	0.1199
75-	0.0924
80-	0.0693
85-	0.0079
90-	0.0068

Distribution of year of Exposure

Year	%
1986	0.287
1987	0.247
1988	0.218
1989	0.194
1990	0.054

Gender distribution

Sex	%
Male	44.59
Female	55.41

Table 4.5.3. Age- and sex-related mortality, Canada, 2000-2002 data used for future projections

Age (yr)	Female	Male	Age (yr)	Female	Male
0	0.00467	0.00577	55	0.00372	0.0059
1	0.00035	0.00035	56	0.0041	0.00654
2	0.0002	0.00021	57	0.00451	0.00726
3	0.00015	0.00021	58	0.00494	0.00805
4	0.00012	0.0002	59	0.00538	0.0089
5	0.0001	0.00017	60	0.00587	0.00982
6	0.00008	0.00013	61	0.00641	0.01085
7	0.00007	0.00009	62	0.00704	0.01198
8	0.00007	0.00008	63	0.00774	0.01321
9	0.00007	0.00008	64	0.0085	0.01451
10	0.00009	0.0001	65	0.00933	0.01593
11	0.00009	0.0001	66	0.01026	0.01752
12	0.00013	0.00015	67	0.01131	0.0193
13	0.00016	0.00023	68	0.01243	0.02124
14	0.0002	0.00034	69	0.01362	0.02329
15	0.00024	0.00046	70	0.01493	0.02555
16	0.00028	0.00057	71	0.01645	0.0281
17	0.00031	0.00066	72	0.01823	0.03104
18	0.00033	0.00072	73	0.02019	0.03429
19	0.00034	0.00078	74	0.0223	0.03779
20	0.00034	0.00082	75	0.02467	0.04165
21	0.00034	0.00085	76	0.02742	0.04599
22	0.00034	0.00087	77	0.03066	0.05091
23	0.00033	0.00087	78	0.03424	0.05631
24	0.00033	0.00085	79	0.03807	0.0621
25	0.00033	0.00083	80	0.0424	0.06846
26	0.00033	0.00081	81	0.04748	0.07555
27	0.00033	0.0008	82	0.05354	0.08353
28	0.00035	0.00082	83	0.06068	0.09214
29	0.00037	0.00084	84	0.06872	0.10129
30	0.00039	0.00088	85	0.07755	0.11135
31	0.00042	0.00091	86	0.08703	0.12268
32	0.00046	0.00096	87	0.09704	0.13566
33	0.0005	0.001	88	0.10767	0.15005
34	0.00055	0.00105	89	0.11899	0.16558
35	0.00061	0.0011	90	0.13088	0.18264
36	0.00067	0.00116	91	0.14322	0.2016
37	0.00073	0.00123	92	0.15588	0.22283
38	0.00079	0.00132	93	0.17087	0.22086
39	0.00085	0.00141	94	0.1868	0.23867
40	0.00092	0.00152	95	0.20376	0.25754
41	0.00099	0.00164	96	0.22177	0.27751
42	0.00109	0.00178	97	0.24083	0.29858
43	0.0012	0.00195	98	0.26094	0.32077
44	0.00132	0.00213	99	0.28209	0.34406
45	0.00145	0.00233	100	0.30425	0.36846
46	0.0016	0.00255	101	0.3274	0.39396
47	0.00176	0.00279	102	0.35151	0.42053
48	0.00193	0.00304	103	0.37651	0.44815
49	0.0021	0.00331	104	0.40237	0.47678
50	0.00229	0.0036	105	0.42902	0.50637
51	0.00251	0.00394	106	0.45638	0.53687
52	0.00276	0.00434	107	0.48439	0.56822
53	0.00305	0.00481	108	0.51296	0.60036
54	0.00337	0.00533	109	0.542	0.6332

Source: Statistics Canada - Catalogue No. 84-537-XIE[294]

Table 5.3.1. Baseline clinical and serological features of post-transfusion claimant cohort, 2010

Characteristics	Male		Female		Total	
	N=3230	61.8%	N=1994	38.2%	N=5225	
	N	%*	N	%*	N	%*
Survival status at 2007						
Alive	2183	67.6	1623	81.4	3806	72.8
Dead	1047	32.4	371	18.6	1419	27.2
Biopsy evidence						
Yes	729	22.6	503	25.2	1232	23.6
No	2501	77.4	1491	74.8	3993	76.4
Level of compensation[‡]						
Level 1	444	15.7	395	20.4	839	17.6
Level 2	839	29.7	640	33.1	1479	31.1
Level 3	770	27.3	507	26.2	1277	26.8
Level 4	163	5.8	116	6.0	279	5.9
Level 5	238	8.4	108	5.6	346	7.3
Level 6	370	13.1	170	8.8	540	11.3
Missing	406	.	58	.	465	.
HCV antibody[†]						
Positive	2398	95.2	1565	95.1	3964	95.1
Negative	122	4.8	81	4.9	203	4.9
Unknown	710	.	348	.	1058	.
HCV RNA[§]						
Positive	2011	96.5	1311	97.0	3322	96.9
Negative	66	3.2	40	3.0	106	3.1
Unknown	1153	.	643	.	1797	.
HCV therapy						
Yes	764	23.7	481	24.1	1245	23.8
No	2466	76.3	1513	75.9	3980	76.2
HIV Positive						
Yes	523	17.5	13	0.7	536	11.1
No	2440	81.8	1798	98.4	4239	88.1
Indeterminate	20	0.7	17	0.9	37	0.8
Missing	247	.	166	.	413	.
Hemophilics						
Yes	1183	36.6	152	7.6	1335	25.6
No	2047	63.4	1842	92.4	3890	74.4
Blood transfusion						
Yes	2024	62.7	1811	90.8	3836	73.4
No	1206	37.3	183	9.2	1389	26.6

Table 5.3.1. Baseline clinical and serological features of post-transfusion claimant cohort, 2010 (continued)

Characteristics	Male		Female		Total	
	N=3230	61.8%	N=1994	38.2%	N=5225	
	N	%*	N	%*	N	%*
Age at first blood transfusion (yr)						
0-9	157	7.8	115	6.4	272	7.1
10-19	120	6.0	126	7.0	246	6.5
20-29	272	13.5	382	21.3	654	17.2
30-39	333	16.5	383	21.3	716	18.8
40-49	308	15.3	276	15.4	584	15.3
50-59	358	17.8	216	12.0	574	15.1
60-69	365	18.1	199	11.1	564	14.8
70+	100	5.0	99	5.5	200	5.2
Missing	1217	.	198	.	1415	.
Year at first blood transfusion						
<1986	269	13.4	298	16.6	567	14.9
1986	400	19.9	358	19.9	759	19.9
1987	409	20.3	361	20.1	770	20.2
1988	389	19.3	321	17.9	710	18.6
1989	393	19.5	332	18.5	725	19.0
1990	153	7.6	128	7.1	281	7.4
Missing	1217	.	196	.	1413	.
Number of blood transfusions, 1986-1990						
1	736	36.6	665	37.0	1402	36.8
2	480	23.8	496	27.6	976	25.6
3	317	15.7	248	13.8	565	14.8
4	188	9.3	145	8.1	333	8.7
5	112	5.6	86	4.8	198	5.2
>5	180	8.9	158	8.8	338	8.9
Missing	1217	.	196	.	1413	.
Duration of HCV infection, mean (SD) years (among alive: n=2844)	23.4(3.9)		23.9(4.9)		23.6(4.5)	
Current age, mean (SD) years (among alive: n=3806)	54.8 (18.6)		58.3 (17.6)		56.3 (18.2)	

*Percentages were calculated based on available observations excluding missing and unknown categories.
†Based on disease Level 1 (lvl1_fl).
§Based on disease Level 2 (lvl2_fl).
‡Level of compensation: Level 1, HCV antibody positive; Level 2, HCV RNA positivity; Level 3, non-bridging fibrosis; Level 4, bridging fibrosis; Level 5, cirrhosis, unresponsive porphyria cutanea tarda, unresponsive thrombocytopenia; Level 6, liver transplant, decompensation of the liver, hepatocellular carcinoma, B-cell lymphoma, symptomatic mixed cryoglobulinemia, glomerulonephritis, renal failure.
HCV, hepatitis C virus; RNA, ribonucleic acid; SD, standard deviation.

Table 5.3.2. Baseline clinical and serological features of post-transfusion claimant cohort (2010): comparison between hemophilics and non-hemophilics

	Total	Hemophilics		non-Hemophilics		Statistical test	
Characteristics	N=5225	N=1335		N=3890			
	N	N	%*	N	%*	Chi	P
Sex							
Male	3230	1183	88.6	2047	52.6	545.1	<0.0001
Female	1994	152	11.4	1842	47.4	.	.
Missing	1	.	.	1	.	.	.
Survival status at 2007							
Alive	3806	895	67.0	2911	74.8	30.5	<0.0001
Dead	1419	440	33.0	979	25.2	.	.
Biopsy evidence							
Yes	1232	265	19.9	967	24.9	13.8	0.0002
No	3993	1070	80.1	2923	75.1	.	.
Level of compensation							
Level 1	839	150	14.3	689	18.6	106.0	<0.0001
Level 2	1479	221	21.1	1258	33.9	.	.
Level 3	1277	360	34.4	917	24.7	.	.
Level 4	279	76	7.3	203	5.5	.	.
Level 5	346	111	10.6	235	6.3	.	.
Level 6	540	130	12.4	410	11.0	.	.
Missing	465	287	.	178	.	.	.
HCV-antibody[†]							
Positive	3964	922	95.7	3042	94.9	1.0	0.3127
Negative	203	41	4.3	162	5.1	.	.
Unknown	1058	372	.	686	.	.	.
HCV RNA[§]							
Positive	3322	800	96.6	2522	97.0	0.3	0.5806
Negative	106	28	3.4	78	3.0	.	.
Unknown	1797	507	.	1290	.	.	.
HCV therapy							
Yes	1245	362	27.1	883	22.7	10.7	0.0011
No	3980	973	72.9	3007	77.3	.	.
HIV Positive							
Yes	536	522	41.3	14	0.4	1579.4	<0.0001
No	4239	743	58.7	3496	98.6	.	.
Indeterminate	37	.	.	37	1.0	.	.
Missing	413	70	.	343	.	.	.

Table 5.3.2. Baseline clinical and serological features of post-transfusion claimant cohort (2010): comparison between hemophilics and non-hemophilics (continued)

	Total	Hemophilics		non-Hemophilics		Statistical test	
Characteristics	N=5225	N=1335		N=3890			
	N	N	%*	N	%*	Chi	P
Age at first blood transfusion (yr)							
0-9	272	.	.	272	7.1	4.8	0.6811
10-19	246	.	.	246	6.5	.	.
20-29	654	1	100.0	653	17.1	.	.
30-39	716	.	.	716	18.8	.	.
40-49	584	.	.	584	15.3	.	.
50-59	574	.	.	574	15.1	.	.
60-69	564	.	.	564	14.8	.	.
70+	200	.	.	200	5.3	.	.
Missing	1415	1334	.	81	.	.	.
Year at first blood transfusion							
<1986	567	.	.	567	14.9	4.0	0.5460
1986	759	1	100.0	758	19.9	.	.
1987	770	.	.	770	20.2	.	.
1988	710	.	.	710	18.6	.	.
1989	725	.	.	725	19.0	.	.
1990	281	.	.	281	7.4	.	.
Missing	1413	1334	.	79	.	.	.
Number of transfusions, 1986-1990							
1	1402	1	100.0	1401	36.8	1.7	0.8864
2	976	.	.	976	25.6	.	.
3	565	.	.	565	14.8	.	.
4	333	.	.	333	8.7	.	.
5	198	.	.	198	5.2	.	.
>5	338	.	.	338	8.9	.	.
Missing	1413	1334	.	79	.	.	.
Among alive cohort	N=3806	N=895		N=2911			
HIV Positive							
Yes	201	192	22.8	9	0.3	604.8	<0.0001
No	3279	649	77.2	2630	98.6	.	.
Indeterminate	28	.	.	28	1.0	.	.
Missing	298	54	.	244	.	.	.
Sex							
Male	2183	761	85.0	1422	48.8	366.3	<0.0001
Female	1623	134	15.0	1489	51.2	.	.
Current age, mean (SD) years	56.3 (18.2)	47.0 (13.8)		59.1 (18.5)			

*Percentages were calculated based on available observations excluding missing and unknown categories.
[†]Based on disease Level 1 (lvl1_fl).
[§]Based on disease Level 2 (lvl2_fl).
HCV, hepatitis C virus; RNA, ribonucleic acid; SD, standard deviation.

Table 5.3.3. Propensity score* for estimating true stage distribution: logistic model†

Parameter	df	Estimate	SE	Chi-square	P-value
Intercept	1	-1.5922	0.1328	143.65	<0.0001
Age	1	-0.0033	0.0021	2.40	0.1213
Gender – female	1	0.0257	0.0378	0.46	0.4962
HCV treatment – yes	1	1.7679	0.0761	539.50	<0.0001
Deceased at 2010 – yes	1	-0.0793	0.0438	3.28	0.0701
Hemophilic, transfused – yes	1	-0.2132	0.0466	20.96	<0.0001

*Probability of having received a liver biopsy (see text section 5.4 for details of propensity score method).
†Based on 5,225 post-transfusion claimants.
df, degrees of freedom; SE, standard error; HCV, hepatitis C virus.

Table 5.3.4. Observed stage distribution by propensity score: alive non-hemophilic patients

Stage	Propensity score < 0.4			Propensity score ≥ 0.4		
	No LB	With LB	Total	No LB	With LB	Total
RNA- F0	491	2	493	0	0	0
RNA+ F0	997	5	1002	0	0	0
F1/F2	234	171	405	283	237	520
F3	0	48	48	0	129	129
Cirrhosis	33	46	79	8	94	102
Decompensated cirrhosis	22	8	30	13	4	17
Liver transplant	10	0	10	10	2	12
HCC	8	4	12	1	5	6
Other liver disease	30	3	33	11	2	13
Total	1825	287	2112	326	473	799

LB, liver biopsy; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 5.3.5. Observed stage distribution by propensity score: alive hemophilic patients

Stage	Propensity score < 0.4			Propensity score ≥ 0.4		
	No LB	With LB	Total	No LB	With LB	Total
RNA- F0	134	1	135	0	0	0
RNA+ F0	190	0	190	0	0	0
F1/F2	115	34	149	173	31	204
F3	0	31	31	0	45	45
Cirrhosis	14	22	36	13	44	57
Decompensated cirrhosis	11	0	11	16	0	16
Liver transplant	1	0	1	3	0	3
HCC	6	2	8	4	0	4
Other liver disease	3	0	3	2	0	2
Total	474	90	564	211	120	331

HCV, hepatitis C virus; LB, liver biopsy; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 5.4.1. Observed and estimated stage distribution of all living post-transfusion claimants, August 2010

HCV stage	Observed						Adjusted*	
	Total	%	No liver biopsy	%	Liver biopsy	%	N	%
Survival status								
Alive	3806		2836		970			
Deceased	1419		1157		262			
Total alive	3806		2836		970		3806	
RNA- F0	628	16.50	625	22.04	3	0.31	628	16.50
RNA+ F0	1192	31.32	1187	41.85		0.00	1192	31.32
F1/F2	1278	33.58	805	28.39	473	48.76	971	25.51
F3	253	6.65	0	0.00	253	26.08	560	14.71
Cirrhosis	274	7.20	68	2.40	206	21.24	274	7.20
Decompensated cirrhosis	74	1.94	62	2.19		0.00	74	1.94
Liver transplant	26	0.68	24	0.85		0.00	26	0.68
HCC	30	0.79	19	0.67	11	1.13	30	0.79
Other liver disease	51	1.34	46	1.62		0.00	51	1.34

*Adjustment based on propensity score. The adjustment was made for hemophilics and non-hemophilics separately, and the overall adjustment was combined from both.
HCV, hepatitis C virus; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 5.4.2. Observed and estimated stage distribution of living non-hemophilics, August 2010

HCV stage	Observed						Adjusted	
	Total	%	No liver biopsy	%	Liver biopsy	%	N	%
Survival status								
Alive	2911		2151		760			
Deceased	979		772		207			
Total alive	2911		2151		760		2911	
RNA- F0	493	16.94	491	22.83	2	0.26	493	16.94
RNA+ F0	1002	34.42	997	46.35	5	0.66	1002	34.42
F1/F2	925	31.78	517	24.04	408	53.68	774	26.59
F3	177	6.08	.	.	177	23.29	328	11.27
Cirrhosis	181	6.22	41	1.91	140	18.42	181	6.22
Decompensated cirrhosis	47	1.61	35	1.63	12	1.58	47	1.61
Liver transplant	22	0.76	20	0.93	2	0.26	22	0.76
HCC	18	0.62	9	0.42	9	1.18	18	0.62
Other liver disease	46	1.58	41	1.91	5	0.66	46	1.58

HCV, hepatitis C virus; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 5.4.3. Observed and estimated stage distribution of living hemophilics, August 2010

HCV stage	Observed						Adjusted	
	Total	%	No liver biopsy	%	Liver biopsy	%	N	%
Survival status								
Alive	895		685		210			
Deceased	440		385		55			
Total alive	895		685		210		895	
RNA- F0	135	15.08	134	19.56	1	0.48	135	15.08
RNA+ F0	190	21.23	190	27.74	.	.	190	21.23
F1/F2	353	39.44	288	42.04	65	30.95	197	21.97
F3	76	8.49	.	.	76	36.19	232	25.97
Cirrhosis	93	10.39	27	3.94	66	31.43	93	10.39
Decompensated cirrhosis	27	3.02	27	3.94	.	.	27	3.02
Liver transplant	4	0.45	4	0.58	.	.	4	0.45
HCC	12	1.34	10	1.46	2	0.95	12	1.34
Other liver disease	5	0.56	5	0.73	.	.	5	0.56

HCV, hepatitis C virus; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 5.4.4. Adjusted HCV stage distribution of living non-hemophilic patients by age group, August 2010

	<20	20+	30+	40+	50+	60+	70+	80+	90+	Total
HCV stage	N=5	N=225	N=144	N=509	N=665	N=484	N=412	N=329	N=138	N=2911
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
RNA- F0	0.0 (0.0)	35.0 (15.6)	33.0 (22.9)	87.0 (17.1)	110.0 (16.5)	89.0 (18.4)	52.0 (12.6)	62.0 (18.8)	25.0 (18.1)	493.0 (16.9)
RNA+ F0	3.0 (60.0)	87.0 (38.7)	33.0 (22.9)	143.0 (28.1)	183.0 (27.5)	136.0 (28.1)	160.0 (38.8)	166.0 (50.5)	91.0 (65.9)	1002.0 (34.4)
F1/F2	1.4 (28.1)	64.6 (28.7)	49.2 (34.1)	174.9 (34.4)	206.5 (31.1)	132.0 (27.3)	87.1 (21.1)	47.1 (14.3)	11.2 (8.1)	774.0 (26.6)
F3	0.6 (11.9)	27.4 (12.2)	20.8 (14.5)	74.1 (14.6)	87.5 (13.2)	56.0 (11.6)	36.9 (9.0)	19.9 (6.1)	4.8 (3.5)	328.0 (11.3)
F4 (Cirrhosis)	0.0 (0.0)	4.0 (1.8)	5.0 (3.5)	10.0 (2.0)	46.0 (6.9)	47.0 (9.7)	46.0 (11.2)	17.0 (5.2)	6.0 (4.3)	181.0 (6.2)
Decompensated cirrhosis	0.0 (0.0)	2.0 (0.9)	1.0 (0.7)	5.0 (1.0)	9.0 (1.4)	7.0 (1.4)	17.0 (4.1)	6.0 (1.8)	0.0 (0.0)	47.0 (1.6)
Liver transplant	0.0 (0.0)	1.0 (0.4)	0.0 (0.0)	3.0 (0.6)	8.0 (1.2)	4.0 (0.8)	3.0 (0.7)	3.0 (0.9)	0.0 (0.0)	22.0 (0.8)
HCC	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.2)	3.0 (0.5)	4.0 (0.8)	7.0 (1.7)	3.0 (0.9)	0.0 (0.0)	18.0 (0.6)
Other liver disease	0.0 (0.0)	4.0 (1.8)	2.0 (1.4)	11.0 (2.2)	12.0 (1.8)	9.0 (1.9)	3.0 (0.7)	5.0 (1.5)	0.0 (0.0)	46.0 (1.6)

Stage distribution for each age group were adjusted to make the overall distribution same as those adjusted in Table 5.4.2.
HCV, hepatitis C virus; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 5.4.5. Adjusted HCV stage distribution of living hemophilic patients by age group, August 2010

	<20 yr	20+	30+	40+	50+	60+	70+	80+	90+	Total
HCV stage	N=1	N=72	N=217	N=261	N=192	N=83	N=46	N=18	N=5	N=895
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N
RNA- F0	0.0 (0.0)	23.0 (31.9)	43.0 (19.8)	34.0 (13.0)	17.0 (8.9)	11.0 (13.3)	6.0 (13.0)	1.0 (5.6)	0.0 (0.0)	135
RNA+ F0	1.0 (100.0)	16.0 (22.2)	42.0 (19.4)	49.0 (18.8)	37.0 (19.3)	14.0 (16.9)	14.0 (30.4)	12.0 (66.7)	5.0 (100.0)	190
F1/F2	0.0 (0.0)	14.2 (19.8)	49.6 (22.9)	60.2 (23.0)	44.1 (23.0)	20.2 (24.3)	6.9 (15.0)	1.8 (10.2)	0.0 (0.0)	197
F3	0.0 (0.0)	16.8 (23.3)	58.4 (26.9)	70.8 (27.1)	51.9 (27.0)	23.8 (28.7)	8.1 (17.6)	2.2 (12.0)	0.0 (0.0)	232
F4 (Cirrhosis)	0.0 (0.0)	2.0 (2.8)	18.0 (8.3)	33.0 (12.6)	29.0 (15.1)	8.0 (9.6)	3.0 (6.5)	0.0 (0.0)	0.0 (0.0)	93
Decompensated cirrhosis	0.0 (0.0)	0.0 (0.0)	5.0 (2.3)	7.0 (2.7)	7.0 (3.6)	4.0 (4.8)	4.0 (8.7)	0.0 (0.0)	0.0 (0.0)	27
Liver transplant	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.4)	2.0 (1.0)	1.0 (1.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	4
HCC	0.0 (0.0)	0.0 (0.0)	1.0 (0.5)	3.0 (1.1)	2.0 (1.0)	1.0 (1.2)	4.0 (8.7)	1.0 (5.6)	0.0 (0.0)	12
Other liver disease	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	3.0 (1.1)	2.0 (1.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	5

Stage distribution for each age group were adjusted to make the overall distribution same as those adjusted in Table 5.4.3.
HCV, hepatitis C virus; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 5.4.6. Adjusted HCV stage distribution of living male patients by age group, August 2010

	<20 yr	20+	30+	40+	50+	60+	70+	80+	90+	Total
HCV stage	N=4	N=195	N=271	N=462	N=435	N=291	N=256	N=205	N=64	N=2183
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
RNA- F0	. (.)	42.0 (21.5)	53.0 (19.6)	67.0 (14.5)	57.0 (13.1)	42.0 (14.4)	25.0 (9.8)	31.0 (15.1)	6.0 (9.4)	323.0 (14.8)
RNA+ F0	4.0 (100.0)	68.0 (34.9)	56.0 (20.7)	107.0 (23.2)	97.0 (22.3)	75.0 (25.8)	99.0 (38.7)	109.0 (53.2)	46.0 (71.9)	661.0 (30.3)
F1/F2	. (.)	50.0 (25.6)	87.0 (32.1)	151.0 (32.7)	134.0 (30.8)	75.0 (25.8)	50.0 (19.5)	28.0 (13.7)	5.0 (7.8)	580.0 (26.6)
F3	. (.)	28.0 (14.4)	48.0 (17.7)	84.0 (18.2)	74.0 (17.0)	41.0 (14.1)	28.0 (10.9)	16.0 (7.8)	2.0 (3.1)	321.0 (14.7)
F4 (Cirrhosis)	. (.)	3.0 (1.5)	20.0 (7.4)	32.0 (6.9)	46.0 (10.6)	39.0 (13.4)	30.0 (11.7)	12.0 (5.9)	5.0 (7.8)	187.0 (8.6)
Decompensated cirrhosis	. (.)	1.0 (0.5)	5.0 (1.8)	8.0 (1.7)	9.0 (2.1)	6.0 (2.1)	12.0 (4.7)	4.0 (2.0)	. (.)	45.0 (2.1)
Liver transplant	. (.)	. (.)	. (.)	1.0 (0.2)	6.0 (1.4)	4.0 (1.4)	2.0 (0.8)	1.0 (0.5)	. (.)	14.0 (0.6)
HCC	. (.)	. (.)	1.0 (0.4)	3.0 (0.6)	3.0 (0.7)	4.0 (1.4)	7.0 (2.7)	1.0 (0.5)	. (.)	19.0 (0.9)
Other liver disease	. (.)	3.0 (1.5)	1.0 (0.4)	9.0 (1.9)	9.0 (2.1)	5.0 (1.7)	3.0 (1.2)	3.0 (1.5)	. (.)	33.0 (1.5)

Stage distribution for each age group were adjusted to make the overall distribution same as those adjusted in Table 5.4.1.
HCV, hepatitis C virus; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 5.4.7. Adjusted HCV stage distribution of living female patients by age group, August 2010

	<20 yr	20+	30+	40+	50+	60+	70+	80+	90+	Total
HCV stage	N=2	N=102	N=90	N=308	N=422	N=276	N=202	N=142	N=79	N=1623
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
RNA- F0	. (.)	16.0 (15.7)	23.0 (25.6)	54.0 (17.5)	70.0 (16.6)	58.0 (21.0)	33.0 (16.3)	32.0 (22.5)	19.0 (24.1)	305.0 (18.8)
RNA+ F0	. (.)	35.0 (34.3)	19.0 (21.1)	85.0 (27.6)	123.0 (29.1)	75.0 (27.2)	75.0 (37.1)	69.0 (48.6)	50.0 (63.3)	531.0 (32.7)
F1/F2	1.0 (50.0)	28.0 (27.5)	27.0 (30.0)	90.0 (29.2)	113.0 (26.8)	72.0 (26.1)	38.0 (18.8)	17.0 (12.0)	6.0 (7.6)	391.0 (24.1)
F3	1.0 (50.0)	17.0 (16.7)	16.0 (17.8)	55.0 (17.9)	69.0 (16.4)	44.0 (15.9)	23.0 (11.4)	10.0 (7.0)	3.0 (3.8)	239.0 (14.7)
F4 (Cirrhosis)	. (.)	3.0 (2.9)	3.0 (3.3)	11.0 (3.6)	29.0 (6.9)	16.0 (5.8)	19.0 (9.4)	5.0 (3.5)	1.0 (1.3)	87.0 (5.4)
Decompensated cirrhosis	. (.)	1.0 (1.0)	1.0 (1.1)	4.0 (1.3)	7.0 (1.7)	5.0 (1.8)	9.0 (4.5)	2.0 (1.4)	. (.)	29.0 (1.8)
Liver transplant	. (.)	1.0 (1.0)	. (.)	3.0 (1.0)	4.0 (0.9)	1.0 (0.4)	1.0 (0.5)	2.0 (1.4)	. (.)	12.0 (0.7)
HCC	. (.)	. (.)	. (.)	1.0 (0.3)	2.0 (0.5)	1.0 (0.4)	4.0 (2.0)	3.0 (2.1)	. (.)	11.0 (0.7)
Other liver disease	. (.)	1.0 (1.0)	1.0 (1.1)	5.0 (1.6)	5.0 (1.2)	4.0 (1.4)	. (.)	2.0 (1.4)	. (.)	18.0 (1.1)

Stage distribution for each age group were adjusted to make the overall distribution same as those adjusted in Table 5.4.1.
HCV, hepatitis C virus; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 6. Summary of transition probabilities used in the 2010 HCV Markov prediction model

Type of transition probability	Short Expression	Variable Name in Markov model	Baseline Probability	Low	High	Source
Proportion of whole cohort with RNA- in F0 study population, six months post infection	RNA-	pRNAnegative	0.20			[35]
Proportion of whole cohort with RNA$^+$ in F0 study population, 6 months post infection	RNA+	pRNApositive	0.80			
Proportion of whole cohort with RNA- in F0 study population, year 2010	RNA-	pRNAnegative	0.165			Table 5.4.1
Transition from RNA+ to RNA- (without treatment)	RNA+→RNA-	PRNApostoRNAneg	0.017	0.011	0.022	Table 4.1
Transition from RNA$^-$ to recover	RNA- to recover	pRNAnegtoRecover	0.002	0.001	0.004	1998 Report
Transition from F0 RNA negative to fibrosis 1	RNA- to F1	pRNAnegtofibrosis1	0.000	0.000	0.000	
Transition from F0 RNA positive to fibrosis 1	RNA+ → F1	pRNApostoFibrosis1	0.057	0.044	0.073	[23], cohort data, calibrated
Transition from Fibrosis stage 1 to stage 2	F1→F2	pFibrosis1toFibrosis2	0.145	0.112	0.189	[23], cohort data, calibrated
Transition from Fibrosis stage 2 to stage 3	F2→F3	pFibrosis2toFibrosis3	0.150	0.120	0.188	[23], cohort data, calibrated
Transition from Fibrosis stage 3 to stage 4	F3→Cirr.	pFibrosis3toFibrosis4	0.120	0.087	0.164	[23], cohort data, calibrated
Transition from Fibrosis stage 4 (Cirrhosis) to liver decompensation	Cirr.→Dec.	PFibrosis4toDecom.	0.065	0.033	0.092	[19,22,97,118,120,290]
Transition from Fibrosis stage 1 directly to HCC	F1→HCC	pFibrosis1toHCC	0.0001	0.000	0.002	1998 Report Table 1
Transition from Fibrosis stage 2 directly to HCC	F2→HCC	pFibrosis2toHCC	0.0001	0.000	0.002	1998 Report Table 1
Transition from Fibrosis stage 3 directly to HCC	F3→HCC	pFibrosis3toHCC	0.001	0.0001	0.020	1998 Report Table 1
Transition from Fibrosis stage 4 directly to HCC	Cirr.→HCC	pFibrosis4toHCC	0.033	0.024	0.046	[19,123]; Table 4.4.1
Transition from Decomp. cirrhosis to Liver transplantation	Dec.→Transp	pDecomCtoTransp	0.033	0.017	0.049	1998 Report Table 1
Transition from HCC to Liver transplantation	HCC→Transp	pHCCtoTrans	0.100	0.050	0.180	Assumption
HCC to death	HCC →Death	pHCCtoDeath	0.350	0.316	0.699	[19-22]
Liver transplantation to Death (first year)	Tran.→Death	pTransptoFail	0.146	0.127	0.210	[19]; 1998 Report Table 1
Liver transplantation to Death (after first year)			0.044	0.035	0.053	[19]; 1998 Report Table 1
Decompensation to liver-related death	Dec.→Death	PDecomCtoDeath	0.186	0.137	0.250	[19]; 1998 Report Table 1
Effect of HCV treatment[*]:						Tables 4.3.1.1-4.3.1.2
Annual treatment rate[†] < 65: F0: 0%	RNA+ to F1	Treateffect1	0			
Annual treatment rate[†] < 65: F1-F3: 10% Treatment efficacy (SVR): 49%	F1 to F2 F2 to F3 F3 to F4	Treateffect2	0.049	0.0245	0.0735	Cohort data; Table 4.3.1.1-4.3.1.3
Annual treatment rate[†] < 65: F4: 10% Treatment efficacy (SVR): 31%	F4 to Decomp.	Treateffect3	0.031	0.0155	0.0465	Cohort data; Table 4.3.1.1-4.3.1.3
Annual treatment rate[†] > 65: F0: 0%	RNA+ to F1	Treateffect1'	0			Cohort data; Table 4.3.1.1-4.3.1.3
Annual treatment rate[†] > 65: F1-F3: 3.3% Treatment efficacy (SVR): 49%	F1 to F2 F2 to F3	Treateffect2'	0.0163	0.0082	0.0245	Cohort data; Table 4.3.1.1-4.3.1.3

	F3 to F4					
Annual treatment rate† <65: F4: 3.3% Treatment efficacy (SVR): 31%	F4 to Decomp.	Treateffect3’	0.0103	0.0052	0.0154	Cohort data; [71]
Excess mortality attributable to transfusion			Table 4.5.1	0.5x	1.5x	Table 4.5.1
Effect of HIV status on fibrosis progression rates			2.122	1.518	2.967	[295]
Excess mortality associated with HIV infection			6.24	5.43	7.18	Table 4.3.4.2

*Product of the annual treatment rate and the response rate.

†Annual treatment rates for people < 65 or > 65 years age groups were based on the cohort.

SVR, sustained virological response rates were updated based on the literature.

Table 7.1. Model validation: observed and predicted liver disease among living post-transfusion claimant cohort at August 2010

HCV stage	Observed-Adjusted[†]		Predicted*
	Total (%)	Non-hemophilics (%)	Non-hemophilics (%)
F0	47.82	51.36	51.12
F1/F2	25.51	26.59	28.58
F3	14.71	11.27	11.37
Cirrhosis	7.20	6.22	6.79
Decompensated cirrhosis	1.94	1.61	1.23
Liver transplant	0.68	0.76	0.23
HCC	0.79	0.62	0.68
Other liver disease	1.34	1.58	---

Adjustment based on propensity score. The adjustment was made for hemophilics and non-hemophilics separately, and the overall adjustment was combined from both.

*Based on the post-transfusion claimant cohort fibrosis stage transition rates, literature-derived fibrosis stage transition rates, annual treatment rate, and model calibration (Table 6); 10% annual HCV treatment rate for patients in stage F1 to F4, (age < 65 years), and 3.3% for age >=65 years. The cumulative treatment rate in all patients is 21.5% (similar to observed).

Table 7.2. Model validation: observed and predicted liver disease among living non-hemophilic patients – comparing 2002, 2004, 2007, and 2010 models

	2002 Model		2004 Model		2007 Model		2010 Model	
HCV stage	Observed-Adj	Predicted	Observed-Adj	Predicted	Observed-Adj	Predicted	Observed-Adj	Predicted
	%	%	%	%	%	%	%	%
F0	45.8	30.9	53.8	44.4	53.0	51.78	51.36	51.12
F1	22.3	33.0	24.4	32.0	24.4*	30.85*	26.59	28.58
F2/F3	13.9	27.8	11.0	15.9	12.0†	7.82	11.27	11.37
Cirrhosis	12.5	8.4	6.6	6.2	6.20	7.84	6.22	6.79
Decompensated cirrhosis	2.9	0.9	1.5	0.7	1.67	1.21	1.61	1.23
Liver transplant	1.3	0.0	0.8	0.3	0.73	0.11	0.76	0.23
HCC	0.5	0.1	0.7	0.5	0.52	0.38	0.62	0.68
Other liver disease	0.9	---	1.1	---	1.53	---	1.58	---

*F1 and F2 combined.
†F3 only.

Table 7.3. Model validation: Life-time predicted HCV outcome of the non-hemophilic patients – comparing 1998, 2002, 2004, 2007, and 2010 models

Outcome	1998*	2002	2004	2007	2010
	30-year risk	life-time risk	life-time risk	life-time risk	life-time risk
Cirrhosis					
Overall	29.4 (24.9)[†]	37.0	33.4	34.8	34.5
Age group (yr)					
10-19	36.7	53.4	42.5	46.8	.
20-29	35.1	52.3	49.7	45.1	47.8
30-39	32.7	49.7	44.1	48.7	46.4
40-49	31.0	49.4	41.3	46.1	44.6
50-59	21.3	41.9	41.6	43.3	42.3
60-69	16.8	38.0	33.0	34.6	37.1
70-79	6.1	24.6	22.5	26.2	29.0
Liver-related death					
Overall	16.9 (12.3)[†]	22.0	17.3	20.0	20.4
Age group (yr)					
10-19	12.3	39.4	27.7	34.3	
20-29	11.8	37.2	30.7	31.0	36.0
30-39	10.9	32.6	25.2	34.5	34.9
40-49	10.2	30.3	21.8	29.5	30.5
50-59	6.6	23.9	20.8	25.0	26.0
60-69	4.2	21.0	14.6	17.7	19.3
70-79	1.0	12.0	8.0	11.0	13.3

*Life time prediction by age group in 1998 is not available, so only 30 year prediction post-transfusion was listed for reference.

[†]Numbers out of the brackets are predicted based on claimants who were alive in 1999, 2002, 2004, 2007, and 2010. Numbers in the brackets are for entire transfused population.

Table 8.1.1. Hepatitis C prognosis by calendar year: All living patients

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	10.0	24.3	32.2	36.3	37.9	38.5
HCC	0.8	4.0	7.0	9.1	10.1	10.5
Liver transplant	0.7	2.9	3.6	3.9	4.1	4.2
Non-liver-related death		21.9	38.3	52.3	63.4	70.3
Liver-related death		7.0	14.6	20.0	22.8	24.0
All cause death		29.0	52.9	72.2	86.3	94.3
Sex distribution (%)						
Female	42.64	44.4	45.7	47.4	49.5	50.2
Age distribution (%)						
25 yr	7.9	0.2				
35 yr	9.5	10.0	0.3			
45 yr	20.3	11.5	13.1	0.4		
55 yr	22.5	24.9	14.1	18.9	0.8	
65 yr	14.9	26.4	29.9	18.1	30.8	1.4
75 yr	12.1	15.6	28.4	35.1	24.7	53.3
85 yr	9.1	9.0	11.8	23.7	34.9	29.5
95 yr	3.7	2.4	2.5	3.8	8.9	15.8
Stage distribution (%)†						
RNA- F0	16.7	22.2	27.4	32.6	37.4	42.0
RNA+ F0	31.7	15.8	8.4	4.5	2.4	1.3
Fibrosis 1	13.2	12.2	10.3	9.2	9.0	8.2
Fibrosis 2	12.7	13.2	12.3	11.8	11.8	11.8
Fibrosis 3	14.9	16.4	17.1	16.8	16.7	17.0
Cirrhosis	7.3	14.1	16.2	16.2	14.1	11.6
Decompensated cirrhosis	2.0	3.5	4.3	4.1	3.4	2.9
Liver transplant	0.7	1.5	2.5	3.2	3.9	4.1
HCC	0.8	1.2	1.5	1.5	1.3	1.0

*Proportion computed with reference to the number of patients who were alive in year 2010.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).
Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.
HCC, hepatocellular carcinoma; RNA, ribonucleic acid.

Table 8.1.2. Hepatitis C prognosis by calendar year: Living non-hemophilic patients

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)						
Cirrhosis	8.7	20.6	28.1	32.3	33.9	34.5
HCC	0.6	3.2	5.9	7.8	8.8	9.1
Liver transplant	0.8	2.7	3.2	3.5	3.7	3.8
Non-liver-related death		24.3	41.9	56.3	67.5	74.0
Liver-related death		5.6	11.9	16.7	19.3	20.4
All cause death		30.0	53.8	72.9	86.9	94.4
Sex distribution (%)						
Female	51.2	53.1	54.7	56.6	58.8	59.1
Age distribution (%)						
25 yr	7.9	0.2	.	.	.	.
35 yr	5.0	10.2	0.3	.	.	.
45 yr	17.5	6.5	13.7	0.5	.	.
55 yr	22.8	22.8	8.6	20.2	0.9	.
65 yr	16.6	28.1	28.8	12.0	33.9	1.6
75 yr	14.2	18.1	31.4	35.6	17.8	59.0
85 yr	11.3	11.0	14.0	27.1	37.0	22.0
95 yr	4.7	3.1	3.1	4.6	10.5	17.4
Stage distribution (%)						
RNA- F0	17.2	22.9	27.9	32.9	37.6	42.2
RNA+ F0	35.0	17.4	9.2	4.9	2.6	1.4
Fibrosis 1	14.5	13.2	11.0	9.7	9.6	8.7
Fibrosis 2	12.5	13.9	13.0	12.4	12.2	12.2
Fibrosis 3	11.5	15.4	16.6	16.2	16.1	16.4
Cirrhosis	6.3	12.2	15.0	15.7	13.8	11.5
Decompensated cirrhosis	1.6	2.8	3.8	4.0	3.3	2.9
Liver transplant	0.8	1.3	2.1	2.8	3.6	3.7
HCC	0.6	1.0	1.4	1.5	1.3	0.9

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.3. Hepatitis C prognosis by calendar year: Living hemophilic patients

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)						
Cirrhosis	14.0	36.5	45.4	49.4	51.0	51.6
HCC	1.4	6.4	10.7	13.3	14.5	15.0
Liver transplant	0.5	3.7	4.7	5.3	5.6	5.6
Non-liver-related death		14.0	26.7	39.2	50.2	58.3
Liver-related death		11.7	23.4	30.7	34.2	35.6
All cause death		25.6	50.1	69.9	84.4	93.9
Sex distribution (%)						
Female	15.0	15.9	16.6	17.6	19.2	21.4
Age distribution (%)						
25 yr	8.1	0.1	.	.	.	.
35 yr	24.2	9.4	0.2	.	.	.
45 yr	29.2	27.7	11.2	0.2	.	.
55 yr	21.5	31.7	31.8	14.5	0.3	.
65 yr	9.3	20.8	33.4	38.0	20.7	0.6
75 yr	5.1	7.4	18.5	33.6	47.2	34.9
85 yr	2.0	2.5	4.5	12.6	28.0	53.7
95 yr	0.6	0.3	0.5	1.0	3.8	10.8
Stage distribution (%)						
RNA- F0	15.2	20.1	25.8	31.7	36.7	41.4
RNA+ F0	21.4	10.4	5.9	3.4	1.7	1.0
Fibrosis 1	11.0	8.9	8.0	7.5	7.1	6.4
Fibrosis 2	11.1	10.8	10.1	10.0	10.5	10.7
Fibrosis 3	26.1	19.7	18.7	18.8	18.8	19.1
Cirrhosis	10.5	20.4	20.1	17.7	15.1	12.0
Decompensated cirrhosis	3.0	5.9	5.9	4.6	3.7	2.7
Liver transplant	0.5	2.0	3.7	4.7	5.0	5.3
HCC	1.4	1.8	1.8	1.6	1.5	1.2

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Note: Tables 8.1.4. and 8.1.5. Hepatitis C prognosis by calendar year: hemophilics and non-hemophilics, Age 10-19 are not created because there are very few patients in this group.

Table 8.1.6. Hepatitis C prognosis by calendar year: Non-hemophilics, Age 20-29

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	3.1	18.3	30.0	38.6	44.4	47.8
Decompensated cirrhosis	0.9	4.3	10.5	16.5	21.1	24.1
HCC	0.0	2.1	6.1	10.3	13.6	15.9
Liver transplant	0.4	3.2	3.9	4.6	5.3	5.7
Non-liver-related death	0.0	0.7	1.8	4.2	9.4	20.1
Liver-related death	0.0	3.6	11.7	21.4	29.9	36.0
All cause death	0.0	4.3	13.6	25.6	39.3	56.1
Alive	100	95.7	86.4	74.4	60.7	43.9
Stage distribution (%)†						
RNA- F0	15.5	21.2	25.8	30.4	35.2	39.7
RNA+ F0	39.8	19.3	10.0	5.3	2.7	1.5
Fibrosis 1	15.8	14.8	12.7	11.2	10.3	9.4
Fibrosis 2	13.4	14.8	14.0	13.4	13.3	13.3
Fibrosis 3	12.4	16.1	17.4	17.3	16.9	16.9
Cirrhosis	1.8	10.4	14.1	14.8	13.7	11.8
Decompensated cirrhosis	0.9	2.0	3.4	3.8	3.3	2.8
Liver transplant	0.4	0.7	1.5	2.5	3.3	3.7
HCC	0.0	0.7	1.2	1.3	1.2	1.0

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.7. Hepatitis C prognosis by calendar year: Hemophilics, Age 20-29

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	2.7	24.7	34.7	40.4	43.6	45.3
Decompensated cirrhosis	0.0	7.0	14.9	20.0	23.0	24.5
HCC	0.0	3.4	7.8	11.2	13.5	14.9
Liver transplant	0.0	2.7	3.7	4.5	5.0	5.3
Non-liver-related death	0.0	1.8	4.5	9.1	17.7	31.0
Liver-related death	0.0	5.2	16.3	25.6	31.8	35.5
All cause death	0.0	7.0	20.8	34.6	49.5	66.4
Alive	100.0	93.0	79.2	65.4	50.5	33.6
Stage distribution (%)†						
RNA- F0	31.5	36.2	42.5	48.8	54.2	58.0
RNA+ F0	23.3	10.1	5.1	2.7	1.4	0.8
Fibrosis 1	9.7	8.4	7.2	6.3	5.9	5.3
Fibrosis 2	9.8	9.3	8.5	8.2	8.0	8.0
Fibrosis 3	23.0	16.1	14.7	14.0	13.4	13.4
Cirrhosis	2.7	14.2	14.1	12.4	10.5	8.9
Decompensated cirrhosis	0	3.8	4.4	3.5	2.5	1.8
Liver transplant	0	0.7	2.0	2.9	3.2	3.2
HCC	0	1.1	1.3	1.2	0.9	0.8

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.8. Hepatitis C prognosis by calendar year: Non-hemophilics, Age 30-39

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	4.2	21.3	33.0	40.3	44.4	46.4
Decompensated cirrhosis	0.7	5.3	12.2	18.0	21.7	23.5
HCC	0	2.8	7.3	11.4	14.1	15.6
Liver transplant	0	2.8	3.5	4.3	4.9	5.1
Non-liver-related death	0.0	1.2	3.8	9.4	20.4	39.7
Liver-related death	0.0	4.3	13.7	23.5	30.8	34.9
All cause death	0.0	5.5	17.5	32.9	51.2	74.6
Alive	100	94.5	82.5	67.1	48.8	25.4
Stage distribution (%)†						
RNA- F0	23.2	27.3	31.9	37.2	42.5	47.5
RNA+ F0	23.2	11.3	5.9	3.2	1.6	0.8
Fibrosis 1	18.7	12.0	9.8	8.7	7.9	7.1
Fibrosis 2	15.9	14.7	12.4	11.7	11.5	11.5
Fibrosis 3	14.7	18.0	17.6	16.6	16.0	15.7
Cirrhosis	3.5	12.7	15.5	14.7	12.7	10.3
Decompensated cirrhosis	0.7	2.5	3.8	3.9	3.1	2.3
Liver transplant	0.0	0.5	1.7	2.6	3.4	3.6
HCC	0.0	0.9	1.4	1.4	1.2	1.1

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.9. Hepatitis C prognosis by calendar year: Hemophilics, Age 30-39

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	10.6	35.5	46.0	51.3	53.9	55.0
Decompensated cirrhosis	2.3	12.4	21.4	26.6	29.3	30.3
HCC	0.5	5.4	10.7	14.2	16.3	17.2
Liver transplant	0.0	3.6	4.8	5.6	6.0	6.2
Non-liver-related death	0.0	3.0	8.2	17.0	29.0	43.9
Liver-related death	0.0	10.3	24.3	34.2	39.8	42.4
All cause death	0.0	13.2	32.4	51.2	68.9	86.4
Alive	100.0	86.8	67.6	48.8	31.1	13.6
Stage distribution (%)†						
RNA- F0	19.8	24.7	30.8	36.9	42.1	47.1
RNA+ F0	19.4	8.9	5.0	2.8	1.5	0.8
Fibrosis 1	11.4	8.4	7.2	6.9	6.5	5.9
Fibrosis 2	11.5	10.5	9.7	9.4	9.6	9.7
Fibrosis 3	26.9	19.5	18.0	17.7	17.5	17.4
Cirrhosis	8.3	19.4	18.7	16.4	13.8	11.3
Decompensated cirrhosis	2.3	5.6	5.7	4.3	3.3	2.2
Liver transplant	0.0	1.4	3.2	4.1	4.5	4.5
HCC	0.5	1.6	1.7	1.5	1.3	1.1

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.10. Hepatitis C prognosis by calendar year: Non-hemophilics, Age 40-49

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	3.2	20.7	32.7	40.1	43.6	44.6
Decompensated cirrhosis	1.0	5.0	11.6	17.1	20.1	21.0
HCC	0.2	2.7	7.1	10.8	13.0	13.7
Liver transplant	0.6	3.1	3.8	4.5	5.0	5.1
Non-liver-related death	0.0	2.8	9.3	22.1	43.4	64.1
Liver-related death	0.0	4.4	13.4	22.6	28.5	30.5
All cause death	0.0	7.2	22.7	44.7	71.9	94.6
Alive	100	92.8	77.3	55.3	28.1	5.4
Stage distribution (%)†						
RNA- F0	17.4	21.9	26.2	31.2	36.0	40.1
RNA+ F0	28.6	13.9	7.3	3.9	2.0	1.2
Fibrosis 1	19.0	13.5	11.2	9.6	8.7	7.8
Fibrosis 2	16.4	15.7	13.6	12.9	12.6	12.4
Fibrosis 3	14.9	18.7	18.7	18.1	17.5	17.2
Cirrhosis	2.0	12.4	15.8	15.7	14.2	12.3
Decompensated cirrhosis	1.0	2.3	3.8	4.2	3.6	2.9
Liver transplant	0.6	0.9	1.9	3.0	4.0	4.6
HCC	0.2	0.9	1.4	1.5	1.5	1.5

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.11. Hepatitis C prognosis by calendar year: Hemophilics, Age 40-49

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	16.7	40.7	50.5	55.1	56.9	57.3
Decompensated cirrhosis	2.7	14.3	23.0	27.4	29.2	29.6
HCC	1.2	7.1	12.3	15.5	17.0	17.3
Liver transplant	0.4	4.1	5.3	6.0	6.3	6.3
Non-liver-related death	0.0	6.4	17.0	30.4	45.5	56.8
Liver-related death	0.0	13.0	27.1	35.8	39.8	41.0
All cause death	0.0	19.5	44.0	66.2	85.3	97.8
Alive	100.0	80.5	56.0	33.8	14.7	2.2
Stage distribution (%)†						
RNA- F0	13.2	17.7	23.1	28.6	33.7	39.0
RNA+ F0	19.0	9.3	5.4	3.2	1.8	1.0
Fibrosis 1	11.6	8.7	7.9	7.4	6.8	5.8
Fibrosis 2	11.7	11.0	10.4	10.3	10.4	9.8
Fibrosis 3	27.4	20.5	19.6	19.7	19.7	20.3
Cirrhosis	12.8	22.4	21.5	19.4	16.5	13.9
Decompensated cirrhosis	2.7	6.4	6.2	4.7	3.9	2.7
Liver transplant	0.4	2.0	3.8	5.0	5.5	5.7
HCC	1.2	1.9	2.0	1.8	1.7	1.9

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.12. Hepatitis C prognosis by calendar year: Non-hemophilics, Age 50-59

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	9.6	24.4	34.9	40.6	42.2	42.3
Decompensated cirrhosis	1.4	6.6	12.8	17.1	18.4	18.5
HCC	0.5	3.7	7.8	10.6	11.5	11.6
Liver transplant	1.2	3.5	4.2	4.8	5.0	5.0
Non-liver-related death	0.0	6.9	21.0	45.0	68.1	73.9
Liver-related death	0.0	6.6	15.6	22.9	25.7	26.0
All cause death	0.0	13.5	36.7	67.9	93.8	99.9
Alive	100	86.5	63.3	32.1	6.2	0.1
Stage distribution (%)†						
RNA- F0	16.8	21.7	26.4	31.8	37.1	45.0
RNA+ F0	28.0	13.9	7.4	4.0	1.8	.
Fibrosis 1	17.1	13.0	10.4	8.5	7.3	6.4
Fibrosis 2	14.6	14.8	13.1	12.0	11.3	13.6
Fibrosis 3	13.4	17.2	17.9	17.2	16.9	12.1
Cirrhosis	7.0	13.8	16.6	16.4	15.2	13.6
Decompensated cirrhosis	1.4	2.9	4.1	4.6	3.8	2.1
Liver transplant	1.2	1.6	2.6	3.7	4.8	3.6
HCC	0.5	1.0	1.5	1.8	1.8	3.6

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.13. Hepatitis C prognosis by calendar year: Hemophilics, Age 50-59

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	20.1	43.1	51.7	55.1	55.8	55.8
Decompensated cirrhosis	3.7	15.4	22.7	25.7	26.4	26.4
HCC	1.1	7.2	11.7	13.8	14.4	14.4
Liver transplant	1.1	4.5	5.5	5.9	6.0	6.0
Non-liver-related death	0.0	15.0	33.1	51.2	63.5	65.8
Liver-related death	0.0	14.1	26.3	32.4	34.1	34.2
All cause death	0.0	29.1	59.3	83.5	97.6	100.0
Alive	100.0	70.9	40.7	16.5	2.4	0.0
Stage distribution (%)†						
RNA- F0	9.0	13.1	17.8	22.6	27.3	25.9
RNA+ F0	19.5	9.9	6.1	3.6	1.7	.
Fibrosis 1	11.6	9.0	7.9	7.5	6.4	7.4
Fibrosis 2	11.7	11.5	11.0	10.2	9.9	11.1
Fibrosis 3	27.3	21.5	20.9	20.8	21.6	40.7
Cirrhosis	15.3	23.5	23.2	21.4	18.2	3.7
Decompensated cirrhosis	3.7	6.8	6.5	5.6	4.9	.
Liver transplant	1.1	2.7	4.6	6.1	7.3	7.4
HCC	1.1	2.0	2.1	2.3	2.8	3.7

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.14. Hepatitis C prognosis by calendar year: Non-hemophilics, Age 60-69

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	12.2	25.7	34.4	36.9	37.1	37.1
Decompensated cirrhosis	1.5	7.7	13.0	14.8	15.0	15.0
HCC	0.8	4.5	7.6	8.8	8.9	8.9
Liver transplant	0.8	2.8	3.4	3.7	3.7	3.7
Non-liver-related death	0.0	17.1	46.8	74.3	80.5	80.7
Liver-related death	0.0	7.6	15.4	18.9	19.3	19.3
All cause death	0.0	24.7	62.2	93.2	99.8	100.0
Alive	100	75.3	37.8	6.8	0.2	.
Stage distribution (%)†						
RNA- F0	18.7	24.2	29.8	36.5	46.2	.
RNA+ F0	28.6	14.6	7.8	4.1	0.6	.
Fibrosis 1	15.0	11.0	7.9	6.2	7.7	.
Fibrosis 2	12.8	13.1	11.0	9.0	5.1	.
Fibrosis 3	11.8	15.9	16.3	14.8	10.9	.
Cirrhosis	9.9	14.8	17.7	17.5	17.3	.
Decompensated cirrhosis	1.5	3.6	4.9	5.1	3.8	.
Liver transplant	0.8	1.6	2.8	4.4	5.8	.
HCC	0.8	1.2	1.7	2.4	2.6	.

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.15. Hepatitis C prognosis by calendar year: Hemophilics, Age 60-69

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	15.6	39.5	46.7	48.2	48.2	48.2
Decompensated cirrhosis	4.8	14.1	19.6	21.0	21.1	21.1
HCC	1.2	5.8	9.0	9.9	9.9	9.9
Liver transplant	1.2	3.8	4.5	4.7	4.8	4.8
Non-liver-related death	0.0	29.8	55.3	72.6	75.8	75.8
Liver-related death	0.0	12.2	21.0	23.9	24.2	24.2
All cause death	0.0	42.0	76.3	96.5	99.9	100.0
Alive	100.0	58.0	23.7	3.5	0.1	.
Stage distribution (%)†						
RNA- F0	13.3	17.6	23.1	30.2	50.0	.
RNA+ F0	16.9	8.9	5.4	3.2	1.5	.
Fibrosis 1	12.1	7.5	5.7	4.6	1.5	.
Fibrosis 2	12.2	10.9	8.6	7.3	7.4	.
Fibrosis 3	28.7	21.0	18.4	16.3	8.8	.
Cirrhosis	9.6	23.1	24.5	22.7	17.6	.
Decompensated cirrhosis	4.8	6.4	7.3	6.2	4.4	.
Liver transplant	1.2	2.7	4.5	6.9	7.4	.
HCC	1.2	2.0	2.4	2.6	1.5	.

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.16. Hepatitis C prognosis by calendar year: Non-hemophilics, Age 70-79

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	16.2	25.1	28.6	29.0	29.0	29.0
Decompensated cirrhosis	4.2	9.3	11.4	11.6	11.6	11.6
HCC	1.7	4.7	5.9	6.1	6.1	6.1
Liver transplant	0.7	2.4	2.7	2.7	2.7	2.7
Non-liver-related death	0.0	40.4	78.2	86.5	86.7	86.7
Liver-related death	0.0	9.3	12.8	13.3	13.3	13.3
All cause death	0.0	49.7	91.0	99.8	100.0	100.0
Alive	100	50.3	9.0	0.2	.	.
Stage distribution (%)†						
RNA- F0	12.7	19.6	25.5	26.2	.	.
RNA+ F0	39.1	20.6	11.5	7.7	.	.
Fibrosis 1	11.5	12.9	9.9	8.2	.	.
Fibrosis 2	9.8	12.9	11.8	9.3	.	.
Fibrosis 3	9.0	13.8	15.7	17.5	.	.
Cirrhosis	11.3	13.5	16.7	14.2	.	.
Decompensated cirrhosis	4.2	3.8	4.1	4.4	.	.
Liver transplant	0.7	1.9	2.9	7.1	.	.
HCC	1.7	1.2	2.0	5.5	.	.

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.17. Hepatitis C prognosis by calendar year: Hemophilics, Age 70-79

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	15.2	27.9	30.2	30.4	30.4	30.4
Decompensated cirrhosis	8.7	12.8	14.3	14.4	14.4	14.4
HCC	8.7	10.9	11.8	11.9	11.9	11.9
Liver transplant	0.0	2.8	3.0	3.0	3.0	3.0
Non-liver-related death	0.0	50.3	75.9	80.6	80.7	80.7
Liver-related death	0.0	16.2	19.0	19.3	19.3	19.3
All cause death	0.0	66.5	95.0	99.9	100.0	100.0
Alive	100.0	33.5	5.0	0.1	.	.
Stage distribution (%)†						
RNA- F0	13.0	20.8	27.1	30.9	.	.
RNA+ F0	30.4	17.6	10.1	9.3	.	.
Fibrosis 1	7.5	10.4	8.1	2.1	.	.
Fibrosis 2	7.5	10.5	10.2	7.2	.	.
Fibrosis 3	17.6	15.7	15.4	11.3	.	.
Cirrhosis	6.5	15.9	18.4	18.6	.	.
Decompensated cirrhosis	8.7	4.7	4.6	8.2	.	.
Liver transplant	0.0	3.0	4.0	6.2	.	.
HCC	8.7	1.5	2.1	6.2	.	.

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.18. Hepatitis C prognosis by calendar year: Non-hemophilics, Age 80-89

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	8.1	12.2	12.7	12.7	12.7	12.7
Decompensated cirrhosis	1.9	3.6	3.9	3.9	3.9	3.9
HCC	0.9	2.0	2.1	2.1	2.1	2.1
Liver transplant	0.9	1.5	1.5	1.5	1.5	1.5
Non-liver-related death	0	78.6	95.7	96.0	96.0	96.0
Liver-related death	0	3.5	4.0	4.0	4.0	4.0
All cause death	0	82.1	99.7	100.0	100.0	100.0
Alive	100	17.9	0.3	.	.	.
Stage distribution (%)†						
RNA- F0	19.1	27.2	29.2	.	.	.
RNA+ F0	51.2	25.1	16.2	.	.	.
Fibrosis 1	7.9	13.6	9.4	.	.	.
Fibrosis 2	6.7	11.7	9.4	.	.	.
Fibrosis 3	6.1	10.1	12.1	.	.	.
Cirrhosis	5.3	7.9	11.8	.	.	.
Decompensated cirrhosis	1.9	2.1	4.4	.	.	.
Liver transplant	0.9	1.4	4.1	.	.	.
HCC	0.9	0.9	3.2	.	.	.

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.19. Hepatitis C prognosis by calendar year: Hemophilics, Age 80-89

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	0.0	4.6	4.9	4.9	4.9	4.9
Decompensated cirrhosis	0.0	0.6	0.7	0.7	0.7	0.7
HCC	4.4	4.8	4.9	4.9	4.9	4.9
Liver transplant	0.0	0.8	0.8	0.8	0.8	0.8
Non-liver-related death	0.0	83.4	95.3	95.5	95.5	95.5
Liver-related death	0.0	4.3	4.5	4.5	4.5	4.5
All cause death	0.0	87.6	99.8	100.0	100.0	100.0
Alive	100.0	12.4	0.2	.	.	.
Stage distribution (%)†						
RNA- F0	4.4	14.7	19.8	.	.	.
RNA+ F0	73.9	36.5	17.6	.	.	.
Fibrosis 1	3.9	17.8	11.5	.	.	.
Fibrosis 2	3.9	11.8	10.4	.	.	.
Fibrosis 3	9.6	9.8	15.4	.	.	.
Cirrhosis	0.0	6.2	18.1	.	.	.
Decompensated cirrhosis	0.0	1.4	3.3	.	.	.
Liver transplant	0.0	0.9	2.2	.	.	.
HCC	4.4	0.9	1.6	.	.	.

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.1.20. Hepatitis C prognosis by calendar year: Non-hemophilics, Age 90+

	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*						
Cirrhosis	4.4	5.5	5.5	5.5	5.5	5.5
Decompensated cirrhosis	0	0.7	0.7	0.7	0.7	0.7
HCC	0	0.4	0.4	0.4	0.4	0.4
Liver transplant	0	0.1	0.1	0.1	0.1	0.1
Non-liver-related death	0	97.5	99.5	99.5	99.5	99.5
Liver-related death	0	0.5	0.5	0.5	0.5	0.5
All cause death	0	98.0	100.0	100.0	100.0	100.0
Alive	100	2.0	0.0	.	.	.
Stage distribution (%)†						
RNA- F0	18.1	27.7	50.0	.	.	.
RNA+ F0	65.9	30.7	.	.	.	.
Fibrosis 1	4.4	15.9	.	.	.	.
Fibrosis 2	3.7	10.7	.	.	.	.
Fibrosis 3	3.5	7.5	.	.	.	.
Cirrhosis	4.4	5.0	.	.	.	.
Decompensated cirrhosis	0.0	1.1	.	.	.	.
Liver transplant	0.0	0.6	.	.	.	.
HCC	0.0	1.0	50.0	.	.	.

*Proportion computed with reference to the number of patients who were alive in year 2010.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g., 2010, 2020,…, 2060).

Stage distribution of the living patients in year 2010 is taken from the post-transfusion claimant cohort data with propensity adjustment for those without liver biopsy.

Table 8.2.1. Monte Carlo simulation describing overall uncertainty in the prediction model: Predicted cumulative rates of hepatitis C-related major events among living post-transfusion claimants at August 2010

Event	2020	2030	2040	2050	2060
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Cirrhosis (%)	24.3 (20.6-28.0)	32.2 (26.9-37.5)	36.3 (30.3-42.3)	37.9 (31.7-44.1)	38.5 (32.2-44.8)
Hepatocellular carcinoma (%)	4.0 (2.4-5.6)	7.0 (4.4-9.6)	9.1 (5.8-12.4)	10.1 (6.5-13.7)	10.5 (6.8-14.2)
Liver-related death (%)	7.0 (5.3-8.7)	14.6 (11.5-17.7)	20.0 (16.0-24.0)	22.8 (18.4-27.2)	24.0 (19.5-28.5)

Table 9.1.4. Estimated current distribution of living non-hemophilic HCV patients who were infected during 1986-1990, and have not claimed for compensation prior to 2010

	Predicted Stage	Observed adjusted stage	Assumed total number of patients infected during 1986 and 1990 and alive now																	
			9239			8104			7000			6000			5000			4000		
			Pred	Un-known	Un-known	Pred	Un-known	Un-known	Pred	Un-known	Un-known	Pred	Un-known	Un-known	Pred	Un-known	Un-known	Pred	Un-known	Un-known
	%	N	N	N	%	N	N	%	N	N	%	N	N	%	N	N	%	N	N	%
RNA+/-	51.12	1495	4723	3228	50.6	4143	2648	50.5	3578	2083	50.4	3068	1573	50.1	2556	1061	49.5	2045	550	54.1
F1	15.29	417	1413	996	15.6	1239	822	15.7	1070	653	15.8	917	500	15.9	765	348	16.2	612	195	19.1
F2	13.29	357	1228	871	13.7	1077	720	13.7	930	573	13.9	797	440	14.0	665	308	14.4	532	175	17.2
F3	11.37	328	1050	722	11.3	921	593	11.3	796	468	11.3	682	354	11.3	569	241	11.2	455	0	0.0
F4	6.79	181	627	446	7.0	550	369	7.1	475	294	7.1	407	226	7.2	340	159	7.4	272	91	8.9
Decomp	1.23	47	114	67	1.1	100	53	1.0	86	39	1.0	74	27	0.9	62	15	0.7	49	2	0.2
HCC	0.23	18	21	3	0.05	19	1	0.01	16	0	0.00	14	0	0.00	12	0	0.00	9	0	0.00
Transplant	0.68	22	63	41	0.64	55	33	0.63	48	26	0.62	41	19	0.60	34	12	0.56	27	5	0.51
Total	100.0	2865	9239	6374	100.0	8105	5239	100.0	7000	4137	100.0	6001	3140	100.0	5000	2142	100.0	4000	1017	100.0

Note: The estimation is approached through following steps:
1. Predict the number of patients in each stage using predicted distribution to multiply the assumed total number of patients infected.
2. Find the difference between the predicted number of patients by stage.
3. Compute the proportion of patients in each stage by taking total difference as the base.
4. The observed number of patients with HCC and transplant are much higher than predicted.
We assume that the claimant data may have been contaminated by infections before 1986, and ignore these patients.
HCV, hepatitis C virus; RNA, ribonucleic acid; Decomp, decompensated cirrhosis; HCC, hepatocellular carcinoma.

12. Figures

Figure 2.1 Structure of Decision Model

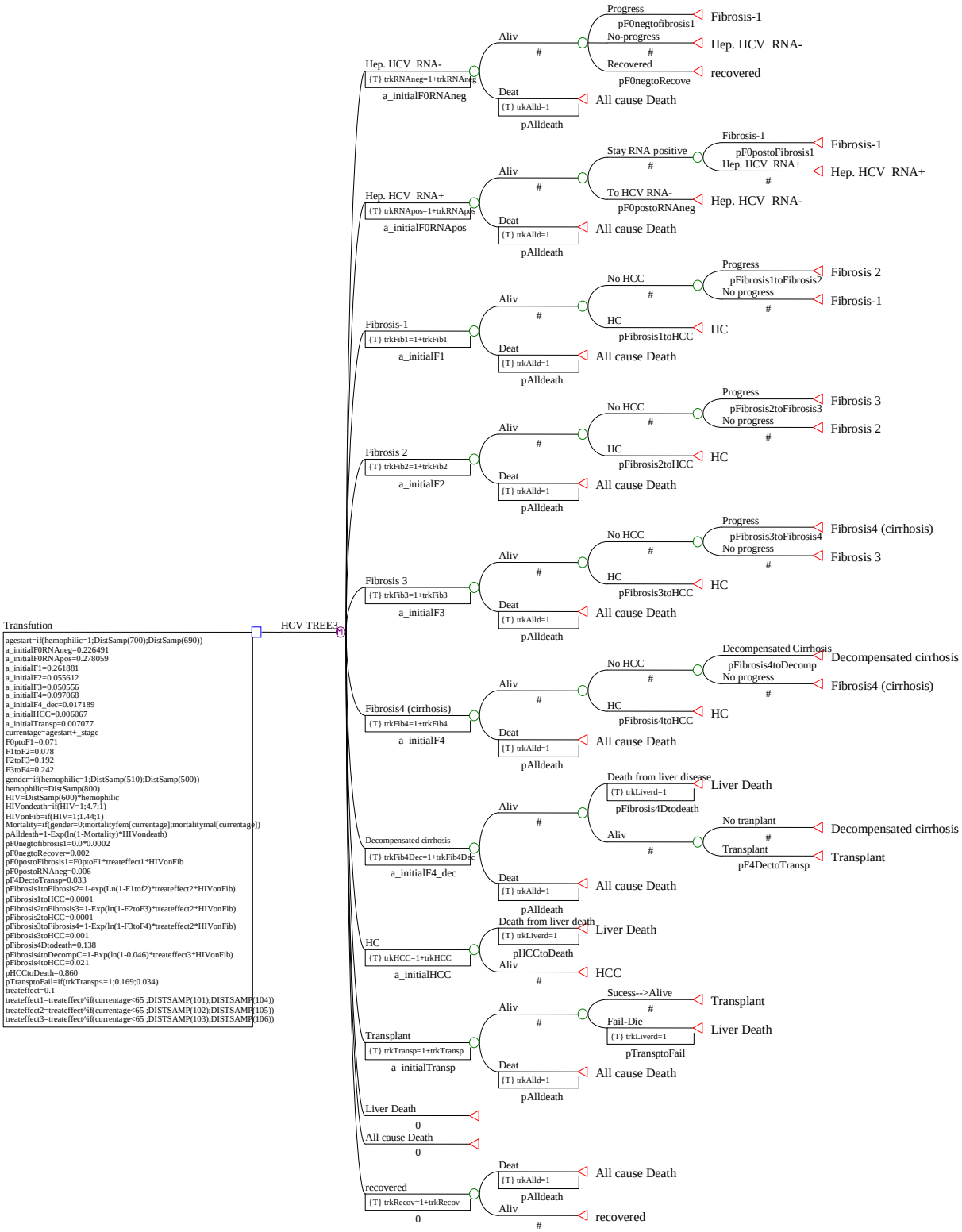
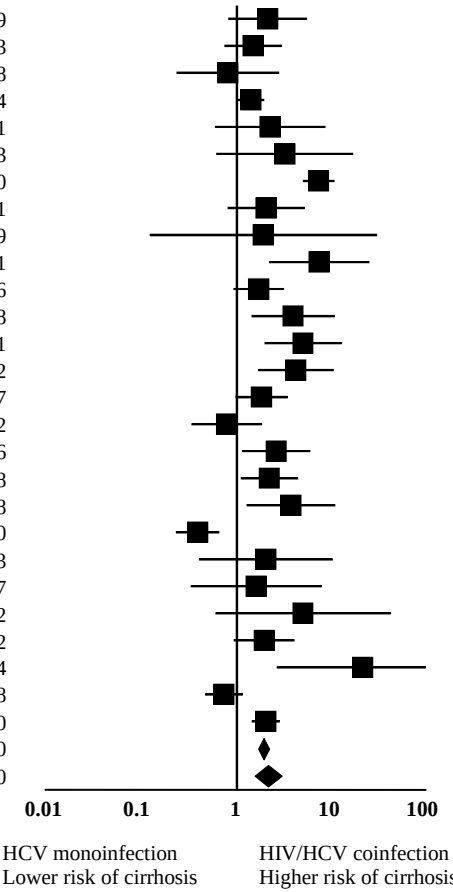


Figure 4.3.3. Risk of cirrhosis: Comparison between HCV monoinfection and HIV/HCV coinfection – meta-analysis

Study	Risk ratio	Lower limit	Upper limit	Z-Value	P-value	Sample	Covariates adjusted
Allory, 2000	2.114	0.804	5.562	1.517	0.129	116	Age at HCV, gender, duration of HCV, mode of HCV, alcohol
Benhamou, 1999	1.484	0.733	3.004	1.096	0.273	244	Age at HCV, gender, duration of HCV, mode of HCV, alcohol
Bierhoff, 1997	0.800	0.228	2.811	-0.348	0.728	55	
Brau, 2006	1.404	1.010	1.951	2.019	0.044	656	
Di Martino, 2001	2.245	0.581	8.683	1.172	0.241	160	Age, gender, duration of HCV, mode of HCV
Eyster, 1993	3.200	0.601	17.033	1.363	0.173	156	Age
Gaslightwala & Bini, 2006	7.289	4.938	10.760	9.998	0.000	708	Age, gender, current alcohol use, genotype
Gonzalez, 2006	2.037	0.789	5.254	1.471	0.141	206	
Grabczewska, 2005	1.905	0.119	30.452	0.456	0.649	82	
Lesens, 1999	7.400	2.174	25.194	3.202	0.001	134	Age
Macias, 2005	1.698	0.911	3.165	1.666	0.096	234	
Makris, 1996	3.920	1.418	10.836	2.633	0.008	138	Age at HCV, severity of hemophilia
Marine'-Barjoan, 2004	5.000	1.940	12.887	3.332	0.001	348	Age at HCV, gender, duration of HCV
Martinez-Sierra, 2003	4.195	1.665	10.567	3.042	0.002	188	Age, gender, duration of HCV, alcohol
Mohsen, 2003	1.814	0.958	3.434	1.830	0.067	208	Age, gender, duration of HCV, mode of HCV, ALT
Monto, 2005	0.778	0.327	1.854	-0.566	0.572	464	Age at HCV, gender
Pol, 1998a	2.600	1.123	6.021	2.230	0.026	553	Age at HCV, duration of HCV, alcohol, immune status
Pol, 1998b	2.200	1.088	4.450	2.194	0.028	210	Alcohol
Ragni, 2001	3.720	1.249	11.080	2.359	0.018	157	Age at HCV, duration of HCV, alcohol, HBsAg positivity
Rodriguez-Torres, 2006	0.384	0.225	0.656	-3.501	0.000	470	Age at HCV, gender, alcohol, ALT, genotype
Romeo, 2000	2.014	0.391	10.381	0.837	0.403	163	Gender, duration of HCV, alcohol
Sarmento-Castro, 2007	1.595	0.322	7.904	0.572	0.567	133	
Serfaty, 2001	5.000	0.584	42.797	1.469	0.142	76	Age, age at HCV, gender, duration of HCV, mode of HCV, alcohol
Soto, 1997	1.940	0.919	4.095	1.738	0.082	547	Age, gender, duration of HCV, mode of HCV
Telfer, 1994	21.400	2.612	175.317	2.855	0.004	183	Duration of HIV infection
Valle Tovo, 2007	0.727	0.457	1.156	-1.346	0.178	696	
Verma, 2006	2.015	1.421	2.858	3.928	0.000	381	
Fixed effects	1.901	1.662	2.174	9.383	0.000		
Random effects	2.122	1.518	2.967	4.401	0.000		

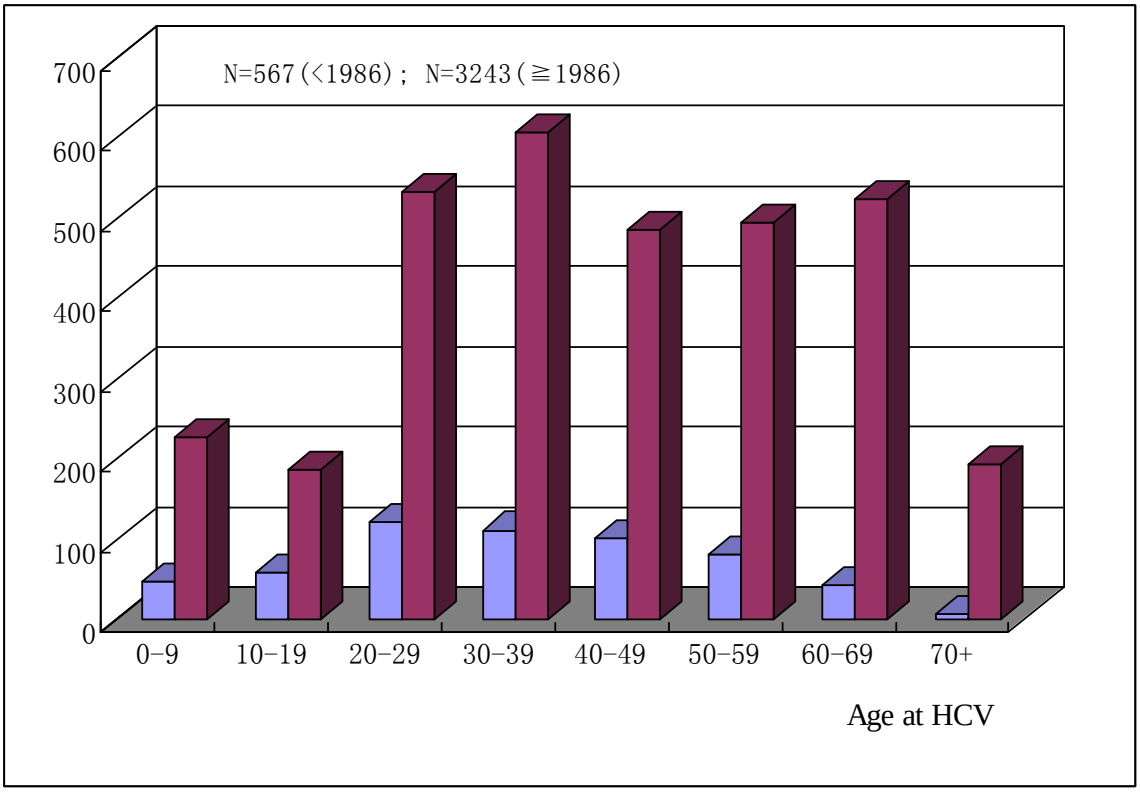


References: [74,82,83,85-91,147,162,175,177,188,190,192,195,296-304]

Risk ratios were calculated from available data. Adjusted relative risk were obtained directly from the following papers:[82,83,85-90]

HIV, human immunodeficiency virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen.

Figure 5.1. Distribution of age at time of hepatitis C virus infection among post-transfusion compensation claimants, 2010



HCV, hepatitis C virus

Figure 5.2. Percentage of post-transfusion compensation claimants by province of residence, 2010

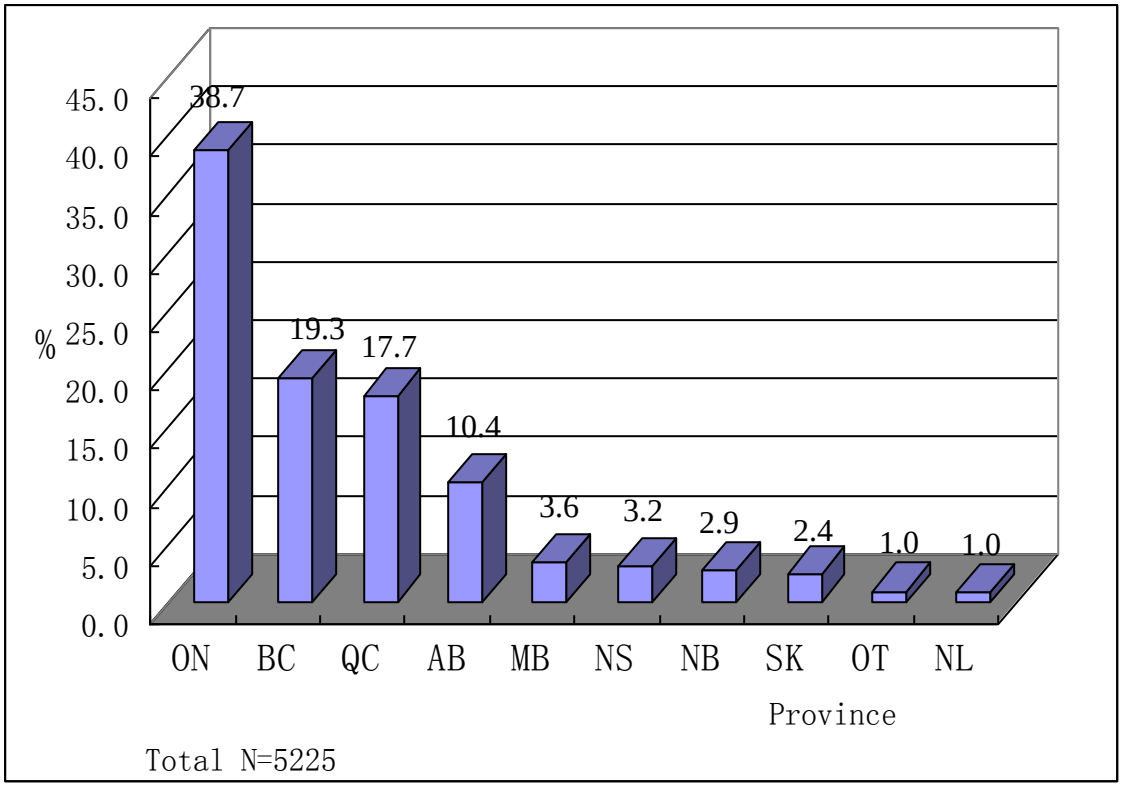
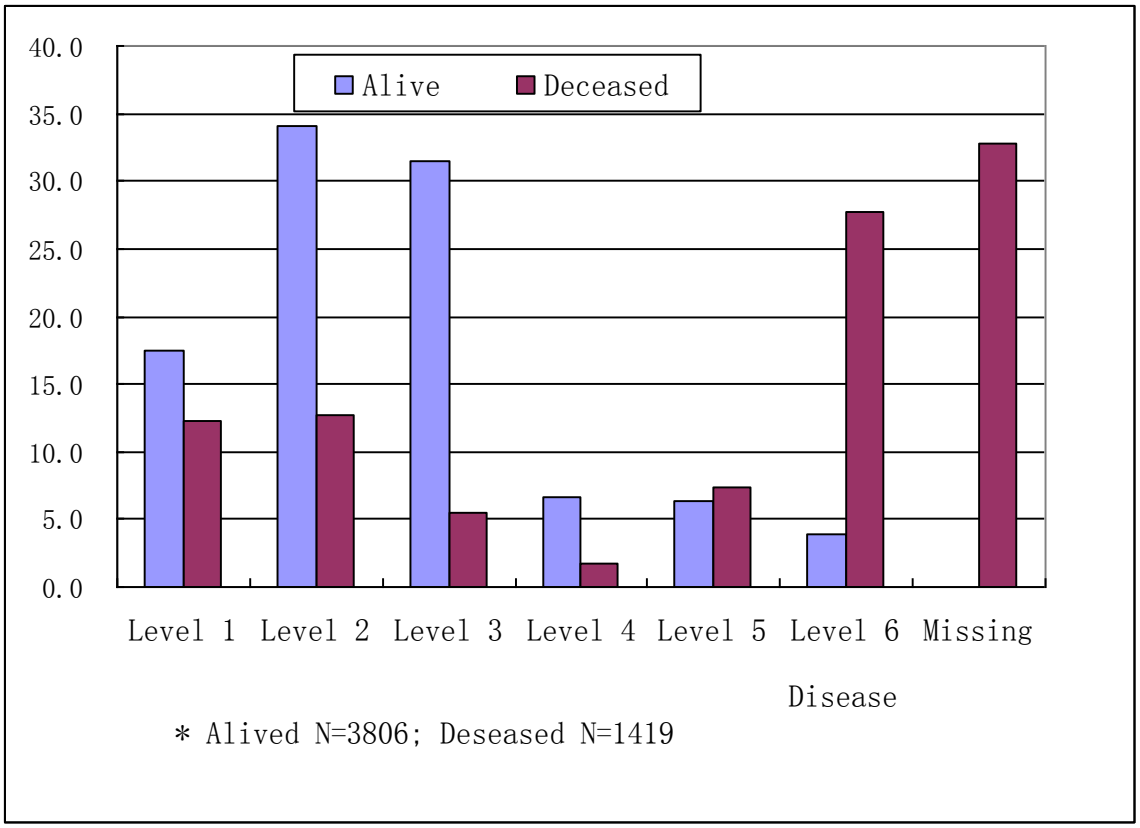
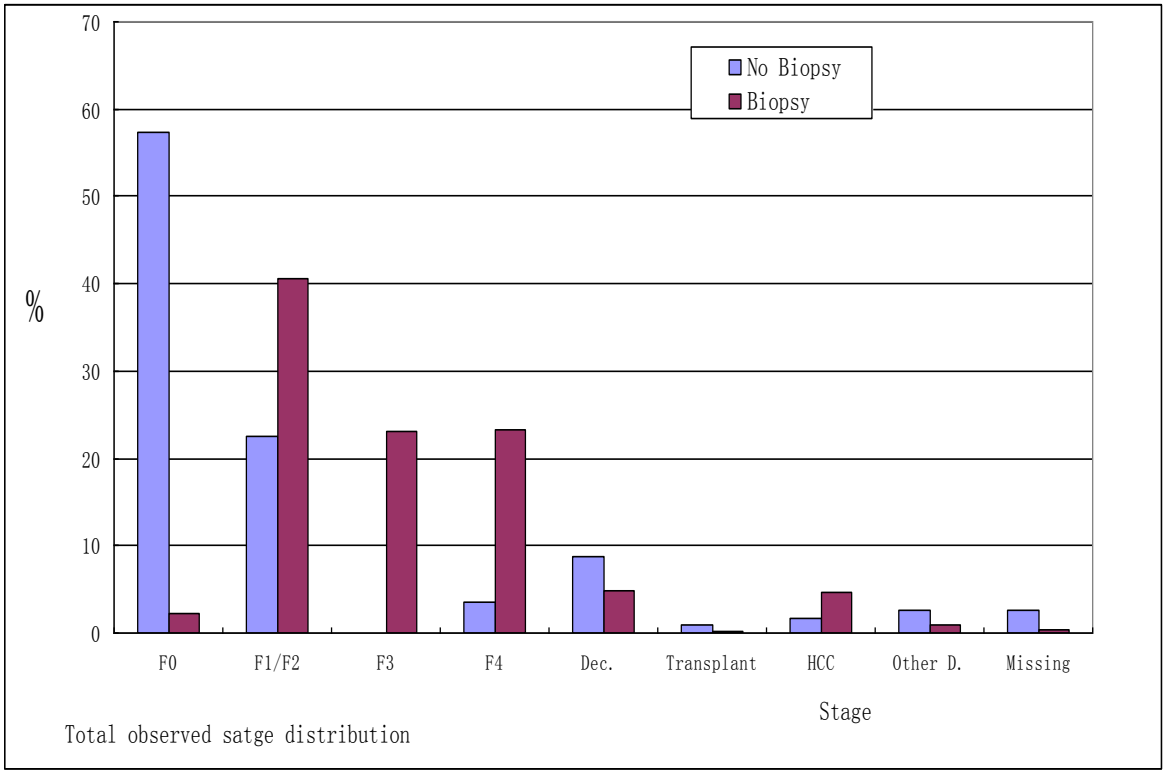


Figure 5.3. Compensation level of post-transfusion compensation claimants by survival status at August 2010



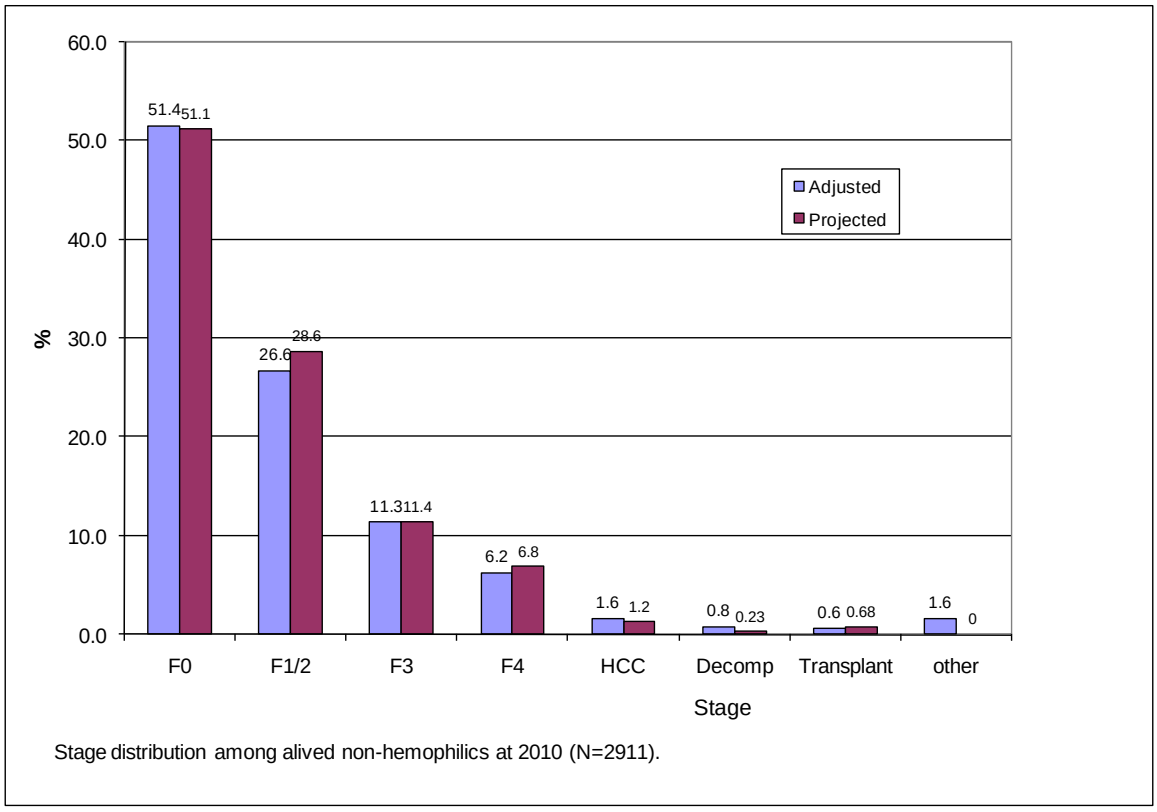
Level 1, HCV antibody positivity ; Level 2, HCV-RNA positivity; Level 3, Non-bridging fibrosis; Level 4, Bridging fibrosis; Level 5, Cirrhosis of liver, unresponsive porphyria cutanea tarda, unresponsive thrombocytopenia; Level 6, liver transplant, decompensation of the liver, hepatocellular cancer (HCC), B-cell lymphoma, symptomatic mixed cryoglobulinema, glomerulonephritis, renal failure.

Figure 5.4. Hepatitis C stage distribution among post-transfusion compensation claimants by liver biopsy availability



F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis; HCC, hepatocellular carcinoma; decomp, decompensated cirrhosis; transplant, liver transplant

Figure 5.5. Distribution of projected and adjusted HCV stage distribution among living non-hemophilic post-transfusion compensation claimants at August 2010



HCV, hepatitis C virus; F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis; HCC, hepatocellular carcinoma; decomp, decompensated cirrhosis; transplant, liver transplant

Appendix A. Publications derived from this study:

1. Thein HH, Yi Q, Heathcote EJ, Krahn MD. Prognosis of hepatitis C virus-infected Canadian post-transfusion compensation claimant cohort. J Viral Hepat 2009;16:802-813.
2. Krahn M, Wong JB, Heathcote J, Scully L, Seeff L. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. Med Decis Making 2004;24:20-29.
3. Wang P, Yi Q, Scully L, Heathcote J, Krahn M. Indications for interferon/ribavirin therapy in hepatitis C patients: findings from a survey of Canadian hepatologists. Can J Gastroenterol 2003;17:183-186.
4. Yi Q, Wang PP, Krahn M. Improving the accuracy of long-term prognostic estimates in hepatitis C virus infection. J Viral Hepat 2004;11:166-174.

Appendix B. SAS Code Used in the Markov-Maximum Likelihood Method

```
options ls=75;

%macro transition(pdis,year);
proc iml;
  use &pdis;
  read all into p;
  year=&year;
  ini={0.10 0.10 0.10 0.10};
  x={1 0  0 0 0};

do i=1 to 30000;
  tran=j(5,5,0);
  tran[1,2]=ini[1];tran[2,3]=ini[2];tran[3,4]=ini[3];
  tran[4,5]=ini[4];tran[5,5]=1;
  tran[1,1]=1-ini[1];tran[2,2]=1-ini[2];tran[3,3]=1-ini[3];
  tran[4,4]=1-ini[4];

tran5=tran**year;
xtran5=x*tran5;
rs=xtran5-p; rs2=rs*rs`;

if rs2<=0.000001 then do;
       tranrate=ini; p_end=xtran5;p_begin=p; residual=rs2;
       iteration=i;
     print"Estimated transition probability";
     print p_begin;
     print p_end  residual;
     print tranrate iteration;
     stop;
end;
  do j=1 to 4;
  if rs[26] < 0 then ini[26] = ini[26]-0.00001;
  if rs[26] > 0 then ini[26] = ini[26]+0.00001;
  end;
end;
if rs2>0.000001 then do;
print"Estimated transition probability without converge";

     print xtran5;
     print ini;
     print  p rs2 i;
end;
quit;
%mend;

*******example:                        ****;
*******Kenny Walsh (excluding 20% RNA-)****;
```

```
data tt;
input f0 f1 f2 f3 f4;
cards;
0.490 0.34 0.10 0.05 0.02
;
run;        %transition(tt,17)
```

Appendix C: Survey

P. Peter Wang, M.D., Ph.D
Assistant Professor
Department of Public Health Sc
University of Toronto
Fax: 416-340-4105
e-mail: wang@uhnres.utoronto.ca

Date: Nov. 22, 2004

Dear Dr. xxx,

You may recall that in 2001 we sent you a questionnaire about your antiviral treatment practices for hepatitis C patients. We very much appreciated your help then. Your clinical insights were incorporated into the prognostic models we developed for the Joint Committee administering the $1.1 billion compensation agreement for individuals who acquired hepatitis C through the blood supply.

Three years have passed and now we have been asked to revise our prognostic models. Once again, the effects of antiviral treatment remain as important part of our predictions of the long term prognosis of these individuals. As you know, peginterferon, which has been proven to be more effective in treating chronic hepatitis patients, has become a mainstream therapy in the past few years. Thus we suspect that these changes may have affected or will affect physicians' practice. We are writing to ask for your help by answering two brief questions. I realize that this request is only one of many demands on your time and trust that you can help with this very important task. To save your time, you can either fax or e-mail your answers with question numbers back to me.

Thank you

Peter

Questions 1.

By June, year 2001, 2466 Canadian hepatitis C patients filed claims for financial compensation. In the 2001 data set, the proportion who had ever received anti-viral treatment was **14.1%.** By June 2004, the number of claimants (including deceased) increased to 4,530. In the 2004 data, the proportion of those who ever received antiviral treatment increased to **16.2%**. Now we would like to ask your opinions (your best estimate) in terms of the proportion of patients who will have received antiviral treatment 10 years from now. _____%

For your reference, the following two tables provide disease and patient characteristics associated with the patients of interest.

Table 1. **Estimated Fibrosis stage** distribution in compensation claimants in June, 2004.

	F0	F1	F2-F3	Cirrhosis	Transplant	Decompensated cirrhosis	HCC	Others
N	1751	929	490	255	62	24	22	36
%	49.2	26.1	13.5	7.2	1.74	0.67	0.62	1.01

Table 2. Other selected characteristics

Age Mean ≈53	<40 >40	25% 75%
Sex	Male Female	53% 47%
Hemophilia	Yes No	27.3% 72.7%

Question 2.

2A: What percentage of patients with mild hepatitis/no-fibrosis do you treat? _____%

2B: What percentage of patients with moderate-severe hepatitis with fibrosis do you treat? _____%

2C: What percentage of patients with well compensated cirrhosis do you treat? _____%

2D: What percentage of patients with decompensated cirrhosis do you treat? _____%

2004 Hepatologist survey

Physician	Q1 (%)	Q2a (%)	Q2b (%)	Q2c (%)	Q2d (%)
1	35	10	70	40	0
2	60	10	95	99	20
3	30	5	90	80	0
4	50	15	75	75	25
5	27	30	60	60	0
6	50	25	90	80	0
7	30	20	60	20	0
8	40	10	90	100	0
9	25	10	70	10	2
Average	38.6%	15.0%	77.8%	62.7%	5.2%
Result from last survey		13.8	80	75	0

Q2.

Q2a: What percentage of patients with mild hepatitis/no-fibrosis do you treat? _____%

Q2b: What percentage of patients with moderate-severe hepatitis with fibrosis do you treat? ___%

Q2c: What percentage of patients with well compensated cirrhosis do you treat? _____%

Q23: What percentage of patients with decompensated cirrhosis do you treat? _____%

Based on currently treating pattern and HCV stage distribution, we have estimated the proportion who are under treatment of 39.1%. $P=\Sigma d_i \times p_i$ where P is the proportion of people receiving anti-viral treatment; d_i is proportion of adjusted HCV stage i in current cohort, p_i is the physician estimated proportion receiving treatment for people in stage i.

References

1. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Empirically calibrated model of hepatitis C virus infection in the United States. Am J Epidemiol 2002;156:761-773.
2. Comeau P. Hepatitis C compensation may be extended. CMAJ 2005;172:25.
3. The hepatitis C prevention, support and research program: Health Canada Initiatives on hepatitis C. Health Canada. Can J Public Health 2000;9:S27-31.
4. Remis RS, Hogg RS, Krahn MD, Preiksaitis JK, Sherman M, Palmer RWH. Estimating the number of blood transfusion recipients infected by hepatitis C virus in Canada, 1960-85 and 1990-92: Report to Health Canada; 1998.
5. Zou S, Tepper M, Giulivi A. Current status of hepatitis C in Canada. Can J Public Health 2000;91 Suppl 1:S10-15, S10-16.
6. Stevens CE, Taylor PE, Pindyck J, Choo QL, Bradley DW, Kuo G, et al. Epidemiology of hepatitis C virus. A preliminary study in volunteer blood donors. JAMA 1990;263:49-53.
7. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. Ann Intern Med 1997;127:855-865.
8. Wong JB. Interferon treatment for chronic hepatitis B or C infection: costs and effectiveness. Acta Gastroenterol Belg 1998;61:238-242.
9. Krahn M, Heathcote J, Scully L, Seeff L, Wong J. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. Toronto: University Health Network; 1999.
10. Krahn M, Wang P, Yi Q, Scully L, Sherman M, Heathcote EJ. Estimating the prognosis of Canadians infected with the hepatitis C virus through the blood supply, 1986-1990 - Second revision of prognostic model incorporating data from the compensation claimant cohort. Toronto: University Health Network; 2005.
11. Krahn M, Wong JB, Heathcote J, Scully L, Seeff L. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. Med Decis Making 2004;24:20-29.
12. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology 2004;127:1372-1380.
13. Terrault NA. Hepatitis C virus and liver transplantation. Semin Gastrointest Dis 2000;11:96-114.
14. Alali J, Ramji A, Ho JK, Scudamore CH, Erb SR, Cheung E, et al. Liver transplant candidacy unsuitability: a review of the British Columbia experience. Can J Gastroenterol 2006;20:95-99.
15. TreeAge Software I. Data Pro for Health Care User's Manual. Williamstown, MA: TreeAge Software, INC.; 2001.
16. Vamvakas EC, Moore SB. Length of survival after perioperative transfusion. Transfus Med 1997;7:115-121.
17. Vamvakas EC, Taswell HF. Long-term survival after blood transfusion. Transfusion 1994;34:471-477.
18. Yi Q, Wang PP, Krahn M. Improving the accuracy of long-term prognostic estimates in hepatitis C virus infection. J Viral Hepat 2004;11:166-174.

19. Hutchinson SJ, Bird SM, Goldberg DJ. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. Hepatology 2005;42:711-723.
20. Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, et al. Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. Gut 2000;47:131-136.
21. El-Serag HB, Mason AC, Key C. Trends in survival of patients with hepatocellular carcinoma between 1977 and 1996 in the United States. Hepatology 2001;33:62-65.
22. Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, et al. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. Hepatology 2006;43:1303-1310.
23. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: A meta-analysis and meta-regression. Hepatology 2008;48:418-431.
24. Datz C, Cramp M, Haas T, Dietze O, Nitschko H, Froesner G, et al. The natural course of hepatitis C virus infection 18 years after an epidemic outbreak of non-A, non-B hepatitis in a plasmapheresis centre. Gut 1999;44:563-567.
25. 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.
26. Poynard T, Ratziu V, Benmanov Y, Di Martino V, Bedossa P, Opolon P. Fibrosis in patients with chronic hepatitis C: detection and significance. Semin Liver Dis 2000;20:47-55.
27. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med 1999;340:1228-1233.
28. Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. N Engl J Med 1992;327:1899-1905.
29. Barrera JM, Bruguera M, Ercilla MG, Gil C, Celis R, Gil MP, et al. Persistent hepatitis C viremia after acute self-limiting posttransfusion hepatitis C. Hepatology 1995;21:639-644.
30. Mattsson L, Sonnerborg A, Weiland O. Outcome of acute symptomatic non-A, non-B hepatitis: a 13-year follow-up study of hepatitis C virus markers. Liver 1993;13:274-278.
31. Farci P, London WT, Wong DC, Dawson GJ, Vallari DS, Engle R, et al. The natural history of infection with hepatitis C virus (HCV) in chimpanzees: comparison of serologic responses measured with first- and second-generation assays and relationship to HCV viremia. J Infect Dis 1992;165:1006-1011.
32. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA 2000;284:450-456.
33. Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology 1999;29:908-914.
34. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006;13:34-41.
35. Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. Hepatology 1997;26:15S-20S.

36. Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. Hepatology 2000;32:91-96.
37. Wiese M, Grungreiff K, Guthoff W, Lafrenz M, Oesen U, Porst H. Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany--a 25-year multicenter study. J Hepatol 2005;43:590-598.
38. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289-293.
39. Seeff LB. Natural history of hepatitis C. Hepatology 1997;26:21S-28S.
40. Matsumura H, Moriyama M, Goto I, Tanaka N, Okubo H, Arakawa Y. Natural course of progression of liver fibrosis in Japanese patients with chronic liver disease type C--a study of 527 patients at one establishment. J Viral Hepat 2000;7:268-275.
41. Sobesky R, Mathurin P, Charlotte F, Moussalli J, Olivi M, Vidaud M, et al. Modeling the impact of interferon alfa treatment on liver fibrosis progression in chronic hepatitis C: a dynamic view. The Multivirc Group. Gastroenterology 1999;116:378-386.
42. Wali M, Lewis S, Hubscher S, Harrison R, Ahmed M, Elias E, et al. Histological progression during short-term follow-up of patients with chronic hepatitis C virus infection. J Viral Hepat 1999;6:445-452.
43. Yano M, Kumada H, Kage M, Ikeda K, Shimamatsu K, Inoue O, et al. The long-term pathological evolution of chronic hepatitis C. Hepatology 1996;23:1334-1340.
44. Ghany MG, Kleiner DE, Alter H, Doo E, Khokar F, Promrat K, et al. Progression of fibrosis in chronic hepatitis C. Gastroenterology 2003;124:97-104.
45. Mathurin P, Moussalli J, Cadranel JF, Thibault V, Charlotte F, Dumouchel P, et al. Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal alanine transaminase activity. Hepatology 1998;27:868-872.
46. Ryder SD, Irving WL, Jones DA, Neal KR, Underwood JC. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. Gut 2004;53:451-455.
47. Zarski JP, Mc Hutchison J, Bronowicki JP, Sturm N, Garcia-Kennedy R, Hodaj E, et al. Rate of natural disease progression in patients with chronic hepatitis C. J Hepatol 2003;38:307-314.
48. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513-1520.
49. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696-699.
50. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol 1991;13:372-374.
51. Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology 2001;34:395-403.
52. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958-965.
53. Camma C, Di Bona D, Schepis F, Heathcote EJ, Zeuzem S, Pockros PJ, et al. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: a meta-analysis of individual patient data. Hepatology 2004;39:333-342.

54. Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303-1313.
55. Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. Clin Infect Dis 2004;39:1540-1543.
56. Currie SL, Ryan JC, Tracy D, Wright TL, George S, McQuaid R, et al. A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus. Drug Alcohol Depend 2008;93:148-154.
57. Dalgard O. Follow-up studies of treatment for hepatitis C virus infection among injection drug users. Clin Infect Dis 2005;40 Suppl 5:S336-338.
58. Reichard O, Glaumann H, Fryden A, Norkrans G, Wejstal R, Weiland O. Long-term follow-up of chronic hepatitis C patients with sustained virological response to alpha-interferon. J Hepatol 1999;30:783-787.
59. Rodriguez-Torres M, Rodriguez-Orengo JF, Rios-Bedoya CF, Fernandez-Carbia A, Marxuach-Cuetara AM, Lopez-Torres A, et al. Effect of hepatitis C virus treatment in fibrosis progression rate (FPR) and time to cirrhosis (TTC) in patients co-infected with human immunodeficiency virus: a paired liver biopsy study. J Hepatol 2007;46:613-619.
60. John-Baptiste AA, Tomlinson G, Hsu PC, Krajden M, Heathcote EJ, Laporte A, et al. Sustained Responders Have Better Quality of Life and Productivity Compared With Treatment Failures Long After Antiviral Therapy for Hepatitis C. Am J Gastroenterol 2009.
61. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147:677-684.
62. Heathcote EJ, Shiffman ML, Cooksley WG, Dusheiko GM, Lee SS, Balart L, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000;343:1673-1680.
63. Veldt BJ, Saracco G, Boyer N, Camma C, Bellobuono A, Hopf U, et al. Long term clinical outcome of chronic hepatitis C patients with sustained virological response to interferon monotherapy. Gut 2004;53:1504-1508.
64. Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998;352:1426-1432.
65. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, Jr., et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975-982.
66. Hadziyannis SJ, Sette H, Jr., Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346-355.
67. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. JAMA 2004;292:2839-2848.

68. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med 2004;351:451-459.
69. Laguno M, Murillas J, Blanco JL, Martinez E, Miquel R, Sanchez-Tapias JM, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. AIDS 2004;18:F27-36.
70. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004;351:438-450.
71. Fernandez-Rodriguez CM, Alonso S, Martinez SM, Forns X, Sanchez-Tapias JM, Rincon D, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: outcomes and factors predicting response. Am J Gastroenterol 2010;105:2164-2172; quiz 2173.
72. Poynard T, McHutchison J, Davis GL, Esteban-Mur R, Goodman Z, Bedossa P, et al. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. Hepatology 2000;32:1131-1137.
73. Yamakawa Y, Sata M, Suzuki H, Noguchi S, Tanikawa K. Higher elimination rate of hepatitis C virus among women. J Viral Hepat 1996;3:317-321.
74. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology 1999;30:1054-1058.
75. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, Lloyd AR, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology 2001;34:809-816.
76. Freeman AJ, Law MG, Kaldor JM, Dore GJ. Predicting progression to cirrhosis in chronic hepatitis C virus infection. J Viral Hepat 2003;10:285-293.
77. Ostapowicz G, Watson KJ, Locarnini SA, Desmond PV. Role of alcohol in the progression of liver disease caused by hepatitis C virus infection. Hepatology 1998;27:1730-1735.
78. Roudot-Thoraval F, Bastie A, Pawlotsky JM, Dhumeaux D. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6,664 patients. The Study Group for the Prevalence and the Epidemiology of Hepatitis C Virus. Hepatology 1997;26:485-490.
79. Serfaty L, Chazouilleres O, Poujol-Robert A, Morand-Joubert L, Dubois C, Chretien Y, et al. Risk factors for cirrhosis in patients with chronic hepatitis C virus infection: results of a case-control study. Hepatology 1997;26:776-779.
80. Wiley TE, McCarthy M, Breidi L, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. Hepatology 1998;28:805-809.
81. Bonacini M, Puoti M. Hepatitis C in patients with human immunodeficiency virus infection: diagnosis, natural history, meta-analysis of sexual and vertical transmission, and therapeutic issues. Arch Intern Med 2000;160:3365-3373.
82. Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. J Infect Dis 2001;183:1112-1115.
83. Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with

human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr 1993;6:602-610.
84. Graham CS, Baden LR, Yu E, Mrus JM, Carnie J, Heeren T, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis 2001;33:562-569.
85. Lesens O, Deschenes M, Steben M, Belanger G, Tsoukas CM. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. J Infect Dis 1999;179:1254-1258.
86. Makris M, Preston FE, Rosendaal FR, Underwood JC, Rice KM, Triger DR. The natural history of chronic hepatitis C in haemophiliacs. Br J Haematol 1996;94:746-752.
87. Pol S, Fontaine H, Carnot F, Zylberberg H, Berthelot P, Brechot C, et al. Predictive factors for development of cirrhosis in parenterally acquired chronic hepatitis C: a comparison between immunocompetent and immunocompromised patients. J Hepatol 1998;29:12-19.
88. Pol S, Lamorthe B, Thi NT, Thiers V, Carnot F, Zylberberg H, et al. Retrospective analysis of the impact of HIV infection and alcohol use on chronic hepatitis C in a large cohort of drug users. J Hepatol 1998;28:945-950.
89. Soto B, Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengoechea M, Hernandez-Quero J, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. J Hepatol 1997;26:1-5.
90. Telfer P, Sabin C, Devereux H, Scott F, Dusheiko G, Lee C. The progression of HCV-associated liver disease in a cohort of haemophilic patients. Br J Haematol 1994;87:555-561.
91. Grabczewska E, Pawlowska M. Morphological liver changes of chronic hepatitis C in antiretroviral-naive HIV-infected patients. Przegl Epidemiol 2005;59:423-430.
92. Yee TT, Griffioen A, Sabin CA, Dusheiko G, Lee CA. The natural history of HCV in a cohort of haemophilic patients infected between 1961 and 1985. Gut 2000;47:845-851.
93. Perrillo RP. The role of liver biopsy in hepatitis C. Hepatology 1997;26:57S-61S.
94. Hui CK, Belaye T, Montegrande K, Wright TL. A comparison in the progression of liver fibrosis in chronic hepatitis C between persistently normal and elevated transaminase. J Hepatol 2003;38:511-517.
95. Kyrlagkitsis I, Portmann B, Smith H, O'Grady J, Cramp ME. Liver histology and progression of fibrosis in individuals with chronic hepatitis C and persistently normal ALT. Am J Gastroenterol 2003;98:1588-1593.
96. Arora S, O'Brien C, Zeuzem S, Shiffman ML, Diago M, Tran A, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. J Gastroenterol Hepatol 2006;21:406-412.
97. Hu KQ, Tong MJ. The long-term outcomes of patients with compensated hepatitis C virus-related cirrhosis and history of parenteral exposure in the United States. Hepatology 1999;29:1311-1316.
98. Kobayashi M, Tanaka E, Sodeyama T, Urushihara A, Matsumoto A, Kiyosawa K. The natural course of chronic hepatitis C: a comparison between patients with genotypes 1 and 2 hepatitis C viruses. Hepatology 1996;23:695-699.

99. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. J Hepatol 2001;34:730-739.
100. Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002;36:S35-46.
101. Ikkala E, Helske T, Myllyla G, Nevanlinna HR, Pitkanen P, Rasi V. Changes in the life expectancy of patients with severe haemophilia A in Finland in 1930-79. Br J Haematol 1982;52:7-12.
102. Larsson SA, Wiechel B. Deaths in Swedish hemophiliacs, 1957-1980. Acta Med Scand 1983;214:199-206.
103. Soucie JM, Nuss R, Evatt B, Abdelhak A, Cowan L, Hill H, et al. Mortality among males with hemophilia: relations with source of medical care. The Hemophilia Surveillance System Project Investigators. Blood 2000;96:437-442.
104. Triemstra M, Rosendaal FR, Smit C, Van der Ploeg HM, Briet E. Mortality in patients with hemophilia. Changes in a Dutch population from 1986 to 1992 and 1973 to 1986. Ann Intern Med 1995;123:823-827.
105. Darby SC, Ewart DW, Giangrande PL, Spooner RJ, Rizza CR, Dusheiko GM, et al. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. Lancet 1997;350:1425-1431.
106. Arnold DM, Julian JA, Walker IR. Mortality rates and causes of death among all HIV-positive individuals with hemophilia in Canada over 21 years of follow-up. Blood 2006;108:460-464.
107. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Hepatology 2001;33:1358-1364.
108. Adinolfi LE, Utili R, Ruggiero G. Body composition and hepatic steatosis as precursors of fibrosis in chronic hepatitis C patients.[comment]. Hepatology 1999;30:1530-1531.
109. Lam NP, Pitrak D, Speralakis R, Lau AH, Wiley TE, Layden TJ. Effect of obesity on pharmacokinetics and biologic effect of interferon-alpha in hepatitis C. Dig Dis Sci 1997;42:178-185.
110. Fiore G, Fera G, Napoli N, Vella F, Schiraldi O. Liver steatosis and chronic hepatitis C: a spurious association? Eur J Gastroenterol Hepatol 1996;8:125-129.
111. Gordon SC, Bayati N, Silverman AL. Clinical outcome of hepatitis C as a function of mode of transmission. Hepatology 1998;28:562-567.
112. Rodger AJ, Roberts S, Lanigan A, Bowden S, Brown T, Crofts N. Assessment of long-term outcomes of community-acquired hepatitis C infection in a cohort with sera stored from 1971 to 1975. Hepatology 2000;32:582-587.
113. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002;21:1559-1573.
114. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21:589-624.
115. Colombo M. Hepatitis C virus and hepatocellular carcinoma. Epidemiol Rev 1999;21:180-187.
116. Fattovich G, Giustina G, Realdi G, Corrocher R, Schalm SW. Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon

alfa. European Concerted Action on Viral Hepatitis (EUROHEP). Hepatology 1997;26:1338-1342.
117. Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, et al. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. Hepatology 1998;28:1687-1695.
118. Serfaty L, Aumaitre H, Chazouilleres O, Bonnand AM, Rosmorduc O, Poupon RE, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998;27:1435-1440.
119. Kato Y, Hamasaki K, Aritomi T, Nakao K, Nakata K, Eguchi K. Most of the patients with cirrhosis in Japan die from hepatocellular carcinoma. Oncology Reports 1999;6:1273-1276.
120. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463-472.
121. Mazzeo C, Azzaroli F, Giovanelli S, Dormi A, Festi D, Colecchia A, et al. Ten year incidence of HCV infection in northern Italy and frequency of spontaneous viral clearance. Gut 2003;52:1030-1034.
122. del Olmo JA, Serra MA, Rodriguez F, Escudero A, Gilabert S, Rodrigo JM. Incidence and risk factors for hepatocellular carcinoma in 967 patients with cirrhosis. J Cancer Res Clin Oncol 1998;124:560-564.
123. Sweeting MJ, De Angelis D, Brant LJ, Harris HE, Mann AG, Ramsay ME. The burden of hepatitis C in England. J Viral Hepat 2007;14:570-576.
124. Bralet MP, Regimbeau JM, Pineau P, Dubois S, Loas G, Degos F, et al. Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. Hepatology 2000;32:200-204.
125. Yatsuhashi H, Yano M. Natural history of chronic hepatitis C. J Gastroenterol Hepatol 2000;15:E111-116.
126. Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. Am J Cardiol 2003;92:1447-1451.
127. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-2281.
128. Vogt M, Lang T, Frosner G, Klingler C, Sendl AF, Zeller A, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. N Engl J Med 1999;341:866-870.
129. Barrett S, Goh J, Coughlan B, Ryan E, Stewart S, Cockram A, et al. The natural course of hepatitis C virus infection after 22 years in a unique homogenous cohort: spontaneous viral clearance and chronic HCV infection. Gut 2001;49:423-430.
130. Lehmann M, Meyer MF, Monazahian M, Tillmann HL, Manns MP, Wedemeyer H. High rate of spontaneous clearance of acute hepatitis C virus genotype 3 infection. J Med Virol 2004;73:387-391.
131. Spada E, Mele A, Berton A, Ruggeri L, Ferrigno L, Garbuglia AR, et al. Multispecific T cell response and negative HCV RNA tests during acute HCV infection are early prognostic factors of spontaneous clearance. Gut 2004;53:1673-1681.

132. Santantonio T, Medda E, Ferrari C, Fabris P, Cariti G, Massari M, et al. Risk factors and outcome among a large patient cohort with community-acquired acute hepatitis C in Italy. Clin Infect Dis 2006;43:1154-1159.
133. Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team [see comments]. N Engl J Med 1992;327:1899-1905.
134. Messick K, Sanders JC, Goedert JJ, Eyster ME. Hepatitis C viral clearance and antibody reactivity patterns in persons with haemophilia and other congenital bleeding disorders. Haemophilia 2001;7:568-574.
135. Bortolotti F, Resti M, Marcellini M, Giacchino R, Verucchi G, Nebbia G, et al. Hepatitis C virus (HCV) genotypes in 373 Italian children with HCV infection: changing distribution and correlation with clinical features and outcome. Gut 2005;54:852-857.
136. Grebely J, Conway B, Raffa JD, Lai C, Krajden M, Tyndall MW. Hepatitis C virus reinfection in injection drug users. Hepatology 2006;44:1139-1145.
137. Posthouwer D, Fischer K, van Erpecum KJ, Mauser-Bunschoten EP. The natural history of childhood-acquired hepatitis C infection in patients with inherited bleeding disorders. Transfusion 2006;46:1360-1366.
138. Scott JD, McMahon BJ, Bruden D, Sullivan D, Homan C, Christensen C, et al. High rate of spontaneous negativity for hepatitis C virus RNA after establishment of chronic infection in Alaska Natives. Clin Infect Dis 2006;42:945-952.
139. Harris HE, Eldridge KP, Harbour S, Alexander G, Teo CG, Ramsay ME. Does the clinical outcome of hepatitis C infection vary with the infecting hepatitis C virus type? J Viral Hepat 2007;14:213-220.
140. Yeung LT, To T, King SM, Roberts EA. Spontaneous clearance of childhood hepatitis C virus infection. J Viral Hepat 2007;14:797-805.
141. Krahn M, Wang PP, Yi QL, Scully L, Heathcote EJ. Estimating the Prognosis of Canadians Infected With the Hepatitis C Virus Through the Blood Supply, 1986-1990 --Second revision of Prognostic Model Incorporating
Data From the Compensation Claimant Cohort. 2005.
142. Alter HJ, Conry-Cantilena C, Melpolder J, Tan D, Van Raden M, Herion D, et al. Hepatitis C in asymptomatic blood donors. Hepatology 1997;26:29S-33S.
143. Silva GF, Coelho KI, Nishimura NF, Soares EC. Progression of liver fibrosis in blood donors infected with hepatitis C virus. Rom J Gastroenterol 2004;13:291-297.
144. Dalgard O, Jeansson S, Skaug K, Raknerud N, Bell H. Hepatitis C in the general adult population of Oslo: prevalence and clinical spectrum. Scand J Gastroenterol 2003;38:864-870.
145. Saadoun D, Asselah T, Resche-Rigon M, Charlotte F, Bedossa P, Valla D, et al. Cryoglobulinemia is associated with steatosis and fibrosis in chronic hepatitis C. Hepatology 2006;43:1337-1345.
146. Serra MA, Rodriguez F, del Olmo JA, Escudero A, Rodrigo JM. Influence of age and date of infection on distribution of hepatitis C virus genotypes and fibrosis stage. J Viral Hepat 2003;10:183-188.
147. Verma S, Bonacini M, Govindarajan S, Kanel G, Lindsay KL, Redeker A. More advanced hepatic fibrosis in hispanics with chronic hepatitis C infection: role of patient

demographics, hepatic necroinflammation, and steatosis. Am J Gastroenterol 2006;101:1817-1823.
148. Hu K-Q, Lee SM, Hu SX, Xia VW, Hillebrand DJ, Kyulo NL. Clinical presentation of chronic hepatitis C in patients with end-stage renal disease and on hemodialysis versus those with normal renal function. Am J Gastroenterol 2005;100:2010-2018.
149. Martin P, Carter D, Fabrizi F, Dixit V, Conrad AJ, Artinian L, et al. Histopathological features of hepatitis C in renal transplant candidates. Transplantation 2000;69:1479-1484.
150. Sezer S, Ozdemir BH, Arat Z, Turan M, Ozdemir NF, Haberal M. Spectrum of liver damage and correlation with clinical and laboratory parameters in HCV infected hemodialysis patients. Ren Fail 2001;23:807-818.
151. Sterling RK, Sanyal AJ, Luketic VA, Stravitz RT, King AL, Post AB, et al. Chronic hepatitis C infection in patients with end stage renal disease: characterization of liver histology and viral load in patients awaiting renal transplantation. Am J Gastroenterol 1999;94:3576-3582.
152. Toz H, Ok E, Yilmaz F, Akarca US, Erensoy S, Zeytinoglu A, et al. Clinicopathological features of hepatitis C virus infection in dialysis and renal transplantation. Journal of Nephrology 2002;15:308-312.
153. Varaut A, Fontaine H, Serpaggi J, Verkarre V, Vallet-Pichard A, Nalpas B, et al. Diagnostic accuracy of the fibrotest in hemodialysis and renal transplant patients with chronic hepatitis C virus. Transplantation 2005;80:1550-1555.
154. Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, et al. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. Hepatology 2004;40:1426-1433.
155. Levine RA, Sanderson SO, Ploutz-Snyder R, Murray F, Kay E, Hegarty J, et al. Assessment of fibrosis progression in untreated irish women with chronic hepatitis C contracted from immunoglobulin anti-D. Clin Gastroenterol Hepatol 2006;4:1271-1277.
156. Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. Hepatology 2000;32:91-96.
157. Cournot M, Glibert A, Castel F, Druart F, Imani K, Lauwers-Cances V, et al. Management of hepatitis C in active drugs users: experience of an addiction care hepatology unit. Gastroenterol Clin Biol 2004;28:533-539.
158. Grando-Lemaire V, Goisset P, Sorge F, Trinchet J-C, Castera L, Roulot D, et al. Hepatitis C virus screening in drug users in an addiction out-patient unit. Gastroenterol Clin Biol 2002;26:1091-1096.
159. Puoti M, Bonacini M, Spinetti A, Putzolu V, Govindarajan S, Zaltron S, et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and human immunodeficiency virus. J Infect Dis 2001;183:134-137.
160. Rai R, Wilson LE, Astemborski J, Anania F, Torbenson M, Spoler C, et al. Severity and correlates of liver disease in hepatitis C virus-infected injection drug users. Hepatology 2002;35:1247-1255.
161. Wilson LE, Torbenson M, Astemborski J, Faruki H, Spoler C, Rai R, et al. Progression of liver fibrosis among injection drug users with chronic hepatitis C. Hepatology 2006;43:788-795.

162. Allory Y, Charlotte F, Benhamou Y, Opolon P, Le Charpentier Y, Poynard T. Impact of human immunodeficiency virus infection on the histological features of chronic hepatitis C: a case-control study. The MULTIVIRC group. Hum Pathol 2000;31:69-74.
163. Asselah T, Boyer N, Guimont MC, Cazals-Hatem D, Tubach F, Nahon K, et al. Liver fibrosis is not associated with steatosis but with necroinflammation in French patients with chronic hepatitis C. Gut 2003;52:1638-1643.
164. Bedossa P, Moucari R, Chelbi E, Asselah T, Paradis V, Vidaud M, et al. Evidence for a role of nonalcoholic steatohepatitis in hepatitis C: a prospective study. Hepatology 2007;46:380-387.
165. Cheung RC, Currie S, Shen H, Ho SB, Bini EJ, Anand BS, et al. Chronic hepatitis C in Latinos: natural history, treatment eligibility, acceptance, and outcomes. Am J Gastroenterol 2005;100:2186-2193.
166. Cholet F, Nousbaum JB, Richecoeur M, Oger E, Cauvin JM, Lagarde N, et al. Factors associated with liver steatosis and fibrosis in chronic hepatitis C patients. Gastroenterol Clin Biol 2004;28:272-278.
167. Costa LB, Ferraz ML, Perez RM, Ferreira AS, Matos CA, Lanzoni VP, et al. Effect of host-related factors on the intensity of liver fibrosis in patients with chronic hepatitis C virus infection. Braz J Infect Dis 2002;6:219-224.
168. Erhardt A, Maschner-Olberg A, Mellenthin C, Kappert G, Adams O, Donner A, et al. HFE mutations and chronic hepatitis C: H63D and C282Y heterozygosity are independent risk factors for liver fibrosis and cirrhosis. J Hepatol 2003;38:335-342.
169. Fernandez-Rodriguez CM, Gutierrez ML, Serrano PL, Lledo JL, Santander C, Fernandez TP, et al. Factors influencing the rate of fibrosis progression in chronic hepatitis C. Dig Dis Sci 2004;49:1971-1976.
170. Fernandez Salazar LI, Alvarez Gago T, Aller de la Fuente R, Ordun~a Domingo A, Arranz Santos T, de la Calle Valverde F, et al. Iron overload and genotype 3 are associated with liver steatosis in chronic hepatitis C. Rev Esp Enferm Dig 2004;96:818-828.
171. Fontaine H, Nalpas B, Poulet B, Carnot F, Zylberberg H, Brechot C, et al. Hepatitis activity index is a key factor in determining the natural history of chronic hepatitis C. Hum Pathol 2001;32:904-909.
172. Fontana RJ, Kleiner DE, Bilonick R, Terrault N, Afdhal N, Belle SH, et al. Modeling hepatic fibrosis in African American and Caucasian American patients with chronic hepatitis C virus infection. Hepatology 2006;44:925-935.
173. Forrest EH, Thorburn D, Spence E, Oien KA, Inglis G, Smith CA, et al. Polymorphisms of the renin-angiotensin system and the severity of fibrosis in chronic hepatitis C virus infection. J Viral Hepat 2005;12:519-524.
174. Freeman A, Hamid S, Morris L, Vowler S, Rushbrook S, Wight DG, et al. Improved detection of hepatocyte proliferation using antibody to the pre-replication complex: an association with hepatic fibrosis and viral replication in chronic hepatitis C virus infection. J Viral Hepat 2003;10:345-350.
175. Gaslightwala I, Bini EJ. Impact of human immunodeficiency virus infection on the prevalence and severity of steatosis in patients with chronic hepatitis C virus infection. J Hepatol 2006;44:1026-1032.

176. Geier A, Reugels M, Weiskirchen R, Wasmuth HE, Dietrich CG, Siewert E, et al. Common heterozygous hemochromatosis gene mutations are risk factors for inflammation and fibrosis in chronic hepatitis C. Liver International 2004;24:285-294.
177. Gonzalez SA, Liu RC, Edlin BR, Jacobson IM, Talal AH. HIV/hepatitis C virus-coinfected patients with normal alanine aminotransferase levels. J Acquir Immune Defic Syndr 2006;41:582-589.
178. Haber MM, West AB, Haber AD, Reuben A. Relationship of aminotransferases to liver histological status in chronic hepatitis C. Am J Gastroenterol 1995;90:1250-1257.
179. Hezode C, Roudot-Thoraval F, Nguyen S, Grenard P, Julien B, Zafrani ES, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. Hepatology 2005;42:63-71.
180. Hofer H, Neufeld JB, Oesterreicher C, Grundtner P, Wrba F, Gangl A, et al. Bi-allelic presence of the interleukin-10 receptor 1 G330R allele is associated with cirrhosis in chronic HCV-1 infection. Genes Immun 2005;6:242-247.
181. Hollander A, Glaumann H, Weiland O. Histological findings, genotype distribution and percentage of patients fulfilling the treatment criteria among patients with chronic hepatitis C virus infection in a single Swedish centre. Scand J Gastroenterol 2004;39:164-167.
182. Huang H, Shiffman ML, Cheung RC, Layden TJ, Friedman S, Abar OT, et al. Identification of two gene variants associated with risk of advanced fibrosis in patients with chronic hepatitis C. Gastroenterology 2006;130:1679-1687.
183. Imazeki F, Yokosuka O, Fukai K, Kawai S, Kanda T, Kojima H, et al. Lower incidence of hepatic failure than hepatocellular carcinoma in Japanese patients with chronic hepatitis C. Liver Int 2005;25:772-778.
184. Khan MH, Farrell GC, Byth K, Lin R, Weltman M, George J, et al. Which patients with hepatitis C develop liver complications? Hepatology 2000;31:513-520.
185. Kryczka W, Chrapek M, Paluch K, Zarebska-Michaluk D, Urbaniak A. Rate of liver fibrosis progression among patients with chronic hepatitis C in Poland. Pol Arch Med Wewn 2003;110:869-875.
186. Lagging LM, Westin J, Svensson E, Aires N, Dhillon AP, Lindh M, et al. Progression of fibrosis in untreated patients with hepatitis C virus infection. Liver 2002;22:136-144.
187. Leroy V, Monier F, Bottari S, Trocme C, Sturm N, Hilleret MN, et al. Circulating matrix metalloproteinases 1, 2, 9 and their inhibitors TIMP-1 and TIMP-2 as serum markers of liver fibrosis in patients with chronic hepatitis C: comparison with PIIINP and hyaluronic acid. Am J Gastroenterol 2004;99:271-279.
188. Macias J, Japon MA, Saez C, Palacios RB, Mira JA, Garcia-Garcia JA, et al. Increased hepatocyte fas expression and apoptosis in HIV and hepatitis C virus coinfection. J Infect Dis 2005;192:1566-1576.
189. Marine-Barjoan E, Fontas E, Pradier C, Ouzan D, Saint-Paul MC, Sattonnet C, et al. Registry of liver biopsies from hepatitis C infected patients in the Alpes-Maritimes (France). Results from the first 2 years. Gastroenterol Clin Biol 2002;26:57-61.
190. Martinez-Sierra C, Arizcorreta A, Diaz F, Roldan R, Martin-Herrera L, Perez-Guzman E, et al. Progression of chronic hepatitis C to liver fibrosis and cirrhosis in patients coinfected with hepatitis C virus and human immunodeficiency virus. Clin Infect Dis 2003;36:491-498.

191. Metwally MA, Zein CO, Zein NN. Clinical significance of hepatic iron deposition and serum iron values in patients with chronic hepatitis C infection. Am J Gastroenterol 2004;99:286-291.
192. Mohsen AH, Easterbrook PJ, Taylor C, Portmann B, Kulasegaram R, Murad S, et al. Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. Gut 2003;52:1035-1040.
193. Monto A, Alonzo J, Watson JJ, Grunfeld C, Wright TL. Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus, and alcohol. Hepatology 2002;36:729-736.
194. Monto A, Patel K, Bostrom A, Pianko S, Pockros P, McHutchison JG, et al. Risks of a range of alcohol intake on hepatitis C-related fibrosis. Hepatology 2004;39:826-834.
195. Monto A, Dove LM, Bostrom A, Kakar S, Tien PC, Wright TL. Hepatic steatosis in HIV/hepatitis C coinfection: prevalence and significance compared with hepatitis C monoinfection. Hepatology 2005;42:310-316.
196. Muller P, Renou C, Harafa A, Jouve E, Kaplanski G, Ville E, et al. Lymph node enlargement within the hepatoduodenal ligament in patients with chronic hepatitis C reflects the immunological cellular response of the host. J Hepatol 2003;39:807-813.
197. Myers RP, Hilsden RJ, Lee SS. Historical features are poor predictors of liver fibrosis in Canadian patients with chronic hepatitis C. J Viral Hepat 2001;8:249-255.
198. Myers RP, Ratziu V, Imbert-Bismut F, Charlotte F, Poynard T. Biochemical markers of liver fibrosis: a comparison with historical features in patients with chronic hepatitis C. Am J Gastroenterol 2002;97:2419-2425.
199. Myers RP, Thibault V, Poynard T. The impact of prior hepatitis B virus infection on liver histology and the response to interferon therapy in chronic hepatitis C. J Viral Hepat 2003;10:103-110.
200. Nguyen HA, Miller AI, Dieperink E, Willenbring ML, Tetrick LL, Durfee JM, et al. Spectrum of disease in U.S. veteran patients with hepatitis C. Am J Gastroenterol 2002;97:1813-1820.
201. Ong JP, Younossi ZM, Speer C, Olano A, Gramlich T, Boparai N. Chronic hepatitis C and superimposed nonalcoholic fatty liver disease. Liver 2001;21:266-271.
202. Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. Am J Gastroenterol 2002;97:2408-2414.
203. Patel K, Norris S, Lebeck L, Feng A, Clare M, Pianko S, et al. HLA class I allelic diversity and progression of fibrosis in patients with chronic hepatitis C. Hepatology 2006;43:241-249.
204. Patton HM, Patel K, Behling C, Bylund D, Blatt LM, Vallee M, et al. The impact of steatosis on disease progression and early and sustained treatment response in chronic hepatitis C patients. J Hepatol 2004;40:484-490.
205. Pohl A, Behling C, Oliver D, Kilani M, Monson P, Hassanein T. Serum aminotransferase levels and platelet counts as predictors of degree of fibrosis in chronic hepatitis C virus infection. Am J Gastroenterol 2001;96:3142-3146.
206. Poujol-Robert A, Boelle PY, Wendum D, Poupon R, Robert A. Association between ABO blood group and fibrosis severity in chronic hepatitis C infection. Dig Dis Sci 2006;51:1633-1636.

207. Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology 2001;34:395-403.
208. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1485-1492.
209. Ratziu V, Munteanu M, Charlotte F, Bonyhay L, Poynard T. Fibrogenic impact of high serum glucose in chronic hepatitis C. J Hepatol 2003;39:1049-1055.
210. Renou C, Halfon P, Pol S, Cacoub P, Jouve E, Bronowicki JP, et al. Histological features and HLA class II alleles in hepatitis C virus chronically infected patients with persistently normal alanine aminotransferase levels. Gut 2002;51:585-590.
211. Reynolds WF, Patel K, Pianko S, Blatt LM, Nicholas JJ, McHutchison JG. A genotypic association implicates myeloperoxidase in the progression of hepatic fibrosis in chronic hepatitis C virus infection. Genes Immun 2002;3:345-349.
212. Roiser JP, Rogers RD, Sahakian BJ. Neuropsychological function in ecstasy users: a study controlling for polydrug use. Psychopharmacology (Berl) 2005:1-12.
213. Romero-Gomez M, Castellano-Megias VM, Grande L, Irles JA, Cruz M, Nogales MC, et al. Serum leptin levels correlate with hepatic steatosis in chronic hepatitis C. Am J Gastroenterol 2003;98:1135-1141.
214. Sud A, Hui JM, Farrell GC, Bandara P, Kench JG, Fung C, et al. Improved prediction of fibrosis in chronic hepatitis C using measures of insulin resistance in a probability index. Hepatology 2004;39:1239-1247.
215. Toccaceli F, Laghi V, Capurso L, Koch M, Sereno S, Scuderi M. Long-term liver histology improvement in patients with chronic hepatitis C and sustained response to interferon. J Viral Hepat 2003;10:126-133.
216. Watt K, Uhanova J, Gong Y, Kaita K, Doucette K, Pettigrew N, et al. Serum immunoglobulins predict the extent of hepatic fibrosis in patients with chronic hepatitis C virus infection. J Viral Hepat 2004;11:251-256.
217. Wietzke-Braun P, Braun F, Schott P, Ramadori G. Is laparoscopy an advantage in the diagnosis of cirrhosis in chronic hepatitis C virus infection? World J Gastroenterol 2003;9:745-750.
218. Wilfredo Canchis P, Gonzalez SA, Isabel Fiel M, Chiriboga L, Yee H, Edlin BR, et al. Hepatocyte proliferation in chronic hepatitis C: correlation with degree of liver disease and serum alpha-fetoprotein. Liver Int 2004;24:198-203.
219. Wong V, Caronia S, Wight D, Palmer CR, Petrik J, Britton P, et al. Importance of age in chronic hepatitis C virus infection. J Viral Hepat 1997;4:255-264.
220. Wright M, Goldin R, Hellier S, Knapp S, Frodsham A, Hennig B, et al. Factor V Leiden polymorphism and the rate of fibrosis development in chronic hepatitis C virus infection. Gut 2003;52:1206-1210.
221. de Ledinghen V, Trimoulet P, Winnock M, Foucher J, Bourliere M, Desmorat H, et al. Daily or three times a week interferon alfa-2b in combination with ribavirin or interferon alone for the treatment of patients with chronic hepatitis C. J Hepatol 2002;36:672-680.
222. Castellino S, Lensing S, Riely C, Rai SN, Davila R, Hayden RT, et al. The epidemiology of chronic hepatitis C infection in survivors of childhood cancer: an update of the St Jude Children's Research Hospital hepatitis C seropositive cohort. Blood 2004;103:2460-2466.

223. Guido M, Rugge M, Jara P, Hierro L, Giacchino R, Larrauri J, et al. Chronic hepatitis C in children: the pathological and clinical spectrum. Gastroenterology 1998;115:1525-1529.
224. Guido M, Bortolotti F, Leandro G, Jara P, Hierro L, Larrauri J, et al. Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? Am J Gastroenterol 2003;98:660-663.
225. Mohan P, Colvin C, Glymph C, Chandra RR, Kleiner DE, Patel KM, et al. Clinical spectrum and histopathologic features of chronic hepatitis C infection in children. J Pediatr 2007;150:168-174, 174 e161.
226. Hamada H, Yatsuhashi H, Yano K, Daikoku M, Arisawa K, Inoue O, et al. Impact of aging on the development of hepatocellular carcinoma in patients with posttransfusion chronic hepatitis C. Cancer 2002;95:331-339.
227. Shin JL, Teitel J, Swain MG, Bain VG, Adams PC, Croitoru K, et al. A Canadian multicenter retrospective study evaluating transjugular liver biopsy in patients with congenital bleeding disorders and hepatitis C: Is it safe and useful? Am J Hematol 2005;78:85-93.
228. Giordano HM, Franca AVC, Meirelles L, Escanhoela CAF, Nishimura NF, Santos RLS, et al. Chronic liver disease in kidney recipients with hepatitis C virus infection. Clin Transplant 2003;17:195-199.
229. Kamar N, Rostaing L, Selves J, Sandres-Saune K, Alric L, Durand D, et al. Natural history of hepatitis C virus-related liver fibrosis after renal transplantation. Am J Transplant 2005;5:1704-1712.
230. Reddy KR, Wright TL, Pockros PJ, Shiffman M, Everson G, Reindollar R, et al. Efficacy and safety of pegylated (40-kd) interferon alpha-2a compared with interferon alpha-2a in noncirrhotic patients with chronic hepatitis C. Hepatology 2001;33:433-438.
231. Sulkowski M, Reindollar R, Thomas DL, Brinkley-Laughton S, Hudson M, Yu J. Peginterferon-alpha-2a (40kD) and ribavirin in patients with chronic hepatitis C: a phase II open-label study. BioDrugs 2002;16:105-109.
232. Jeffers LJ, Cassidy W, Howell CD, Hu S, Reddy KR. Peginterferon alfa-2a (40 kd) and ribavirin for black American patients with chronic HCV genotype 1. Hepatology 2004;39:1702-1708.
233. Krawitt EL, Gordon SR, Grace ND, Ashikaga T, Ray MA, Palmer M, et al. A study of low dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. Am J Gastroenterol 2006;101:1268-1273.
234. Gish RG, Arora S, Rajender Reddy K, Nelson DR, O'Brien C, Xu Y, et al. Virological response and safety outcomes in therapy-nai ve patients treated for chronic hepatitis C with taribavirin or ribavirin in combination with pegylated interferon alfa-2a: a randomized, phase 2 study. J Hepatol 2007;47:51-59.
235. Jacobson IM, Brown RS, Jr., McCone J, Black M, Albert C, Dragutsky MS, et al. Impact of weight-based ribavirin with peginterferon alfa-2b in African Americans with hepatitis C virus genotype 1. Hepatology 2007;46:982-990.
236. Shiffman ML, Di Bisceglie AM, Lindsay KL, Morishima C, Wright EC, Everson GT, et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. Gastroenterology 2004;126:1015-1023; discussion 1947.

237. Jacobson IM, Gonzalez SA, Ahmed F, Lebovics E, Min AD, Bodenheimer HC, Jr., et al. A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. Am J Gastroenterol 2005;100:2453-2462.
238. Mathew A, Peiffer LP, Rhoades K, McGarrity T. Sustained viral response to pegylated interferon alpha-2b and ribavirin in chronic hepatitis C refractory to prior treatment. Dig Dis Sci 2006;51:1956-1961.
239. Khalili M, Bernstein D, Lentz E, Barylski C, Hoffman-Terry M. Pegylated interferon alpha-2a with or without ribavirin in HCV/HIV coinfection: partially blinded, randomized multicenter trial. Dig Dis Sci 2005;50:1148-1155.
240. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 2000;343:1666-1672.
241. Bosques-Padilla F, Trejo-Estrada R, Campollo-Rivas O, Cortez-Hernandez C, Dehesa-Violante M, Maldonado-Garza H, et al. Peginterferon alfa-2a plus ribavirin for treating chronic hepatitis C virus infection: analysis of Mexican patients included in a multicenter international clinical trial. Ann Hepatol 2003;2:135-139.
242. Alfaleh FZ, Hadad Q, Khuroo MS, Aljumah A, Algamedi A, Alashgar H, et al. Peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C in Saudi patients commonly infected with genotype 4. Liver Int 2004;24:568-574.
243. Dalgard O, Bjoro K, Hellum KB, Myrvang B, Ritland S, Skaug K, et al. Treatment with pegylated interferon and ribavarin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. Hepatology 2004;40:1260-1265.
244. Pockros PJ, Carithers R, Desmond P, Dhumeaux D, Fried MW, Marcellin P, et al. Efficacy and safety of two-dose regimens of peginterferon alpha-2a compared with interferon alpha-2a in chronic hepatitis C: a multicenter, randomized controlled trial. Am J Gastroenterol 2004;99:1298-1305.
245. Zeuzem S, Hultcrantz R, Bourliere M, Goeser T, Marcellin P, Sanchez-Tapias J, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. J Hepatol 2004;40:993-999.
246. Zeuzem S, Diago M, Gane E, Reddy KR, Pockros P, Prati D, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterology 2004;127:1724-1732.
247. Derbala M, Amer A, Bener A, Lopez AC, Omar M, El Ghannam M. Pegylated interferon-alpha 2b-ribavirin combination in Egyptian patients with genotype 4 chronic hepatitis. J Viral Hepat 2005;12:380-385.
248. Lee SD, Yu ML, Cheng PN, Lai MY, Chao YC, Hwang SJ, et al. Comparison of a 6-month course peginterferon alpha-2b plus ribavirin and interferon alpha-2b plus ribavirin in treating Chinese patients with chronic hepatitis C in Taiwan. J Viral Hepat 2005;12:283-291.
249. Legrand-Abravanel F, Nicot F, Boulestin A, Sandres-Saune K, Vinel JP, Alric L, et al. Pegylated interferon and ribavirin therapy for chronic hepatitis C virus genotype 4 infection. J Med Virol 2005;77:66-69.
250. Mangia A, Ricci GL, Persico M, Minerva N, Carretta V, Bacca D, et al. A randomized controlled trial of pegylated interferon alpha-2a (40 KD) or interferon alpha-2a plus

ribavirin and amantadine vs interferon alpha-2a and ribavirin in treatment-naive patients with chronic hepatitis C. J Viral Hepat 2005;12:292-299.
251. von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology 2005;129:522-527.
252. Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology 2006;130:1086-1097.
253. Bronowicki JP, Ouzan D, Asselah T, Desmorat H, Zarski JP, Foucher J, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. Gastroenterology 2006;131:1040-1048.
254. Derbala MF, Al Kaabi SR, El Dweik NZ, Pasic F, Butt MT, Yakoob R, et al. Treatment of hepatitis C virus genotype 4 with peginterferon alfa-2a: impact of bilharziasis and fibrosis stage. World J Gastroenterol 2006;12:5692-5698.
255. Helbling B, Jochum W, Stamenic I, Knopfli M, Cerny A, Borovicka J, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. J Viral Hepat 2006;13:762-769.
256. Meyer-Wyss B, Rich P, Egger H, Helbling B, Mullhaupt B, Rammert C, et al. Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5 microg/kg) combined with ribavirin in interferon-naive patients with chronic hepatitis C and up to moderate fibrosis. J Viral Hepat 2006;13:457-465.
257. Mimidis K, Papadopoulos VP, Elefsiniotis I, Koliouskas D, Ketikoglou I, Paraskevas E, et al. Hepatitis C virus survival curve analysis in naive patients treated with peginterferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of peginterferon and predictability of sustained viral response from early virologic data. J Gastrointestin Liver Dis 2006;15:213-219.
258. Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara J, et al. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. J Hepatol 2006;44:97-103.
259. Di Marco V, Almasio PL, Ferraro D, Calvaruso V, Alaimo G, Peralta S, et al. Peg-interferon alone or combined with ribavirin in HCV cirrhosis with portal hypertension: a randomized controlled trial. J Hepatol 2007;47:484-491.
260. Yu ML, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut 2007;56:553-559.
261. Mangia A, Minerva N, Bacca D, Cozzolongo R, Ricci GL, Carretta V, et al. Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial. Hepatology 2008;47:43-50.
262. August-Jorg BS, Borovicka J, Dufour JF, Gonvers JJ, Henz S, Hermann R, et al. Twenty-four vs. fourty-eight weeks of re-therapy with interferon alpha 2b and ribavirin in interferon alpha monotherapy relapsers with chronic hepatitis C. Swiss Med Wkly 2003;133:455-460.
263. Taliani G, Gemignani G, Ferrari C, Aceti A, Bartolozzi D, Blanc PL, et al. Pegylated interferon alfa-2b plus ribavirin in the retreatment of interferon-ribavirin nonresponder patients. Gastroenterology 2006;130:1098-1106.

264. Basso M, Torre F, Grasso A, Percario G, Azzola E, Artioli S, et al. Pegylated interferon and ribavirin in re-treatment of responder-relapser HCV patients. Dig Liver Dis 2007;39:47-51.
265. Crespo M, Sauleda S, Esteban JI, Juarez A, Ribera E, Andreu AL, et al. Peginterferon alpha-2b plus ribavirin vs interferon alpha-2b plus ribavirin for chronic hepatitis C in HIV-coinfected patients. J Viral Hepat 2007;14:228-238.
266. Cargnel A, Angeli E, Mainini A, Gubertini G, Giorgi R, Schiavini M, et al. Open, randomized, multicentre italian trial on PEG-IFN plus ribavirin versus PEG-IFN monotherapy for chronic hepatitis C in HIV-coinfected patients on HAART. Antivir Ther 2005;10:309-317.
267. Fuster D, Planas R, Gonzalez J, Force L, Cervantes M, Vilaro J, et al. Results of a study of prolonging treatment with pegylated interferon-alpha2a plus ribavirin in HIV/HCV-coinfected patients with no early virological response. Antivir Ther 2006;11:473-482.
268. Santin M, Shaw E, Garcia MJ, Delejido A, de Castro ER, Rota R, et al. Efficacy and safety of pegylated interferon-alpha2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. AIDS Res Hum Retroviruses 2006;22:315-320.
269. Voigt E, Schulz C, Klausen G, Goelz J, Mauss S, Schmutz G, et al. Pegylated interferon alpha-2b plus ribavirin for the treatment of chronic hepatitis C in HIV-coinfected patients. J Infect 2006;53:36-42.
270. Nunez M, Miralles C, Berdun MA, Losada E, Aguirrebengoa K, Ocampo A, et al. Role of weight-based ribavirin dosing and extended duration of therapy in chronic hepatitis C in HIV-infected patients: the PRESCO trial. AIDS Res Hum Retroviruses 2007;23:972-982.
271. Wang P, Yi Q, Scully L, Heathcote J, Krahn M. Indications for interferon/ribavirin therapy in hepatitis C patients: findings from a survey of Canadian hepatologists. Can J Gastroenterol 2003;17:183-186.
272. Diamondstone LS, Aledort LM, Goedert JJ. Factors predictive of death among HIV-uninfected persons with haemophilia and other congenital coagulation disorders. Haemophilia 2002;8:660-667.
273. Goedert JJ, Eyster ME, Lederman MM, Mandalaki T, De Moerloose P, White GC, 2nd, et al. End-stage liver disease in persons with hemophilia and transfusion-associated infections. Blood 2002;100:1584-1589.
274. Krahn M, Heathcote J, Scully L, Seeff L, Wong J. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. 1999.
275. Darby SC, Kan SW, Spooner RJ, Giangrande PL, Lee CA, Makris M, et al. The impact of HIV on mortality rates in the complete UK haemophilia population. AIDS 2004;18:525-533.
276. Ikeda K, Saitoh S, Koida I, Arase Y, Tsubota A, Chayama K, et al. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. Hepatology 1993;18:47-53.
277. Imberti D, Fornari F, Sbolli G, Buscarini E, Squassante L, Buscarini L. Hepatocellular carcinoma in liver cirrhosis. A prospective study. Scand J Gastroenterol 1993;28:540-544.
278. Mandelli C, Fraquelli M, Fargion S, Barisani D, Piperno A, Braga M, et al. Comparable frequency of hepatocellular carcinoma in cirrhosis of different aetiology Eur J Gastroenterol Hepatol 1994;6:1129-1134.

279. Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, et al. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 1995;346:1051-1055.
280. Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. Hepatology 1995;21:650-655.
281. Mazzella G, Accogli E, Sottili S, Festi D, Orsini M, Salzetta A, et al. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. J Hepatol 1996;24:141-147.
282. Bruno S, Silini E, Crosignani A, Borzio F, Leandro G, Bono F, et al. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. Hepatology 1997;25:754-758.
283. Gentilini P, Laffi G, La Villa G, Romanelli RG, Buzzelli G, Casini-Raggi V, et al. Long course and prognostic factors of virus-induced cirrhosis of the liver. Am J Gastroenterol 1997;92:66-72.
284. Tsai JF, Jeng JE, Ho MS, Chang WY, Hsieh MY, Lin ZY, et al. Effect of hepatitis C and B virus infection on risk of hepatocellular carcinoma: a prospective study. Br J Cancer 1997;76:968-974.
285. Benvegnu L, Chemello L, Noventa F, Fattovich G, Pontisso P, Alberti A. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis. Cancer 1998;83:901-909.
286. Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, et al. Prognosis of chronic hepatitis C: results of a large, prospective cohort study [see comments]. Hepatology 1998;28:1687-1695.
287. Chiaramonte M, Stroffolini T, Vian A, Stazi MA, Floreani A, Lorenzoni U, et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. Cancer 1999;85:2132-2137.
288. Gramenzi A, Andreone P, Fiorino S, Camma C, Giunta M, Magalotti D, et al. Impact of interferon therapy on the natural history of hepatitis C virus related cirrhosis. Gut 2001;48:843-848.
289. Valla DC, Chevallier M, Marcellin P, Payen JL, Trepo C, Fonck M, et al. Treatment of hepatitis C virus-related cirrhosis: a randomized, controlled trial of interferon alfa-2b versus no treatment. Hepatology 1999;29:1870-1875.
290. Fattovich G, Pantalena M, Zagni I, Realdi G, Schalm SW, Christensen E. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. Am J Gastroenterol 2002;97:2886-2895.
291. Mazziotti G, Sorvillo F, Morisco F, Carbone A, Rotondi M, Stornaiuolo G, et al. Serum insulin-like growth factor I evaluation as a useful tool for predicting the risk of developing hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis: a prospective study. Cancer 2002;95:2539-2545.
292. Planas R, Balleste B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol 2004;40:823-830.

293. Bruno R, Sacchi P, Puoti M, Maiocchi L, Patruno S, Carosi G, et al. Natural History of Compensated Viral Cirrhosis in a Cohort of Patients With Human Immunodeficiency Virus Infection. J Acquir Immune Defic Syndr 2007;46:297-303.
294. Life Tables, Canada, Provinces and Territories. 2000 to 2002. Statistics Canada - Catalogue No. 84-537-XIE. Accessed 14 November, 2007, at http://dsp-psd.pwgsc.gc.ca/Collection/Statcan/84-537-X/84-537-XIE2006001.pdf.
295. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS 2008;22:1979-1991.
296. Bierhoff E, Fischer HP, Willsch E, Rockstroh J, Spengler U, Brackmann HH, et al. Liver histopathology in patients with concurrent chronic hepatitis C and HIV infection. Virchows Archiv 1997;430:271-277.
297. Brau N, Salvatore M, Rios-Bedoya CF, Fernandez-Carbia A, Paronetto F, Rodriguez-Orengo JF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol 2006;44:47-55.
298. Di Martino V, Rufat P, Boyer N, Renard P, Degos F, Martinot-Peignoux M, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology 2001;34:1193-1199.
299. Marine-Barjoan E, Saint-Paul MC, Pradier C, Chaillou S, Anty R, Michiels JF, et al. Impact of antiretroviral treatment on progression of hepatic fibrosis in HIV/hepatitis C virus co-infected patients. AIDS 2004;18:2163-2170.
300. Rodriguez-Torres M, Rios-Bedoya CF, Rodriguez-Orengo J, Fernandez-Carbia A, Marxuach-Cuetara AM, Lopez-Torres A, et al. Progression to cirrhosis in Latinos with chronic hepatitis C: differences in Puerto Ricans with and without human immunodeficiency virus coinfection and along gender. J Clin Gastroenterol 2006;40:358-366.
301. Romeo R, Rumi MG, Donato MF, Cargnel MA, Vigano P, Mondelli M, et al. Hepatitis C is more severe in drug users with human immunodeficiency virus infection. J Viral Hepat 2000;7:297-301.
302. Sarmento-Castro R, Horta A, Vasconcelos O, Coelho H, Mendez J, Tavares AP, et al. Impact of peginterferon alpha-2b and ribavirin treatment on liver tissue in patients with HCV or HCV-HIV co-infection. J Infect 2007;54:609-616.
303. Serfaty L, Costagliola D, Wendum D, Picard O, Meyohas MC, Girard PM, et al. Impact of early-untreated HIV infection on chronic hepatitis C in intravenous drug users: a case-control study. AIDS 2001;15:2011-2016.
304. Valle Tovo C, Alves de Mattos A, Ribeiro de Souza A, Ferrari de Oliveira Rigo J, Lerias de Almeida PR, Galperim B, et al. Impact of human immunodeficiency virus infection in patients infected with the hepatitis C virus. Liver Int 2007;27:40-46.

This is Exhibit "N" referred to in the
affidavit of Asvini Krishnamoorthy
sworn before me at Toronto, Ontario
this 29th day of January, 2016

William Knight

A Commissioner for taking affidavits
within the Province of Ontario

Estimating the Prognosis of Canadians Infected With the Hepatitis C Virus through the Blood Supply, 1986-1990

The Fifth Revision of Hepatitis C Prognostic Model Based on the Post-Transfusion Hepatitis C Compensation Claimant Cohort

September 2014

Wendong Chen MD PhD
Qilong Yi MD MSc PhD
William Wong PhD
Murray Krahn MD MSc FRCPC

Corresponding author address:
Murray Krahn MD MSc FRCPC
144 College Street, Rm 600,
Toronto ON
M5S 3M2
Tel: 416 978 6608 (Pharmacy);
416 340 4155 (Toronto General);
Fax: 416 946 3719 Pharmacy;
Email: murray.krahn@theta.utoronto.ca

Table of Contents

List of Abbreviations

AE, adverse event

CASL, Canadian Association for the Study of the Liver

CHC, chronic hepatitis C

CI, confidence interval

HCC, hepatocellular carcinoma

HCV, hepatitis C virus

HIV, human immunodeficiency virus

MMLE, Markov maximum likelihood estimation

PEG-IFN, pegylated interferon

RBV, ribavirin

RNA, ribonucleic acid

RR, risk ratio/relative risk

SD, standard deviation

SE, standard error

SVC, spontaneous viral clearance

SVR, sustained viral response

US FDA, United States Food and Drug Administration

MMWG, medical model working group

Executive Summary

The hepatitis C virus (HCV) is one of the most common causes of liver disease in Canada. Prior to the availability of serologic testing for the presence of hepatitis C in 1990, blood transfusion and the use of blood products were the main sources of HCV infection. Between 1986 and 1990, surrogate marker testing was employed to screen blood donors in the United States to prevent the transmission of viral hepatitis in the general population. However, this practice was not conducted in Canada and as a result many Canadians likely acquired HCV through blood transfusion or blood products during this timeframe. On March 27, 1998 Canadian federal, provincial, and territorial governments announced an offer of financial assistance to individuals who acquired HCV through the blood system between January 1, 1986 and July 1, 1990. In 1999, court orders in British Columbia, Ontario and Québec were obtained approving a settlement agreement which established a compensation fund of approximately $1.1 billion for those Canadians who acquired HCV through blood transfusion or blood products between January 1, 1986 and July 1, 1990.

In order to assist with planning for future compensation, a working group was formed in November of 1998 to provide the best possible estimates for the prognosis of transfusion-acquired HCV claimants who met compensation requirements. A Markov state-transition model, developed to simulate the long-term liver-related health outcomes of compensation claimants, provided data needed for an actuarial model used in future compensation fund estimations. The compensation agreement between governments and plaintiffs requires fund estimates to be reviewed every three years as the accuracy of previous predictions may be substantially affected by newly approved compensation claimants, new antiviral treatments, and updates in the natural

history of HCV. The original HCV prognostic model which simulated approved compensation claimants has undergone a total of five subsequent revisions including the current iteration documented in this current report. The first revision was conducted in 2002 by a working group consisting of five members (Murray Krahn, Jenny Heathcote, Linda Scully, Peter Wang, and Qilong Yi). That revision explicitly linked compensation levels with the stage of liver fibrosis in 2,466 approved compensation claimants. The second revision was conducted in 2005 and one new member (Morris Sherman) was added to the working group. The second revision utilized Markov maximum likelihood estimation (MMLE) to determine stage-specific transition probabilities that were applied to the HCV prognostic model to predict liver-related complications and mortality in 4,530 approved claimants. Also included in the second revision of the HCV prognostic model was a survey of treatment patterns in Canadian hepatologists. That survey incorporated treatment data related to use of the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy which has since replaced conventional interferon-based therapies. The third revision was conducted in 2007 by a working group consisting of three members (Murray Krahn, Qilong Yi, and Hla-Hla Thein). That revision primarily updated baseline information of 5,004 approved compensation claimants and included a more comprehensive meta-analysis to estimate stage-specific transition probabilities. The fourth revision was conducted in 2010 by the same working group as the third revision. That revision maintained the same objectives as before and modified the model structure to include information regarding the transition from hepatocellular carcinoma (HCC) to liver transplantation as well as adopting treatment patterns derived from the claimant cohort.

Since the fourth revision, several new and highly effective antiviral regimens have been developed, some of which are currently available in Canada. Because the new antiviral regimens provide a cure rate of between 70% and 90%, treatment patterns are expected to change substantially and will likely have a significant impact on the prognosis of compensation claimants. Thus, the fifth revision of the HCV prognostic model was requested and a working group consisting of four members (Wendong Chen, Qilong Yi, William Wong, and Murray Krahn) was established in the fall of 2013 to undertake the current revision. The current revision incorporates the result of an on-line survey study of physicians treating HCV patients in Ontario to estimate future treatment patterns with new antiviral regimens, maximizes the use of claimant cohort data to estimate model variables, and revises model predictions for the surviving compensation claimants as of August 31, 2013.

According to the collected claims data as of August 31, 2013, 3,832 surviving compensation claimants, including 884 hemophilics and 2,948 non-hemophilics, were identified to create the claimant cohort for model simulations. The treatment pattern survey attempted to elicit choices for existing standard antiviral therapy, PEG-IFN/RBV, as well as three new types of antiviral regimens (PEG-IFN/RBV-based triple therapy with boceprevir, telaprevir, or faldaprevir; sofosbuvir-based doublets with daclatasvir, ledipasvir or simeprevir; and three direct-acting antiviral regimens plus RBV) in claimants stratified by their status of previous treatment and human immunodeficiency virus (HIV) co-infection. Systematic reviews of randomized clinical trials assessing the three new antiviral regimens were conducted to estimate their treatment efficacy and safety that are needed when developing treatment pattern survey and revising HCV prognostic model. The 1986-1990 HCV Claim Center also conducted a survey of previously

treated claimants to estimate sustained viral response (SVR), the indicator for viral clearance, after previous treatments in current surviving claimants. In order to further improve internal validity of model variables, the current revision has used claims data as the primary data source to estimate the initial distribution of fibrosis stages, natural history of HCV, and non-liver-related mortality for the revised HCV prognostic model. The revised HCV prognostic model has been validated by comparing predicted and observed cumulative rates of liver-related complications and mortality from 2003 to 2013 in treatment-naïve non-hemophilic claimants (decompensated cirrhosis: 6.1% vs. 7.4%; HCC: 1.9% vs. 1.8%; liver transplantation: 0.7% vs. 0.7%; liver-related mortality: 4.1% vs. 7.4%).

By running 50,000 iterations in the revised HCV prognostic model to simulate surviving claimants as of August 31, 2013, the cumulative rates of decompensated cirrhosis, HCC, liver transplantation, and liver-related mortality in the surviving claimants by 2070 are predicted to be 12.1%, 4.3%, 0.9%, and 14.7%, respectively. Further comparisons of model outputs for claimants stratified by their hemophilic status predict that hemophilic claimants will have doubled cumulative rates of liver-related complications (decompensated cirrhosis: 20.7% vs. 9.5%; HCC: 7.3% vs. 3.4%) and mortality (24.9% vs. 11.6%) by 2070 when compared with non-hemophilic claimants. Because the new antiviral regimens are likely to cure most claimants, the long-term prognosis of claimants would be mainly determined by the initial proportions of cirrhosis and liver-related complications. The model outputs of claimants stratified by age strata predict that hemophilic claimants under the age of 80 years will have doubled lifetime cumulative rates of liver-related complications and mortality mainly due to higher initial proportions of cirrhosis.

The current revision has performed sensitivity analyses to assess the impact of major revisions on model predictions. The updated treatment patterns in the current revision are found to reduce cumulative rates of liver-related complications and mortality by half in non-hemophilic claimants when compared to the treatment patterns applied in the fourth revision that was conducted in 2010. Except that the updated lifetime risk of liver transplantation is substantially reduced (0.9% vs. 3.2%), the updated model predictions are not sensitive to changing data source used to estimate model variables for the prognosis of cirrhosis and non-liver-related mortality. Finally, the impact on overall uncertainty associated with model variables on model outputs are explored using two-order Monte Carlo simulation approach and presented with the 95% confidence intervals of their cumulative rates of liver-related complications in 2070 (decompensated cirrhosis: 8.7% to 15.5%; HCC: 3.1% to 5.5%) and mortality (11.0% to 18.4%).

1. Background

HCV is identified as one of the most common causes of liver disease in Canada. Recent studies suggest that the prevalence of HCV infection in the Canadian population is about 0.8 % with an estimated 250,000 to 300,000 Canadians living with HCV.[1-3] Blood transfusion and blood products were the main sources of HCV infection prior to 1990 when serological testing methods came into use for HCV screening in blood donors.[4] Surrogate marker testing was employed to screen blood donors in the United States to reduce the risk of non-A non-B viral hepatitis in the general population from 1986 to 1990 before HCV was discovered.[5] However, surrogate marker testing was not employed in most Canadian jurisdictions[6] and as a result many individuals in Canada likely acquired HCV via blood transfusion or blood products during this four-year period.

On March 27, 1998, federal, provincial, and territorial governments announced an offer of financial assistance to individuals who acquired HCV either directly or indirectly through the blood system between January 1, 1986 and July 1, 1990. Up to $1.1 billion was to be made available to compensate individuals which included hemophilics, secondarily infected HCV claimants, those with HIV who became co-infected with HCV, as well as any others with an HCV infection acquired through blood transfusion during the period in question. In order to settle on an appropriate compensation scheme, the federal and provincial governments as well as the claimants reviewed a number of models of the natural history of HCV. Because of disagreement regarding the natural history of this disease, the Canadian Association for the Study of the Liver (CASL), an impartial body with no stake in the outcome of compensation negotiations, was approached by both stakeholders to produce the best available model simulating the natural history of HCV. In November of 1998, CASL met with individuals with

expertise in hepatitis C epidemiology, hepatitis C clinical care, and decision modeling to assist in the construction of a prognostic model for HCV. These meetings led to the formation of an ad-hoc working group comprised of Drs. Murray Krahn, Jenny Heathcote, Linda Scully, Leonard Seeff and John Wong. This working group evaluated and accepted the structural validity of a simplified version of the Bennet/Wong Markov chain model.[7,8] The working group reviewed each parameter in the model and updated several key parameters, including the excess mortality rate and the incidence rates of cirrhosis, HCC and decompensated cirrhosis, by systematic review of relevant literature. Confidence intervals (CI) and/or plausible ranges were also estimated for key model parameters. With this revised model, the cumulative probability of acquiring cirrhosis, decompensated liver disease, and liver-related death were predicted using baseline characteristics of compensation claimants. For the transfusion cohort as a whole, the 20-year and lifetime cumulative probability of developing liver cirrhosis was 13.4% and 24.9%, respectively. Similarly, the 20-year and cumulative lifetime probability of dying from HCV-related liver disease was 2.5% and 12.3%, respectively. However, the rapid development of HCV treatment options coupled with accumulated clinical information on the natural history of HCV within the compensation cohort have led to a clear demonstration for the need to regularly revise model predictions of long-term prognosis in approved compensation claimants. Doing so will ensure the sufficiency of compensation funds in the future. As well, the compensation agreement between governments and plaintiffs calls for an estimate of the sufficiency of the fund every three years. Four revisions have been conducted thus far (in 2002, 2005, 2007, and 2010) by taking into account the updates on treatment patterns and the natural history of HCV in the approved compensation claimants.

The first revision was conducted in 2002 by a working group consisting of three members from the original research team (Drs. Jenny Heathcote, Linda Scully and Murray Krahn) along with two new members, Dr. Peter Wang (Epidemiology) and Dr. Qilong Yi (Biostatistics). This revision modified the original prognostic model as a fibrosis stage-based Markov model and updated transition probabilities between fibrosis stages using literature-based evidence. This updated Markov model was used to predict the long-term prognosis of compensation claimants over their remaining lifetimes in accordance with HCV severity levels as stipulated in the compensation package.

The second revision of the HCV prognostic model was conducted in 2005. This revision included an updated literature review which was used to estimate transition probabilities and integrated the most updated claims data at that time for model predictions. The third revision was conducted in 2007 and retained the objectives of the second revision along with a fine-tuning of methodology in order to obtain more accurate predictions. The working group conducting the third revision included two members from previous revisions (Drs. Murray Krahn and Qilong Yi) and one new member, Dr. Hla-Hla Thein, who joined the team as a consultant and modeling expert. The fourth revision was conducted by the same working members as in the 2007 revision. This revision categorized claimants into different disease stages based on clinical symptoms and results from laboratory tests. As well, the fourth revision added the transition from HCC to liver transplantation and incorporated treatment pattern data derived from the claimant cohort. The antiviral therapy employed in the fourth revision was the combination of PEG-IFN and RBV. This treatment combination was recommended by clinical practice guidelines at the time of revision.[9]

A number of significant advances have been made for treating CHC since the fourth revision. Boceprevir and telaprevir, two molecules which inhibit HCV replication through binding to active sites of HCV non-structural protein,[10,11] were approved by Health Canada in 2011. These two agents increased SVR rate at 24 weeks, the indicator of a clinical cure for HCV,[12] to over 50% when combined with PEG-IFN/RBV in both treatment-naïve[13,14] or previously treated patients[15,16] with viral genotype 1, the most prevalent genotype (about 70%) in Canadian patients with CHC.[17] In December 2013, Health Canada approved two additional antiviral agents, simeprevir (NS3/4A protease inhibitor) [18] and sofosbuvir (the nucleotide analog NS5B polymerase inhibitor).[19] The combination of these two antiviral agents may provide a cure for more than 90% of treatment-naïve or previously treated viral genotype 1 patients. In addition, this regimen has a much better safety profile and only needs 12 weeks treatment time,[20] while PEG-IFN/RBV usually requires 48 weeks for treatment and causes a series of side effects decreasing treatment compliance. Several other protease inhibitors have been also evaluated by phase II or III trials and they are expected to be launched in Canada within the next year or two. For example, current phase II studies have demonstrated that faldaprevir, a potent, once-daily, HCV NS3/4A protein inhibitor, could produce a doubling of antiviral response when combined with PEG-IFN/RBV in treatment-naïve patients.[21] Sofosbuvir-based doublets with ledipasvir (an inhibitor of the hepatitis C virus HCV NS5A protein) [22,23] or daclatasvir (HCV NS5A replication complex inhibitor) [24] could provide a cure for nearly all treatment-naïve or previously treated viral genotype 1 patients within 12 weeks. The combination of the protease inhibitor ABT-450 with ritonavir (ABT-450/r), the NS5A inhibitor ombitasvir, and the nucleoside polymerase

inhibitor dasabuvir, which are direct-acting antiviral agents known as "3D", could cure 96% of treatment-naïve or previously treated viral genotype 1 patients when combined with RBV.[25]

The emergence of highly effective and safe antiviral regimens is expected to have a profound impact on treatment patterns in patients with CHC, potentially resulting in an end to the era of interferon-based treatment for CHC.[26] Even though the abovementioned new antiviral regimens are extremely costly, the reimbursement policy for this compensation claimant cohort could accelerate the uptake of these regimens, dramatically improving the long-term prognosis of current surviving claimants chronically infected with HCV. Thus, a fifth revision of the HCV prognostic model has been requested to estimate future treatment patterns affected by newly launched and upcoming antiviral regimens and revise model outputs of current surviving claimants accordingly. Additionally, previous revisions of the HCV prognostic model were mainly based on literature-derived model variables because the claimant cohort had a relatively small sample size and limited follow-up time. In order to further improve internal validity of model predictions, the current revision has taken the claims data as its data source to estimate model variables for fibrosis progression, prognosis of cirrhosis, and non-liver-related mortality for the purpose of further improving accuracy of model predictions. A working group consisting of two members (Drs. Murray Krahn and Qilong Yi) from previous working groups along with two new members (Drs. Wendong Chen and William Wong) was created to undertake the fifth revision of the HCV prognostic model and model outputs of current surviving compensation claimants as of August 31, 2013. Dr. Wendong Chen has developed the revision plan, led the revision, and prepared this report.

2. Revisions on HCV prognostic model

2.1. Revisions on model structure

The HCV prognostic model used in the fourth revision has been modified to meet the objectives of the current revision. The HCV prognostic model in the current revision remains as a fibrosis stage-based Markov model. The health states in this model include fibrosis stages classified as 0 to 4 (F_0 to F_4), liver-related complications (decompensated cirrhosis, HCC, liver transplantation, and post-transplant), and death that is further classified as liver-related death and non-liver-related death. Liver-related death is defined as death with prior occurrence of any liver-related complications. The current revision also allows fibrosis to progress in one direction ($F_0 \rightarrow F_1 \rightarrow F_2 \rightarrow F_3 \rightarrow F_4$). However, the fibrosis stages prior to compensated cirrhosis are assumed to stop progression once viral clearance is achieved through spontaneous viral clearance (SVC) or SVR after antiviral therapy. Because compensated cirrhosis still progresses to decompensated cirrhosis or HCC at a lower rate even after successful antiviral therapy,[27] the current revision adds the transitions from compensated cirrhosis with viral clearance to decompensated cirrhosis and HCC in the HCV prognostic model. The current revision also keeps the assumptions made in the fourth revision regarding the rare incidences of HCC and SVC associated with fibrosis stages prior to F_4 in the model. A simplified representation of the structure of the revised HCV prognostic model in the current revision is illustrated in *Figure 1*. Potential transitions associated with each health state in the model are also depicted in *Figures 2 to 10*. The current revision used TREEAGE PRO 2013 to construct the HCV prognostic model and run microsimulation analyses to generate model outputs predicting long-term prognosis of surviving compensated claimants.

2.2. Revisions on model variables

The model variables in the HCV prognostic model include initial distribution of health states, updated treatment patterns, treatment efficacy of antiviral regimens, fibrosis progression, prognosis of cirrhosis, and non-liver-related mortality. Because hemophilic claimants are substantially different from non-hemophilic claimants in age, gender, and comorbidities that can strongly affect disease prognosis, the current revision estimates model variables according to the hemophilic status of claimants in order to generate model outputs for hemophilic and non-hemophilic claimants separately.

2.2.1. Initial distribution of health states

The 1986-1990 Hepatitis C Claims Center provided claims data for 5,368 approved claimants as of August 31, 2013. When compared to the approved claimants (n=5,225) in the last revision performed in 2010, the current claimant cohort includes 143 newly approved claimants. The proportion of hemophilia in the approved 5,368 claimants is 25.1%. The hemophilic claimants differ from non-hemophilic claimants regarding the distributions of male gender (88.4% vs. 52.6%, $p<0.001$) and HIV co-infection (30.6% vs. 3.1%, $p<0.001$). Similar differences in male gender and HIV co-infection between hemophilics and non-hemophilics are also observed in the 3,832 surviving compensation claimants (884 hemophilics and 2,948 non-hemophilics). Additionally, surviving hemophilics are about 12 years younger than surviving non-hemophilics (mean age: 49.7 years vs. 61.8 years, $p<0.001$). Unadjusted comparisons of baseline demographic and clinical characteristics between hemophilic and non-hemophilic claimants are summarized in *Table 1*.

According to the collected treatment records of compensation claimants, about a quarter of compensation claimants (n=1,342) were treated previously. Because the previously treated claimants are not followed up for their treatment outcomes, the claims center has conducted a telephone survey to trace the treatment outcomes in those previously treated claimants. Based on the surveyed claimants giving the information on the outcomes of previous antiviral treatments, 273 out of 454 (60%) surveyed claimants achieved SVR after previous antiviral treatments. Non-hemophilic claimants experienced a better treatment response than hemophilic claimants (SVR rate: 61.6% vs. 46.6%, p=0.001) even though the viral genotype distributions in the two groups were highly comparable. The surveyed claimants have similar baseline characteristics as the entire cohort of surviving claimants. For example, the surveyed hemophilic claimants are also associated with much higher proportions of male, HIV co-infection, and advanced disease stages than the surveyed non-hemophilic claimants (*Table 2.1*). These differences explain the poorer treatment response associated with the surveyed hemophilic claimants.[28,29,30] The comparisons of the baseline characteristics between surveyed hemophilic and non-hemophilic claimants in treatment responders and non-responders (*Table 2.2 and 2.3*) further suggest that the younger age and higher proportions of male and HIV co-infection associated with surveyed hemophilics are not affected by treatment response. However, the proportion of advanced compensation level is significantly higher in the surveyed hemophilic claimants with SVR (7.3% vs. 1.4%, p=0.032). Given that treatment outcomes are not tracked in the claim cohort data, the patterns of baseline characteristics found in the surveyed claimants stratified by SVR status and hemophilic status are used to estimate initial distribution of compensation levels in previously treated claimants. The initial distribution of compensation levels in the treatment-naïve claimants stratified by the status of hemophilia and HIV co-infection is then estimated directly from claims data (*Table 3*).

Because the HCV prognostic model is a fibrosis stage-based state transition (i.e. Markov) model, the initial distribution of compensation levels derived from the current claimant cohort are further converted to the initial distribution of fibrosis stages using the established matching relationship between compensation levels and fibrosis stages in previous revisions. The matching principles are stated below.

- Compensation level 1: F_0 with negative HCV RNA;
- Compensation Level 2: F_0 with positive HCV RNA;
- Compensation level 3: F_1 or F_2 indicating non-bridging fibrosis;
- Compensation level 4: F_3 indicating bridging fibrosis;
- Compensation level 5: F_4 with compensated cirrhosis;
- Compensation level 6: F_4 with decompensated cirrhosis, HCC, and/or post-transplant.

Because only 19.6% of approved claimants had a documented liver biopsy to confirm their compensation level, assessing liver disease severity using compensation level alone could introduce significant uncertainty regarding the true initial distribution of fibrosis stages in the current surviving claimants. Thus, the current revision continues to use the propensity score matching method[31,32] developed in the fourth revision to estimate fibrosis stage distribution in the claimants without liver biopsy. This method includes the following steps.

Step 1. A multiple logistic regression analysis is performed using biopsy status as the dependent variable and age, gender, previous treatment, hemophilic status, and HIV status as independent variables. Claimants with decompensated cirrhosis or HCC are excluded for propensity score matching as the diagnoses of these two complications are

usually based on symptoms and imaging. Claimants with compensation level 1 are also excluded because individuals with a negative HCV RNA status typically do not have hepatic fibrosis. Thus, this multiple logistic regression analysis only includes claimants with compensation levels of 2 through 5.

Step 2. The formula derived in *Step 1* is used to calculate a propensity score. This score is defined as the predicted probability of receiving a liver biopsy for each included claimant. The derived formula is as follows:

Log [p/(1-p)] = a + age*b1 + gender*b2 + previous treatment*b3 + hemophiliacs status*b4 + HIV status*b5;

p is the probability of receiving liver biopsy;

a is the intercept parameter in the multiple logistic regression analysis;

b1....b5 are the coefficients associated with independent variables in the multiple logistic regression analysis.

Step 3. Claimants are stratified on the basis of propensity scores of <0.4 and > 0.4. In each group, we assume that claimants without liver biopsy have the same distribution of fibrosis stage as the claimants who received a liver biopsy if they have the same compensation level.

The current revision has used this method to estimate the initial distribution of fibrosis stages in the surviving hemophilic claimants and non-hemophilic claimants, respectively. The adjusted initial proportions of F_0 with negative HCV RNA, F_0 with positive HCV RNA, F_1/F_2, F_3, compensated cirrhosis, decompensated cirrhosis, HCC, and post-transplant in current surviving hemophilic claimants are 15.8%, 20.3%, 17.8%, 23.3%, 18.1%, 2.9%, 1.3%, and 0.6%,

respectively (*Table 4.1*). The adjusted initial proportions of F_0 with negative HCV RNA, F_0 with positive HCV RNA, F_1/F_2, F_3, compensated cirrhosis, decompensated cirrhosis, HCC, and post-transplant were 17.5%, 33.3%, 26.9%, 10.7%, 8.6%, 1.7%, 0.5%, and 0.7%, respectively (*Table 4.2*).

2.2.2 Efficacies of new antiviral regimens

The medical model working group (MMWG) on the current revision has searched the websites of Health Canada and the United States Food and Drug Administration (US FDA) for newly approved antiviral agents since 2010. As of January 31, 2014, the approved new antiviral agents in both Canada and the United States include boceprevir,[33,34] telaprevir,[35,36] sofosbuvir,[37,38] and simeprevir.[39,40] The MMWG on the current revision has also reviewed the results of recently completed phase III trials evaluating new antiviral regimens for CHC and consulted the hepatologists at the University Health Network (Drs. Jordan Feld, David Wong, and Morris Sherman) for their opinions on any new antiviral agents that could be available to Canadian patients in the next two years. Based on the identified clinical evidence, expert opinions, and discussions among the members of working group, the updated treatment patterns in the current revision have taken into account four antiviral regimens, including current standard treatment with PEG-IFN/RBV; PEG-IFN/RBV-based triple therapy with boceprevir, telaprevir, or faldaprevir; sofosbuvir-based doublets with simeprevir, daclatasvir, or ledipasvir; and 3D regimen plus RBV, in the updated treatment patterns over the next five years in compensation claimants. Thus, the current revision has conducted a systematic review to estimate treatment efficacy and safety of the four selected antiviral regimens that are included in the treatment preference survey study and the revised HCV prognostic model.

The current revision has searched the common medical databases (MEDLINE, EMBASE, Web of Science, and The Cochrane Library) and proceedings of the annual conferences of the American Association of Study Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), the two major international organizations for viral hepatitis, for any published randomized trials assessing the selected new antiviral regimens since 2010. Single-arm meta-analysis method is used to estimate overall SVR and adverse event (AE)-related treatment discontinuation rates associated with the four selected antiviral regimens for patients stratified by their status of previous treatment and HIV co-infection, the two factors having strong impact on treatment efficacy, treatment tolerance, and treatment decision making.

- *PEG-IFN/RBV and PEG-IFN/RBV-based triple therapy*

The current revision has identified 35 trials comparing PEG/RBV-based triple therapy with boceprevir (9 trials), telaprevir (22 trials), or faldaprevir (4 trials) against 24 or 48-week PEG-IFN/RBV.

  - *Treatment-naïve patients without HIV co-infection:* Of the 35 identified trials, 23 trials assessed PEG-IFN/RBV-based triple therapy in treatment-naïve patients without HIV co-infection (5 trials for boceprevir,[41-45] 15 trials for telaprevir,[46-60] and 3 trials for faldaprevir[61-63]). The patients in these 23 trials had an average age of 48 years (n=1,218, 95% CI 46 to 50 years), 57.5% of patients were male (n=5,204, 95% CI 53.7% to 61.2%), 98.3% of patients had viral genotype 1 (n=5,870, 95% CI 96.9% to 99.1%), 84.3% of patients (n=4,967, 95% CI 80.3% to 87.6%) had mild fibrosis (F_0 to F_2), and 13.9% of patients (n=5,523, 95% CI 10.9% to 17.6%) had advanced fibrosis (F_3 or F_4). The pooled estimates of SVR and AE-related treatment discontinuation rates associated with

PEG/RBV-based triple therapy were 70.0% (n=7,149, 95% CI 67.0% to 72.8%) and 12.7% (n=4,072, 95% CI 10.3% to15.4%), respectively. The pooled estimates of SVR and AE-related treatment discontinuation rates associated with PEG-IFN/RBV doublet were 45.5% (n=2,041, 95% CI 43.3% to 47.8%) and 8.7% (n=981, 95% CI 7% to 10.9%), respectively.

- *Treatment-naïve patients with HIV co-infection:* Of the identified 35 trials, three trials compared PEG-IFN/RBV-based triple therapy (1 trial for boceprevir [64] and 2 trials for telaprevir[65,66]) versus PEG-IFN/RBV in treatment-naïve patients with HIV co-infection. Two trials which were comprised of 71 patients with reported patient baseline characteristics, including age (mean 42 years) and proportions of male (73.1%, 95% CI 61.5% to 82.1%), viral genotype 1 (97.8%, 95% CI 87.3% to 99.7%), and mild fibrosis stage (84.7%, 95% CI 74.3% to 91.4%). The pooled estimates of SVR and AE-related treatment discontinuation rates associated with PEG-IFN/RBV-based triple therapy were 73.5% (n=171, 95% CI 64.4% to 80.9%) and 20.0% (n=64, 95% CI 11.9% to 31.6%). The pooled estimate of SVR rate associated with PEG-IFN/RBV was 37.1% (n=62, 95% CI 26% to 49.8%). These three trials did not report AE-related treatment discontinuation rate associated with PEG-IFN/RBV. Thus, the current revision has assumed that HIV co-infection has the similar impact on AE-related treatment discontinuation associated with PEG-IFN/RBV and PEG-IFN/RBV-based triple therapy. The AE-related treatment discontinuation rate associated with PEG-IFN/RBV in treatment-naïve patients with HIV co-infection is estimated by multiplying the relative risk (RR) of AE-related treatment discontinuation associated with HIV co-infection for PEG-IFN/RBV-based triple therapy

by the AE-related treatment discontinuation rate associated with PEG-IFN/RBV in treatment-naïve patients without HIV co-infection.

- *Previously treated patients without HIV co-infection:* Of the identified 35 trials, 9 trials compared PEG-IFN/RBV-based triple therapy (4 trials for boceprevir,[67-70] 5 trials for telaprevir,[71-75] and 1 trial for faldaprevir[76]) against PEG-IFN/RBV in previously treated patients without HIV co-infection. The average age of patients in these 9 trials was 50 years (n=333, 95% CI 49 to 51 years), 66.8% of patients were male (n=2,980, 95% CI 64.4% to 69.2%), 97.0% of patients had viral genotype 1 (n=2,980, 95% CI 95.0% to 98.2%), and 74.0% of patients had mild fibrosis (n=1,048, 95% CI 68.7% to 78.6%). The pooled estimate of SVR and AE-related treatment discontinuation rates associated with PEG-IFN/RBV-based triple therapy in these patients were 53.8% (n=2,377, 95% CI 45.2% to 62.3%) and 16.6% (n=1,773, 95% CI 11.1% to 24.2%), respectively. Of these 9 trials, five trials reported the rates of SVR (n=382, 37.4%, 95% CI 32.2% to 42.8%) and AE-related treatment discontinuation (n=233, 10.1%, 6.8% to 14.7%) rates associated with PEG-IFN/RBV.

- *Previously treated patients with HIV co-infection:* One trial[77] compared PEG-IFN/RBV/telaprevir triple therapy against PEG-IFN/RBV in 31 previously treated patients with HIV co-infection. The average age of these patients was 50 years. The proportions of male, viral genotype 1, and mild fibrosis in these 31 patients were 88.9%, 97.0%, and 90.6%, respectively. The reported SVR rate associated with PEG-IFN/RBV-based triple therapy was 73.8% (95% CI 55.6% to 86.4%). This trial only included 8

patients receiving PEG-IFN/RBV and this sample size was too small to have enough power for reliable estimation. Additionally, the SVR rate in these 8 patients was 50%, which was higher than the SVR rate in treatment-naïve patients. This finding was against many other trials reporting less treatment response associated with HIV co-infection. Thus, the current revision disregards the reported SVR rate associated with PEG-IFN/RBV in this trial but assumes that HIV has the same impact on treatment efficacies of PEG-IFN/RBV and PEG-IFN/RBV-based triple therapy. The RR of SVR associated with HIV co-infection in patients receiving PEG-IFN/RBV-based triple therapy is multiplied by the estimated SVR rate associated with PEG-IFN/RBV in previously treated patients without HIV to estimate SVR rate associated with PEG-IFN/RBV in previously treated patients with HIV co-infection. This trial did not report AE-related treatment discontinuation rates associated with the two antiviral regimens either and the current revision assumes that their AE-related treatment discontinuation rates remained the same as what were reported in previously treated patients without HIV co-infection.

- *Sofosbuvir-based doublets*

The current revision has identified three trials assessing sofosbuvir-based doublets with simeprevir,[78] ledipasvir,[79] or daclatasvir [80] in treatment-naïve or previously treated patients without HIV co-infection.

- *Treatment-naïve patients without HIV co-infection:* One trial reported on 100 patients with an average age of 54 years and a male gender proportion of 52.7%. The proportions of viral genotype 1 and advanced fibrosis stage among studied patients were 97.4% (n=139, 95% CI 92.9% to 99.1%) and 20.4% (n=130, 95% CI 12.9% to 30.8%),

respectively. The pooled rates of SVR and AE-related treatment discontinuation associated with sofosbuvir-based doublets in these patients were 94.6% (n=139, 88.5% to 97.6%) and 2.2% (n=100, 0.6% to 8.4%), respectively.

- *Previously treated patients without HIV co-infection:* One trial reported on 21 patients with an average age of 59 years and a male gender proportion of 61.9%. The proportions of viral genotype 1 and advanced fibrosis stage among studied patients were 97.1% (n=50, 95% CI 87.0% to 99.4%) and 14.3% (n=21, 95% CI 4.7% to 36.2%), respectively. The pooled rates of SVR and AE-related treatment discontinuation associated with sofosbuvir-based doublets in these patients were 95.4% (n=69, 86.6% to 98.5%) and 2.2% (n=100, 0.6% to 8.4%), respectively.

- *3D regimen plus RBV*

Two phase III trials assessed treatment efficacy and safety associated with 3D regimen plus RBV in treatment-naïve (SAPPHIRE-I) [25] and previously treated patients (SAPPHIRE-II),[81] respectively. The 3D regimen consists of a boosted protease inhibitor ABT-450/ritonavir, NS5A inhibitor ABT-267, and non-nucleoside polymerase inhibitor ABT-333. In the SAPPHIRE-I trial, 473 previously untreated adult, non-cirrhotic, and viral genotype 1 patients received 12 weeks of 3D regimen plus RBV treatment. The reported SVR and AE-related treatment discontinuation rates associated with 3D regimen plus RBV in these treatment-naïve patients were 96.2% and 0.6%, respectively. In the SAPPHIRE-II trial, 297 previously treated adult, non-cirrhotic, and viral genotype 1 patients received 12 weeks of 3D regimen plus RBV treatment. The reported SVR and AE-related treatment discontinuation rates in these previously treated patients were 96.3% and 1%, respectively.

The current revision has not identified any specific trials that evaluated sofosbuvir-based doublets and 3D regimen plus RBV in patients with HIV co-infection. Based on the recommendations from clinical experts and the working group, HIV co-infection was assumed to have the same impact on SVR and AE-related treatment discontinuation associated with the four selected antiviral regimens when estimating the rates of SVR and AE-related treatment discontinuation associated with sofosbuvir-based doublet and 3D regimen plus RBV in patients with HIV co-infection. The estimated SVR and AE-related treatment discontinuation rates associated with the four selected antiviral regimens are summarized in *Table 5.1 and 5.2, respectively.*

2.2.3. Predicting treatment patterns over the next five years

Physicians are expecting significant change of treatment patterns for CHC because of those highly effective and safe new antiviral regimens. In order to estimate treatment patterns in surviving claimants over the next five years, the current revision has conducted an on-line survey study to measure physician's preferences for treating current surviving claimants with the four selected antiviral regimens discussed in the section of 2.2.2. This survey study invited physicians treating HCV in Ontario to review summarized baseline characteristics of surviving claimants eligible for treatment *(Table 6.1)* and the summarized SVR and AE-related treatment discontinuation rates associated with selected antiviral regimens (*Table 5.1 and 5.2*) and then indicate their likelihood of treating compensation claimants in a 0-100 scale and their treatment choices from the four selected antiviral regimens. This survey study received ethics approval

from the University of Toronto in January 2014 (PROTOCOL REFERENCE #29616) and the survey contents are attached as *Appendix I* of this report.

This survey study contacted approximately 100 Ontario physicians drawn from directories posted by the Canadian Liver Foundation[82] for physicians treating HCV across Canada. 14 physicians gave their written consents to participate in this on-line survey. The likelihoods of treating treatment-naïve and previously treated claimants without HIV co-infection in these 14 physicians were highly comparable (87.5% vs. 91.0%). However, their preferences to treat treatment-naïve and previously treated claimants with HIV co-infection were reduced to 65.8% and 61.7%, respectively. None of these 14 physicians selected PEG-IFN/RBV to treat any types of claimants and small proportions of the surveyed physicians selected PEG-IFN/RBV-based triple therapy to treat claimants (7.1% to 14.3%). When treating naïve claimants without HIV co-infection, sofosbuvir-based doublets were associated with a higher rate of selection than 3D regimen plus RBV (50% vs. 35.7%). However, 3D regimen plus RBV had a higher rate of selection than sofosbuvir-based doublets when treating treatment-naïve claimants with HIV co-infection (66.7% vs. 25%) and previously treated claimants, irrespective of their status of HIV co-infection (without HIV co-infection: 57.1% vs. 35.7%; with HIV co-infection: 83.4% vs. 8.3%) . The results of this survey study are summarized in *Table 6.2.*

2.2.4. Stage-specific fibrosis progression

Previous revisions explicitly described the MMLE method to estimate specific fibrosis stage transition rates using claims data of non-hemophilic claimants without HIV co-infection.[83] The current revision has used the same method to estimate stage-specific fibrosis progression using

updated claims data for non-hemophilic claimants without HIV co-infection. The first blood transfusion date and the latest compensation level associated with non-hemophilic claimants are used to estimate HCV infection time. A Markov model is constructed to simulate fibrosis progression starting from F_0 with an initial set of annual stage-specific fibrosis transition probabilities (0.1 for all transitions between consecutive fibrosis stages). The Markov model is run with iterations and modifications on each stage-specific annual transition probability until the squared residual sum, which indicates the difference between the predicted and observed fibrosis stage distributions, is less than 0.000001. Because the number of non-hemophilic claimants without HIV co-infection in the current revision only increases slightly to 3863 from 3839 in the last revision, the estimates of annual stage-specific transition probabilities in these two revisions are highly comparable. Calibration is also performed to further improve matching between predicted and observed fibrosis stage distributions at the time of claim in the non-hemophilic claimants without HIV co-infection. Similar to what was estimated in the fourth revision, the calibrated annual fibrosis transition probability from F_0 to F_1 is still less than half of annual transition probabilities for fibrosis progression above F_1 in the current revision. The uncalibrated and calibrated annual stage-specific fibrosis transition probabilities in the current revision and the fourth revision are summarized in *Table 7*.

2.2.5. Prognosis of cirrhosis in compensation claimants

In order to further improve internal validity of model outputs, the current revision has used claims data directly to estimate the rates at which decompensated cirrhosis, HCC, liver transplant, and liver-related mortality occurred in claimants with a diagnosis of compensated cirrhosis. This

is another major change from the fourth and previous revisions which mainly relied on literature based estimates.

- *Annual risk of developing decompensated cirrhosis:* 98 non-HIV and treatment naïve claimants were identified and retrospectively followed up from their first diagnosis of compensated cirrhosis to August 31, 2013. The claimants were censored when HCC, decompensated cirrhosis, liver transplant, or death occurred prior to the end of follow-up. 64 claimants developed decompensated cirrhosis over an average follow-up time of 13.1 years. The estimate of annual transition probability of developing decompensated cirrhosis in these claimants was 0.078 (95% CI 0.073 to 0.083).
- *Annual risk of developing HCC:* 98 non-HIV and treatment-naïve claimants were identified and retrospectively followed up from their first diagnosis of decompensated cirrhosis to August 31, 2013. The claimants were censored when HCC, decompensated cirrhosis, liver transplant, or death occurred prior to the end of follow-up. HCC developed in 28 claimants over an average follow-up time of 13.1 years. The estimated annual transition probability of developing HCC in these claimants was 0.025 (95% CI 0.024 to 0.027). Because the risk of developing HCC associated with compensated cirrhosis and decompensated cirrhosis was considered comparable, this estimate on the risk of HCC associated with decompensated cirrhosis was also applied to compensation claimants with compensated cirrhosis in the model.
- *Annual risk of liver transplantation:* 515 claimants with decompensated cirrhosis and/or HCC were identified and retrospectively followed up from their first decompensated cirrhosis or HCC diagnosis to August 31, 2013. 21 claimants were reported to have liver transplantation over an average follow-up time of 10.3 years. The estimate of annual

probability of receiving liver transplantation in these claimants was 0.004 (95% CI 0.0039 to 0.0042).

- *Annual risk of mortality associated with decompensated cirrhosis:* 414 claimants with a diagnosis of decompensated cirrhosis only were identified and retrospectively followed up from their first decompensated cirrhosis diagnosis to August 31, 2013 for any death records. A total of 343 deaths were recorded over an average follow-up period of 10.7 years. The estimate of annual risk of mortality associated with decompensated cirrhosis in these claimants was 0.152 (95% CI 0.146 to 0.158).
- *Annual risk of mortality associated with HCC:* 130 claimants with HCC were identified and retrospectively followed up for any death records after their first HCC diagnosis. A total of 110 deaths were reported in these claimants over an average time of 9.3 years. The estimate of annual risk of mortality associated with HCC in these claimants was 0.182 (95% CI 0.169 to 0.198).
- *Risk of first-year mortality after liver transplantation:* 58 claimants receiving liver transplantation were identified and retrospectively followed up for one year after the reported liver transplantation. A total of 5 deaths were recorded during this period. The estimate of the first-year mortality after liver transplantation in these claimants was 0.086 (95% CI 0.037 to 0.186).
- *Annual risk of mortality associated with post-transplantation*: 53 claimants survived for more than one year after liver transplantation. A total of 24 deaths were recorded in these claimants over an average follow-up time of 15.1 years. The estimate of annual risk of mortality associated with post-transplant in these claimants was 0.039 (95% CI 0.036 to 0.043).

Most claims data-based estimates for the prognosis of cirrhosis are comparable with literature derived estimates except that the annual mortality risk associated with HCC (0.182 vs. 0.35) and first-year mortality associated with liver transplantation (0.086 vs. 0.146) in the compensation claimants were about half of literature-based estimates in the fourth revision. Additionally, the assumed risk of liver transplantation associated with liver-related complications in the fourth revision is 25 times of that observed in the claimants (0.1 vs. 0.004). Thus, using estimates based on claims data in the HCV prognostic model is expected to generate more accurate model outputs than using estimates derived or assumed in the fourth revision. The estimates of the prognosis of cirrhosis derived from claims data and the fourth revision are summarized in *Table 8.*

2.2.6. Non-liver-related mortality

The current revision classifies mortality as liver-related mortality and non-liver-related mortality in order to differentiate death causes in simulated claimants. Liver-related mortality is defined as the death associated with any liver-related complications, such as decompensated cirrhosis, HCC, liver transplantation, or post-transplant. Non-liver-related mortality is defined as the death occurs prior to the diagnosis of any liver-related complications. Thus, non-liver-related mortality is applied to the claimants who have viral clearance due to SVC or successful antiviral therapy and also applied to uncured claimants without developed compensated cirrhosis and/or HCC in the HCV prognostic model. Previous revisions directly used Canada life tables as the source for non-liver-related mortality in the compensation claimants because the health problems which required blood transfusion so long ago in compensation claimants were unlikely to still have a meaningful impact on life expectancy and because current care has made virus-free hemophilics

almost have the same life expectancy as general population. However, these two hypotheses have never been tested before using claims data. Thus, the current revision has estimated the following annual risks of non-liver-related mortality from a group of surviving non-HIV claimants with a compensation level below 6 as of January 1, 2003 to test the two hypotheses through the comparisons with the 2009 to 2011 Canada life tables (*Table 9.1*) .[84]

- *Annual risk of non-liver-related mortality in hemophilic claimants:* 728 hemophilic claimants (589 males and 139 females) met the inclusion criteria for the analysis. These claimants were stratified by the defined age strata (every 10 years from age 20 years to 70 years or above) and gender. A total of 24 non-liver-related deaths (19 males and 5 females) were recorded in these claimants over the 10-year follow-up from 2003 to 2013. The estimated annual risks of non-liver-related mortality associated with the six age stratas increased from 0 to 0.017 in male hemophilics and from 0 to 0.0127 in female hemophilics. When compared with the Canada life tables stratified by age and gender, male hemophilics have comparable annual risk of non-liver-related mortality with general male Canadians except those at age 30 to 39 who have doubled annual non-liver-related mortality rate (0.0029 vs. 0.0001). When compared to general female Canadians, the female hemophilics at ages 40 to 49 (0.0032 vs. 0.0013) and 50 to 59 (0.0062 vs. 0.0031) have doubled annual risk of non-liver-related mortality. However, the sample size of female hemophilics in each age stratum ranged from 10 to 39, which were unlikely to have enough power to generate a reliable estimate from a statistical perspective. Thus, the current revision has used annual non-liver-related mortality rates derived from male hemophilic claimants under the age of 70 years and the female Canada life table to simulate non-liver-related mortality for hemophilics in the HCV prognostic model. Additionally, the Canada life table for males has been used in the model to

simulate non-liver-related mortality in male hemophilics at ages 70 or above due to the lack of claims data for accurate estimations. The estimated annual risks of non-liver-related mortality for hemophilic claimants are summarized in *Table 9.2.*

- *Annual risk of non-liver-related mortality in non-hemophilic claimants:* 2,877 non-hemophilic claimants (1,407 males and 1,470 females) met the inclusion criteria for the analysis of their annual non-liver-related mortality rates. These claimants were further stratified by the defined age strata and gender for a retrospective 10-year follow-up from 2003 to 2013 to identify non-liver-related deaths. A total of 185 non-liver-related deaths (124 males and 61 females) were identified and included for the survival analyses in non-hemophilics. Similar to the mortality patterns in the Canadian general population, non-hemophilic claimants with older age and male gender had higher non-liver-related mortality. The annual risk of non-liver-related mortality associated with the six age strata increased from 0.0017 to 0.015 in male non-hemophilics and from 0 to 0.01 in female non-hemophilics. However, male non-hemophilics persistently had substantially higher annual non-liver-related morality rates than general Canadians with male gender (ages 20 to 29: 0.0017 vs. 0.0007; ages 30 to 39: 0.0023 vs. 0.0010; ages 40 to 49: 0.0063 vs. 0.0019; ages 50 to 59: 0.0079 vs. 0.0048) until their ages reached to 60 years. Female non-hemophilics at ages 30 to 59 also had higher annual non-liver-related mortality rates than general Canadians with female gender (ages 30 to 39: 0.0013 vs. 0.0006; ages 40 to 49: 0.0019 vs. 0.0013; ages 50 to 59: 0.0049 vs. 0.0031). The identified differences in annual non-liver-related mortality between non-hemophilics and general Canadians are considered substantial. Thus, the current revision has applied the estimated annual non-liver-related mortality rates from both male and female non-hemophilic claimants under the age of 70 years for model simulation. The

Canada life tables are only used to simulate non-liver-related mortality in non-hemophilic claimants with ages above 70 years because the claims data are unlikely to give reliable estimations for age 70 to 79, 80 to 89, and 90 or above in the HCV prognostic model. The estimated annual non-liver-related mortality rates derived from male and female non-hemophilic claimants are summarized in *Table 9.3*.

2.2.7. Model estimates from the fourth revision

Even though the current revision aims to further improve accuracy of model outputs by maximizing the use of claims data to estimate model variables, there are still some model variables that can't be derived from claims data due to small sample size and missing information. Thus, the current revision continues to use the following estimates derived from the literature review in the fourth revision.

- *Impact of HIV on disease progression:* About a quarter of surviving claimants with hemophilia have an HIV co-infection that has been proven to accelerate disease progression,[85] reduce treatment response to antiviral therapy,[86] and increase non-liver-related mortality.[87] The impact of HIV on the treatment efficacies of the selected four antiviral regimens in the updated treatment patterns has been described in Section 2.2.2. Because nearly all claimants with HIV co-infection have hemophilia and the onset of HCV in hemophilic claimants was difficult to determine the MMLE method can't be used to estimate stage-specific fibrosis progression rates in these claimants with HIV co-infection. The fourth revision[88] conducted a systematic review to estimate the RR (2.12, 95% CI 1.52 to 2.97) of cirrhosis associated with HIV co-infection by comparing 2,636 HIV/HCV co-infection patients with 4,970 HCV mono-infection patients identified from 27 HCV natural

history studies. The fourth revision multiplied this RR by the annual stage-specific fibrosis progression rates in claimants without HIV co-infection to simulate the fibrosis progression in claimants with HIV co-infection. The current revision continues to use this solution to simulate fibrosis progression and also prognosis of cirrhosis in the current surviving claimants with HIV co-infection in the model.

- *Impact of HIV on non-liver-related mortality:* the current revision is able to retrospectively follow 238 claimants with HIV co-infection for 10 years, from 2003 to 2013, to estimate annual non-liver-related mortality rates by age strata and gender. The male claimants in three age strata, ages 20 to 29, 30 to 39, and 40 to 49, have a sample size above 50 and the estimated annual mortality rates from these claimants are higher than hemophilic claimants without HIV co-infection as expected (ages 20 to 29: 0.0083 vs. 0; ages 30 to 39: 0.0036 vs. 0.0029; ages 40 to 49: 0.0051 vs. 0.0022) (*Table 10*). Thus, the estimated non-liver-related mortality rates from these three age strata are considered reliable and used in the model to simulate non-liver-related mortality for male HIV-infected claimants with ages 20 to 50 years. However, the current revision has to simulate non-liver-related morality in other claimants with HIV co-infection using the estimated excess mortality associated with HIV (RR 6.24) from a meta-analysis comparing 5,168 HIV negative hemophilics with 2,979 HIV positive hemophilics for all-cause mortality in the fourth revision.[88]
- *SVC in patients with CHC*: A number of studies investigating the natural history of CHC have reported occurrence of SVC in patients with CHC.[89] The fourth revision identified 21 published studies reporting SVC in patients with CHC. The weighted mean SVC rate in these 21 studies was 0.020 (95% CI, 0.013-0.027). The fourth revision further pooled the estimated SVC rates from the literature and the observed SVC rate in the compensation claimants to

estimate the annual incidence rate of SVC (0.017, 95% CI 0.011 to 0.022) for the HCV prognostic model. Additionally, the fourth revision suggested that the chance of SVC would be reduced in advanced fibrosis stage. Thus, the current revision follows the suggestions made in the fourth revision by applying 0.017 as the annual SVC rate associated with F_0 and F_1, 0.01 as the annual SVC rate associated with F_2, and 0.005 as the annual SVC rate associated with F_3 in the HCV prognostic model.

- *Risk of HCC associated with fibrosis stage prior to cirrhosis:* The fourth revision applied a small annual incidence rate of HCC to non-cirrhotic claimants because HCC was found to develop at an average annual rate of 2.1% in non-cirrhotic patients in Japan[90]. Because Japanese have the highest incidence rate in HCC in the world and the compensation claimants differ from Japanese patients in ethnicity and viral transmission route, the fourth revision adopted the assumption made on this variable in the 1998 model which applied 0.0001 as the annual HCC rate associated with moderate fibrosis and zero for mild fibrosis. The fourth revision converted these rates by assuming that F_0 was comparable with mild fibrosis and F_1 to F_2 were comparable with moderate fibrosis. The fourth revision further assumed the annual rate of HCC associated with F_3 stage as 0.001 because advanced fibrosis stage was expected to have a higher risk of HCC. Thus, the current revision has adopted the same estimates used in the fourth revision for the risk of HCC associated with non-cirrhotic claimants.

2.3. Model assumptions

Assumptions are often made in model studies due to simplifying model structure or the lack of evidence. The current revision has made the following assumptions with respect to model structure and variables:

- *Initial distribution of fibrosis stages:* Because the latest compensation level determinations were unlikely to be made exactly as of August 31, 2013, the current revision has assumed that the latest claimed compensation levels remained unchanged in order to estimate the initial distribution of fibrosis stages in the simulated claimants. Additionally, the matching relationship between compensation level and fibrosis stage does not differentiate F_1 and F_2 in claimants with a compensation level of 3. The current revision has assumed that F_1 stage and F_2 stage are evenly distributed when estimating the initial distribution of fibrosis stages. Finally, the current revision has assumed that the estimated treatment outcomes of previous treatment in surveyed claimants are applicable to all previously treated claimants when estimating initial proportions of claimants with viral clearance and claimants who failed with previous treatments.
- *Natural history of CHC:* Most assumptions made by the fourth revision for fibrosis progression were retained in the current revision. For example, the HCV prognostic model only allowed fibrosis to progress in one direction. As well, fibrosis progression was assumed to stop when SVC or SVR was achieved in claimants with a fibrosis stage prior to compensated cirrhosis. Because HCC and decompensated cirrhosis were still observed in cirrhotic patients who had underwent successful antiviral treatment,[91] the current revision has assumed that successful antiviral therapy would reduce the risk of developing decompensated cirrhosis or HCC by half in cirrhotic claimants. Additionally, the current revision has assumed that CHC wouldn't affect mortality in claimants without any liver-related

complications to reflect the fact that liver-related death typically occurs following the development of liver-related complications.[92] Finally, the liver-related mortality, defined as the mortality associated with decompensated cirrhosis, HCC, and post-transplant, was fixed value and could be lower than non-liver-related mortality when claimants reached old age associated with high non-liver-related mortality. Thus, the model in the current revision would replace liver-related mortality with non-liver-related mortality once age-specific non-liver-related mortality excessed liver-related mortality in claimants with decompensated cirrhosis, HCC, or post-transplant.

- *Treatment patterns:* The current revision has utilized treatment preference data from the surveyed physicians to simulate future treatment patterns over the next five years in claimants chronically infected with HCV. Because the updated treatment patterns have high treatment rate and the new antiviral treatments are highly effective, the current revision has assumed no repeated treatment in the simulated claimants. Additionally, the claimants with developed liver-related complications are assumed not to receive antiviral treatments because SVR has limited impact on the prognosis of liver-related complications.[93]

2.4. Model validation

Different from the fourth revision which compared predicted and observed initial distribution of disease stages in the simulated claimants for model validation, the current revision has validated the revised HCV prognostic model by comparing predicted and observed prognosis of non-hemophilic claimants over a 10-year period from 2003 to 2013. This approach first created the validation cohort by including non-hemophilic claimants who were alive in 2003, had no HIV co-infection, and were treatment naïve. The initial distribution of fibrosis stages in this validation

cohort was estimated through the propensity score method described in the Section of 2.2.1. The revised HCV prognostic model was applied with the estimated initial distribution of disease stages in the validation cohort and model estimates for non-hemophilics to generate model outputs within 10-year time horizon. The predicted and observed cumulative rates of liver-related complications (decompensated cirrhosis: 6.1% vs. 7.4%; HCC: 1.9% vs. 1.8%; 0.7% vs. 0.7%) and all-cause mortality (10.6% vs. 11.9%) in the validation cohort are highly comparable. However, some discrepancies have been observed between the predicted and observed cumulative rates of liver-related mortality (5.5% vs. 7.4%) and non-liver-related mortality (9.0% vs. 4.5%) during 10-year follow-up. Further comparing the predicted and observed proportions of disease stages in the surviving non-hemophilics in 2013 has shown highly comparable proportions of F_0 with negative HCV RNA (25.1% vs. 24.8%), compensated cirrhosis (6.3% vs. 3.8%), decompensated cirrhosis (2.2% vs. 1.5%), HCC (0.9% vs. 0.4%), and post-transplant (0.5% vs. 0.5%). The predicted and observed outcomes in this validation cohort are summarized in *Table 11.*

3. Model predictions for current surviving compensation claimants

The current revision has used the revised HCV prognostic model to create two working models, one for hemophilic claimants and the other for non-hemophilic claimants, by applying the initial distributions of health states in surviving hemophilic and non-hemophilic claimants as of August 31, 2013. The model variables used in the two working models are summarized in *Table 12.* The two working models filled with baseline values of model variables were run with 50,000 iterations to simulate transitions between health states in surviving hemophilic and non-

hemophilic claimants within a time horizon of 57 years from 2013 to 2070. The generated model outputs from the two working models are further analysed for the following model predictions.

3.1. Model predictions for the entire claimant cohort

The proportion of hemophilia in the surviving claimants as of August 31, 2013 has been used to weight the model outputs of hemophilic and non-hemophilic claimants when predicting long-term prognosis of the entire cohort of surviving claimants as of August 31, 2013. The sum of the weighted model outputs from the two working models is used to calculate cumulative rates of liver-related complications and mortality and proportions of disease stages in surviving claimants every 10 years starting from 2020. The cumulative rates of decompensated cirrhosis (from 3.3% to 12.1%), HCC (from 0.7% to 4.3%), and liver-related mortality (0% to 14.7%) in the simulated claimants are predicted to increase persistently from 2013 to 2070. Because the applied treatments in the model can cure most claimants and fibrosis stages prior to cirrhosis are expected to remain unchanged in cured claimants, the predicted proportions of non-cirrhotic stages in surviving claimants only increase slightly. However, the proportion of compensated cirrhosis in surviving claimants is predicted to decrease from 10.8% in 2013 to 1.4% because cured cirrhosis still progresses to decompensated cirrhosis and HCC in the model. Even though liver-related complications are usually associated with high mortality, the continuous progression of cured and uncured compensated cirrhosis can cause newly developed liver-related complications and slow down the declining proportions of liver-related complications in surviving claimants. The model outputs of the entire cohort of surviving claimants are summarized by the defined calendar years in *Table 13.1.*

3.2. Comparing hemophilics versus non-hemophilics for model outputs

Hemophilic claimants are expected to have poorer long-term prognosis than non-hemophilic claimants because the higher prevalence of advanced fibrosis stage, HIV co-infection, and male gender in hemophilic claimants can reduce treatment response and accelerate disease progression. The current revision has compared the model outputs of hemophilic and non-hemophilic claimants and further confirmed this hypothesis. By 2070, hemophilic claimants are predicted to have doubled cumulative rates of decompensated cirrhosis (20.7% vs. 9.5%), HCC (7.3% vs. 3.4%), and liver-related mortality (24.9% vs. 11.6%) when compared to non-hemophilic claimants. Because hemophilic claimants have much higher initial proportion of compensated cirrhosis than non-hemophilic claimants (18.1% vs. 8.6%), the predicted proportions of decompensated cirrhosis and HCC in surviving hemophilics remained two times higher than what are predicted in surviving non-hemophilic claimants until 2040 when the differences in the predicted proportion of compensated cirrhosis between surviving hemophilics and non-hemophilics start to decrease substantially due to the lack of progression from cured claimants with less advanced fibrosis stage. Additionally, the low liver transplantation rate applied in the HCV prognostic model has made the predicted cumulative rates of liver transplantation in hemophilics and non-hemophilics highly comparable but very small (1.0% vs. 0.9%). The model outputs of hemophilic and non-hemophilic claimants are summarized by the selected calendar years in *Table 13.2.*

4. Model outputs stratified by age

In order to help with future planning of compensation funds for current surviving claimants, the current revision has stratified surviving claimants by age strata starting at 20 years with 10-year

interval until 90 years or above for the comparisons of model outputs between hemophilic and non-hemophilic claimants.

4.1. Ages 20 to 29

In this age stratum, hemophilic claimants have a much higher initial proportion of cirrhosis than non-hemophilic claimants (16.8% vs. 9.9%). Thus, these hemophilic claimants are expected to have higher risks of developing liver-related complications and mortality. Additionally, the long life expectancy associated with this age stratum can further increase the occurrences of liver-related complications and mortality. Based on the model outputs by 2070 for these claimants, the predicted cumulative rates of decompensated cirrhosis (18.8% vs. 12.4%), HCC (6.7% vs. 4.9%), and liver-related mortality (23.5% vs. 15.5%) associated with hemophilics are 1.367 to 1.516 times what are predicted in non-hemophilics. The future proportion of compensated cirrhosis in surviving hemophilics is predicted to decline faster than that in non-hemophilics until the calendar year of 2040 when the two predicted proportions become comparable (5.7% vs. 4.3%). Thus, hemophilics and non-hemophilics will also have comparable proportions of liver-related complications after the calendar year of 2040 (decompensated cirrhosis: 0.7 to 2.9% vs. 0.7 to 1.6%; HCC: 0.3 to 1.0% vs. 0.3 to 0.7%; post-transplant: 0.2 to 0.4% vs. 0.3%). The model outputs of hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.1.*

4.2. Ages 30 to 39

Hemophilic claimants in this age stratum continue to have an almost doubled initial proportion of cirrhosis (17% vs. 9.7%) than non-hemophilics. Because this age stratum is associated with

shorter life expectancy than ages 20 to 29, the disease progression time will be shorter and the developments of liver-related complications and mortality in these claimants are also reduced slightly, irrespective of their hemophilic status. Thus, the predicted cumulative rates of decompensated cirrhosis (18.2% vs. 11.3%), HCC (6.1% vs. 4.5%), and liver-related mortality (22.5% vs. 14.4%) in 2070 in hemophilics are 1.356 to1.611 times what are predicted in non-hemophilics. The proportion of compensated cirrhosis in hemophilics is predicted to decline faster than that in non-hemophilics until the calendar year of 2050 when the two predicted proportions are comparable (3.7% vs. 3.1%). Thus, the proportions of liver-related complications in surviving hemophilics and non-hemophilics are predicted to be highly comparable after the calendar year of 2050 (decompensated cirrhosis: 1.3 to 1.8% vs. 1.1% to 1.8%; HCC: 0.6% vs. 0.4 to 0.5%; post-transplant: 0.3% vs. 0.2 to 0.3%). The model outputs for hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.2.*

4.3. Ages 40 to 49

This age stratum is associated with a higher initial proportion of cirrhosis than ages 30 to 39, irrespective of claimant's hemophilic status. Additionally, the initial proportions of decompensated cirrhosis in hemophilic and non-hemophilic claimants in this age stratum have increased to 4.1% and 1.6%, respectively. Even though this age stratum is associated with shorter life expectancy, the high initial proportions of advanced disease stages in these claimants are likely to drive up future occurrences of liver-related complications and mortality. Since the initial proportion of cirrhosis in hemophilics is still two times higher than that in non-hemophilics in this age stratum (23.2% vs. 12.1%), the predicted cumulative rates of decompensated cirrhosis (23.1% vs. 12.9%), HCC (8.3% vs. 5.0%), and liver-related mortality (28.2% vs. 16.5%) by 2070

in hemophilics continue to be substantially higher than what are predicted in non-hemophilics. The proportions of cirrhosis in surviving hemophilics and non-hemophilics are predicted to decline to comparable levels (4.6% vs. 3.2%) in the calendar year of 2050. Surviving hemophilics and non-hemophilics are predicted to have comparable proportions of liver-related complications after the calendar year of 2050 (decompensated cirrhosis: 2.6 to 3.4% vs. 1.6 to 1.9%; HCC: 0.8 to 1.8% vs. 0.7 to 1.4%; post-transplant: 0.5 to 0.8% vs. 0.5 to 0.7%). The model outputs of hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.3.*

4.4. Ages 50 to 59

The initial proportions of cirrhosis (24.9% vs. 12.7%) and liver-related complications (decompensated cirrhosis: 4.8% vs. 2.8%; HCC: 1.9% vs. 0.9%) continue to increase in both hemophilic and non-hemophilic claimants in this age stratum. The shorter life expectancy of claimants in this age stratum begins to demonstrate strong impact on the disease prognosis as the predicted cumulative rates of decompensated cirrhosis, HCC, and liver-related mortality associated with this age stratum start to fall. However, the nearly doubled initial proportions of liver-related complications associated with hemophilics continue to make the predicted cumulative rates of decompensated cirrhosis (22.4% vs. 12.3%), HCC (8.5% vs. 4.3%), and liver-related mortality (27.1% vs. 15.3%) in hemophilics 1.771 to 1.977 times of what are predicted in non-hemophilics in 2070. However, hemophilics are predicted to have lower cumulative rates of liver transplantation than non-hemophilics (0.5% vs. 1.2%) due to substantially higher initial proportion of liver transplantation in non-hemophilics (0.9% vs. 0%). Our model predictions also indicate that no claimants will survive to 2070, irrespective of

hemophilic status. The proportions of compensated cirrhosis in surviving hemophilics and non-hemophilics are predicted to decline to a comparable level in 2060. Therefore, hemophilics are predicted to have persistently higher proportions of decompensated cirrhosis (4.3 to 6.2% vs. 2.2 to 2.9%) and HCC (1.7 to 4.9% vs. 0.7 to 2.5%) than non-hemophilics from 2020 to 2060. The model outputs of hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.4*.

4.5. Ages 60 to 69

Hemophilic and non-hemophilic claimants in this age stratum have the highest initial proportions of cirrhosis (30.8% vs. 14.5%), decompensated cirrhosis (10.2% vs. 4.2%), HCC (0.9% vs. 1.0%), and post-transplant (2.8% vs. 1.4%) in the entire claimant cohort. Even though the short life expectancy associated with this age stratum means no claimants will survive to 2060, the high initial proportions of advanced disease stages are expected to drive the cumulative rates of liver-related complications and mortality to the highest in both hemophilic and non-hemophilic claimants. When compared with non-hemophilics in this age stratum, hemophilics continue to have doubled initial proportions of cirrhosis and liver-related complications. Consequently, hemophilics are also predicted to have nearly doubled lifetime cumulative rates of decompensated cirrhosis (24.2% vs. 12.0%), HCC (6.8% vs. 4.3%), liver transplantation (3.4% vs. 1.7%), and liver-related mortality (28.1% vs. 14.5%) relative to non-hemophilics. Additionally, the much higher initial proportions of cirrhosis and liver-related complications in hemophilics are likely to make hemophilics to have sustainably higher proportions of liver-related complications than non-hemophilics over their survival time (decompensated cirrhosis: 6.8 to 7.8% vs. 2.6 to 5.3%; HCC: 2.3 to 4.6% vs. 1.0 to 2.4%; post-transplant: 2.7 to 4.1% vs.

1.3 to 2.0%). The model outputs of hemophilics and non-hemophilics in this age stratum are summarized in *Table 14.5*.

4.6. Ages 70 to 79

The initial disease stages associated with hemophilics are far more advanced than the initial stages associated with non-hemophilics in this age stratum (cirrhosis: 27.1% vs. 7.8%; decompensated cirrhosis: 12.2% vs. 5.1%; HCC: 6.1% vs. 0.7%, liver transplantation: 2% vs. 0.5%). However, the life expectancy associated with this age stratum is much reduced and no claimants in this age stratum will survive to 2050. Thus, further disease progression beyond 2050 will be stopped accordingly and the lifetime cumulative rates of liver-related complications and mortality in both hemophilic and non-hemophilic claimants are predicted to drop substantially. However, the predicted lifetime cumulative rates of decompensated cirrhosis (18.8% vs. 8.9%), HCC (9.1% vs. 2.6%), liver transplantation (2.5% vs. 0.7%), and liver-related mortality (20.8% vs. 10.1%) in hemophilics continue to be much higher that what are predicted in non-hemophilics. The higher initial proportions of compensated cirrhosis and decompensated cirrhosis associated with hemophilics also make the predicted proportions of liver-related complications in surviving hemophilics sustainably higher than what are predicted in non-hemophilics over their survival time (decompensated cirrhosis: 5.7 to 8.8% vs. 3.1 to 4.3%; HCC: 3.5 to 5.0% vs. 1.1 to 2.0%; post-transplant: 2.3 to 3.0% vs. 0.5 to 0.9%). The model outputs of hemophilic and non-hemophilic claimants in this age strata are summarized in *Table 14.6*.

4.7. Ages 80 to 89

The initial proportions of cirrhosis (7.7% vs. 8.9%) and decompensated cirrhosis (4.2% vs. 3.1%) in hemophilics in this age stratum substantially drop to be comparable with the initial proportions of the two advanced disease stages in non-hemophilics. Thus, the two types of claimants are expected to have similar long-term prognosis in their short life expectancy. Both hemophilics and non-hemophilics in this age stratum are predicted to have no survivors by 2040. Hemophilics and non-hemophilics are predicted to have comparable lifetime cumulative risks of liver-related complications (decompensated cirrhosis: 5.2% vs. 4.7%; HCC: 0.8% vs. 1.6%; liver transplantation: 0.1% vs. 0.4%) and mortality (5.5% vs. 5.2%) and also have comparable proportions of liver-related complications (decompensated cirrhosis: 4.5 to 4.9% vs. 2.5 to 3.0%; HCC: 0.8 to 1.9% vs. 1.1 to 2.1%; post-transplant: 0.1 to 0.4% vs. 0.3 to 0.4%) over their survival time. The model outputs of hemophilic and non-hemophilic claimants in this age stratum are summarized in *Table 14.7.*

4.8. Age strata of 90 years and above

Both hemophilics and non-hemophilics in this age stratum have further dropping but more comparable initial proportion of cirrhosis (4.3% vs. 4.5%). Within the much shortened life expectancy associated with this age stratum, both hemophilics and non-hemophilics are predicted to have very few occurrences of liver-related complications (decompensated cirrhosis: 0.5% vs. 1.8%; HCC: 0.2% vs. 0.6%; liver transplantation: 0% vs. 0.5%) and mortality (0.6% vs. 1.9%) by 2030 when no more claimants are predicted to survive. Thus, hemophilics and non-hemophilics also have highly comparable but extremely low proportions of liver-related complications (decompensated cirrhosis: 1.1% vs. 1.2%; HCC: 0.4% vs. 0.7%; post-transplant: 0%

vs. 0.5%) in 2020, the only defined calendar year with surviving claimants. The model outputs of hemophilics and non-hemophilics in this age stratum are summarized in *Table 14.8.*

5. Comparing model outputs of the current revision and the fourth revision

In order to demonstrate impact of updated treatment pattern and model variables on the long-term prognosis of current surviving claimants, we have compared the model outputs of the current revision and the fourth revision in the defined calendar years from 2020 to 2070. Because claimants only receive PEG-IFN/RBV combination treatment in the fourth revision, about of half of claimants are expected to fail with this treatment and continue to progress to more advanced disease stage. Thus, the predicted cumulative rates of liver-related complications and mortality in the fourth revision increase much faster than what are predicted in the current revision which mainly uses sofosbuvir-based doublet and 3D regimen plus RBV treatments, which can cure most claimants and substantially improve the long-term prognosis of compensation claimants. For example, the cumulative rate of cirrhosis in the fourth revision are predicted to increase from 24.3% in 2020 to 38.5% in 2060 (absolute difference: 14.2%) while the current revision predicts an increase of 2.9% (from 16.9% to 19.8%) for the cumulative rate of cirrhosis during the same period. Similar trends are also found in the comparisons of cumulative rates of HCC, liver transplantation, and liver-related mortality predicted by the fourth revision and the current revision. By 2060, the predicted cumulative rates of cirrhosis (38.5% vs. 19.8%), HCC (10.5% vs. 4.3%), and liver-related mortality (24.0% vs. 14.4%) in the fourth revision are nearly two times what are predicted in the current revision. Because the fourth revision assumed a much higher annual risk of liver-transplantation than the current revision (0.1 vs. 0.0004), the predicted cumulative rate of liver transplantation in the fourth revision in 2060 is 4.7 times the prediction

in the current revision (4.2% vs. 0.9%). Less effective antiviral therapy used in the fourth revision also affects the distribution of disease stages in surviving claimants over their survival time. Different from the relatively stable proportion of cirrhosis from 2020 to 2060 in the fourth revision (11.6% to 16.2%), the predicted proportion of cirrhosis in the current revision declines gradually (9.7% to 2.1%) due to the lack of new progressions from less advanced fibrosis stage. Thus, the fourth revision has persistently higher proportions of decompensated cirrhosis (2.9 to 4.3% vs. 1.5 to 3.2%) and HCC (1 to 1.5% vs. 0.7 to 1.1%) than the current revision over time from 2020 to 2060. The assumed higher annual risk of liver transplantation in the fourth revision could further drive up the predicted proportion of post-transplant in the fourth revision (1.5 to 4.1% vs. 0.5 to 0.7%). The model outputs of the fourth revision and the current revision are summarized in *Table 15*.

6. Sensitivity analyses

The substantial differences in model outputs of the current revision and the fourth revision have suggested that the model outputs of compensation claimants could be highly sensitive to the updates made in the current revision. When compared with the fourth revision, the current revision has updated treatment patterns using new antiviral regimens over the next five years and model estimates for the prognosis of cirrhosis and non-liver-related mortality using claims data. Thus, we have performed the following sensitivity analyses to assess the impact of the main updates on model outputs of current surviving non-hemophilic claimants.

6.1. Data sources of estimates for the prognosis of cirrhosis: Literature review vs. Claims data

The estimates for the prognosis of cirrhosis in the fourth revision were derived from literature review of studies including HCV patients irrespective of viral transmission route. Thus, the literature-based estimates are expected to have better external validity but poorer internal validity as the compensation claimants acquired HCV only through blood transfusion or blood products. The current claims data contain over 5,000 approved claimants and a large number of claimants have been followed up for 16 years since the compensation cohort was created in 1998. Thus, the claims data are believed to have enough sample size and follow-up time to estimate their own prognosis of cirrhosis and improve internal validity of model outputs. We have compared literature-derived estimates in the fourth revision and estimates based on claims data for the prognosis of cirrhosis (*Table 16.1.*). The annual risk of mortality associated with HCC in compensation claimants is about half of the estimate derived from literature (0.182 vs. 0.35). The first-year mortality rate after liver transplantation in compensation claimants is also much lower than what has been reported from literature (0.086 vs. 0.146). The fourth revision made an assumption on the chance of liver transplantation associated with decompensated cirrhosis or HCC due to the lack of literature. However, this assumed estimate is 4.7 times of the rate of liver transplantation (0.1 vs. 0.004) truly observed in compensation claimants. Thus, the estimates derived from claims data are expected to reduce the occurrences of liver-related mortality and liver transplantation. Comparing model outputs based on the two difference data sources has confirmed substantially higher cumulative rate of liver transplantation associated with claims data in 2070 (3.2% vs. 0.9%). However, the estimates based on claims data are unable to reduce liver-related mortality likely due to very low occurrences of HCC. Thus, the model outputs based on these two data sources are highly comparable except more occurrences of liver transplantation due to the assumption made in the fourth revision. The model outputs of non-hemophilics using

estimates derived from literature or claims data for the prognosis of cirrhosis are summarized in *Table 16.2.*

6.2. Non-liver-related mortality: claim cohort vs. 2009 to 2011 Canada life tables

The current revision updated non-liver-related mortality by using claims data for the same purpose of improving the accuracy of model outputs because the comorbidities associated with blood transfusion or blood products could substantially reduce the life expectancy of compensation claimants. We have used the claims data to estimate annual risk of non-liver-related mortality in non-HIV claimants stratified by age, gender, and hemophilic status and compared them with the 2009 to 2011 Canada age- and gender-specific life tables (*Table 17.1*). The comparisons have demonstrated that annual non-liver-related mortality rates associated with both hemophilics (male: 0.00290) and non-hemophilics (male: 0.00233; female: 0.00133) at ages 30 to 39 were nearly two times of the annual mortality rates in general Canadians (male: 0.00111; female: 0.00058) within the same age range. Annual non-liver-related mortality rates associated with male non-hemophilics in ages 40 to 49 (0.00632) and ages 50 to 59 (0.00794) were 3.3 times and 1.6 times of the annual mortality rates for male Canadians in the same age strata (ages 40 to 49: 0.00240; ages 50 to 59: 0.00619). Thus, we have also performed the sensitivity analysis to compare model outputs based on different data sources for non-liver-related mortality, claims data vs. Canada life tables, for any meaningful changes. However, the model outputs are not sensitive to the identified differences in non-liver-related mortality between claimants and general Canadians as the generated model outputs are almost identical. The comparisons observed almost identical model predictions on cumulative rates of liver-related complications and proportions of disease stages in the selected calendar years from 2020 to 2070. Even though

the relative differences in annual non-liver-related mortality rates between some compensation claimants and general Canadians look large, the absolute differences in annual non-liver-related mortality rates between them are too small to cause any obvious changes of model outputs. The model outputs based on annual non-liver-related mortality rates derived from claims data and the Canada life tables for non-hemophilics are summarized in *Table 17.2.*

6.3. Treatment patterns: current revision vs. the fourth revision

Updating treatment patterns with information from new antiviral regimens served as the major revision of the HCV prognostic model in this report. In order to demonstrate the impact of updated treatment patterns on model predictions, we have compared the model outputs of non-hemophilic claimants using treatment patterns estimated in the fourth revision and the current revision for the HCV prognostic model. The treatment patterns estimated in the two revisions are different in both treatment rate and treatment efficacy. The overall treatment rate in the fourth revision was 43.6%, which is about half of the treatment rate derived from the treatment preference survey study in the current revision. PEG-IFN/RBV was the only antiviral regimen used in the fourth revision and the treatment efficacy of this antiviral regimen was only about half of sofosbuvir-based doublets or 3D regimen plus RBV, the two antiviral regimens functioned as the primary methods of treatment in the current revision of the model. The substantially increased treatment rate and treatment efficacy of antiviral regimens associated with the updated treatment patterns in the current revision were expected to provide a cure for most claimants with CHC and significantly improve long-term prognosis of compensation claimants. Comparing the model outputs based on the two treatment patterns demonstrates that the predicted cumulative rates of decompensated cirrhosis (9.5% vs. 19.7%), HCC (3.4% vs.

8.3%), and liver-related mortality (11.6% vs. 24.9%) associated with the updated treatment patterns in the current revision were less than half of the predictions associated with previous treatment patterns used in the fourth revision. Because the treatment patterns in the fourth revision are expected to cure about one-quarter of surviving claimants and uncured claimants will continue the progression to advanced disease stage, the predicted proportion of compensated cirrhosis associated with treatment patterns in the current revision declines much faster than the prediction associated with previous treatment patterns in the fourth revision. Consequently, the proportions of decompensated cirrhosis (5.9 to 6.7% vs. 0.8 to 2.1%), HCC (2.4 to 3.3% vs. 0.4 to 0.9%), and post-transplant (0.8 to 1.3% vs. 0.4 to 0.7%) in non-hemophilic claimants receiving treatment patterns used in the fourth revision are predicted to be persistently higher than the predictions associated with current treatment patterns over their future survival time. The model outputs based on the two treatment patterns for surviving non-hemophilic claimants are summarized in *Table 18*.

7. Overall uncertainty associated with model predictions

The estimates of model variables are associated with more or less uncertainty that can cause model outputs to vary. Uncertainty associated with model variables is usually indicated by 95% CI, which can be used to construct the distributions of model variables. When exploring over uncertainty associated with model outputs, the mean values of the model variables in the disease prognostic model are replaced with the constructed distributions of model variables to calculate 95% CI of model outputs.

The current revision used the abovementioned method to estimate uncertainty associated with the long-term prognosis of surviving compensation claimants as of August 31, 2013. Because the model variables in the HCV prognostic model are probability/proportion variables that are usually associated with beta distribution, we have constructed the distributions of model variables using their 95% CIs and the assumption of beta distribution. After replacing the baseline values of model variables with the constructed model distributions in the HCV prognostic model, two-order Monte Carlo simulation analysis with 1000 trials for the first order and 50,000 trials for the second order was performed to generate 1000 model outputs for surviving hemophilic and non-hemophilic claimants, respectively. In order to estimate 95% CI of model outputs for the entire claimant cohort, the initial proportion of hemophilia in the surviving claimants (23.1%) has been used to determine the number of model outputs randomly selected from the 1000 model outputs for hemophilics and non-hemophilics. Thus, 231 randomly selected model outputs for hemophilics and 769 randomly selected model outputs for non-hemophilics were pooled to create 1000 model outputs representing the distribution of model outputs for the entire claimant cohort. Based on these 1000 model outputs, the estimated 95% CIs of cumulative decompensated cirrhosis, HCC, and liver-related mortality rates by 2070 were 8.7 to 15.5%, 3.1 to 5.5%, and 11.0 to 18.4%, respectively. The 95% CIs of cumulative rates of liver-related complications and mortality in the selected calendar years are summarized in *Table 19*.

8. Implications of current revision on future indirect costs to claimants

The current revision has predicted that the future treatment patterns over the next five years could cure most claimants and substantially reduce liver-related complications, which are usually associated with significant consumptions of health resources and also indirect costs related to

patient time, caregiver time, and out-of-pocket costs. According to a large survey study measuring 738 outpatients living in the metropolitan area of Vancouver, British Columbia, the annual patient time costs, caregiver time costs, and out-of-pocket costs associated with viral clearance were $281, $31, and $427, respectively. These costs associated with viral clearance were substantially lower than the costs associated with non-cirrhotic patients and further lower when compared to those costs associated with cirrhosis.[94] ENREF 1This study also reported the lowest unemployment rate associated with viral clearance. Thus, successful treatment in a high proportion of HCV infected individuals, as is forecast by this model, may substantially reduce societal costs due to morbidity-related work loss, and may substantially reduce out of pocket expenses associated with ongoing HCV infection.

The economic impact of model outputs on compensation claimants is an important consideration for compensation budget planning as most claimants would get rid of the virus and their compensation needs would be substantially reduced. If future estimations on indirect costs to compensation claimants are needed, this Canadian survey study can be used as the source for the reference of indirect costs needed in the HCV prognostic model. For example, the health states used to summarize the annual patient time costs, caregiver time costs, and out-of-pocket time costs in this survey study could be easily matched with the health states in the HCV prognostic model. The reported annual indirect costs associated with the classified health states (*Table 20*) could be directly applied to the HCV prognostic model except treatment costs, which was based on interferon-based treatment. The new treatments are believed to be associated with much less treatment costs (not including drug costs) than interferon-based treatment because the treatment time of new treatments will be reduced to 12 weeks, which is a quarter of treatment time often

needed for interferon-based treatments. Additionally, the interferon-free treatments will cause much less toxicity and reduce indirect costs associated with AE management. Because this survey study also performed multiple regression analyses to assess the relationship between patient baseline characteristics and annual patient and caregiver time costs and out-of-pocket costs (*Table 21*), the reported coefficients associated with patient demographics, virus clearance, and disease stages can be used to construct a formula to predict indirect costs associated with claimants during each model cycle. The same adjustment for indirect costs associated with treatment is also needed in this method in order to reflect the reduced treatment time and toxicity associated with new antiviral regimens used in the current revision.

9. Discussion

The emergence of highly effective antiviral regimens for CHC is expected to substantially alter current treatment patterns as well as significantly improve the long-term prognosis of patients with CHC. Thus, the current revision has primarily focused on updating treatment patterns with new antiviral regimens and revising model predictions for current surviving compensation claimants due to the changed treatment patterns. The current revision has conducted a survey to measure a physician's likelihood of treating claimants and their preferences on treatment options that include current standard treatment and also three new antiviral regimens that will be ready for Canadian patients within two years. The survey results based on data from 14 physicians suggest that they are willing to treat most claimants using the most recently developed antiviral regimens, sofosbuvir-based doublets and 3D antivirals, likely because they can provide a cure for nearly all patients and their expensive costs can be compensated.

When compared with the fourth revision that was conducted in 2010, the current revision predicts that the lifetime cumulative rates of liver-related complications and mortality can be reduced by half mainly due to greatly improved treatment rates and treatment efficacy associated with new treatments. Separate model predictions for claimants stratified by hemophilic status have further confirmed much poorer prognosis associated with hemophilic claimants mainly because of more advanced disease stages and a much higher prevalence of HIV co-infection in hemophilics. When compared with non-hemophilic claimants, hemophilic claimants are predicted to have doubled lifetime cumulative rates of decompensated cirrhosis, HCC, and liver-related mortality. Further comparisons of model outputs between hemophilics and non-hemophilics stratified by age suggest that the higher initial proportion of cirrhosis in hemophilics is the main factor driving up the occurrences of liver-related complications and mortality. Even though the new treatments can cure most claimants, the cured claimants with developed cirrhosis still have a certain risk of progressing to more advanced stages and continue to increase the risks of liver-related complications and mortality.

The MMWG on the current revision has taken several steps to improve the accuracy of model outputs. First, the current revision includes a survey of previously treated claimants to determine their treatment outcomes that have significant impact on long-term prognosis and also treatment pattern. The overall SVR rate among surveyed claimants was 57.8%, which was highly consistent with the reported SVR rate associated with previous standard antiviral therapy using the combination of PEG-IFN and RBV. We believe that treatment outcome patterns in these surveyed claimants are highly valid when used to estimate the initial proportions of treatment responders and non-responders needed by the HCV prognostic model. Second, the current

revision has fully taken into account the possible impact of HIV co-infection and previous treatment on physician treatment preference[95,96] when conducting the treatment pattern survey study. Additionally, the surveyed physicians were asked to give their treatment preferences according to the summarized baseline characteristics of current surviving claimants chronically infected with HCV. Because previous revisions used the treatment patterns data derived from published survey studies for general patients with HCV, the estimated treatment patterns specifically for claimants stratified by the status of HIV co-infection and previous treatment should have much improved internal validity when simulating the same type of claimants in the model. For example, the results of this survey study indicate that over 90% of the surveyed physicians are willing to treat claimants with new treatments which are highly effective and also highly expensive. We believe that this treatment rate will substantially drop if these new treatments cannot be reimbursed. Finally, the current revision has tried to further improve the accuracy of model outputs by estimating model variables using claims data. Previous revisions mainly estimated model variables from literature or assumptions. When compared with model variables for the prognosis of cirrhosis in the fourth revision, the estimates of some model variables derived from claims data were much lower. For example, the assumed annual risk of receiving liver transplantation in the fourth revision is 25 times of the estimate derived from claims data. Using this assumed estimate would increase lifetime cumulative liver transplantation rate by 356% from 0.9% to 3.2% in surviving non-hemophilic claimants. Because liver transplantation increases costs tremendously to both patients and health care system, the revised prediction of the rate of liver transplantation in the future is expected to have significant impact on future compensation budget planning.

The previous revision validated the natural history model through the comparisons of predicted and observed initial distribution of disease stages in the simulated claimants. In contrast, the current revision compared predicted and observed liver-related complications and mortality by following a group of non-hemophilic claimants for 10 years. The predicted and observed liver-related complications are well matched. However, the predicted cumulative liver-related mortality rate was lower than what was observed whereas the predicted non-liver-related mortality was much higher than what was observed. We suspect that recorded liver-related complications present in the claim cohort may be less advanced due to treatment received via the compensation program. The risk of liver-related mortality among the claimant cohort is likely to be less than predicted by the literature because the cohort has received treatment under the compensation plan that those in other studies did not get (presumably due to cost issues). However, the impact of this bias on model predictions should be significantly minimized because the updated treatment patterns are expected to cure the majority of claimants with CHC and the occurrences of liver-related complications will be substantially reduced. Because claims involving deaths not caused by HCV would not be eligible to receive compensation, non-liver-related mortality in compensation claimants may not be fully recorded. The missing information on non-liver-related mortality could make the predicted non-liver-related mortality higher than the recorded non-liver-related mortality in compensation claimants. Because the two types of bias associated with mortality can be neutralized by each other, the predicted and observed all-cause mortalities are comparable. Thus, we believe that the HCV prognostic model used in the current revision is valid and able to generate reliable model predictions on the long-term prognosis of current surviving compensation claimants.

The current revision has also performed sensitivity analysis to assess the changes of model outputs associated with the major revisions made in the HCV prognostic model. The major revisions include the updated treatment patterns with new antiviral regimens and using claims data to estimate model variables for the prognosis of cirrhosis and non-liver-related mortality. These sensitivity analyses have not detected any meaningful changes of model outputs when changing the data sources for the estimations on the prognosis of cirrhosis and non-liver-related mortality. The insensitivity of model outputs to estimates derived from claims data for the prognosis of cirrhosis can be explained by the updated treatment patterns that will cure most of patients and substantially reduce the risk of cirrhosis in the compensation claimants. Thus, the impact of the changes of model variables for the prognosis of cirrhosis is unlikely to be demonstrated in a small number of cirrhotic claimants. Another sensitivity analysis observed almost identical model outputs based on non-liver-related mortality derived from claims data and the latest Canada life tables. Even though the non-liver-related mortality associated with some compensation claimants has been confirmed to be relatively larger than general population, the absolute differences in non-liver-related mortality between them are too small to cause any obvious changes of model outputs. The final sensitivity analysis compared the model outputs based on previous treatment patterns used in the fourth revision and the updated treatment pattern in the current revision. Similar to the comparisons of model outputs in the fourth revision and the current revision, the model predictions on the lifetime risks of liver-related complications and mortality are decreased by half when the updated treatment patterns in the current revision are used. Thus, these performed sensitivity analyses have confirmed that the predicted improvements of long-term prognosis in the current surviving claimants are solely driven by the

updated treatment patterns that will cure over 80% of surviving claimants with HCV over the next five years.

The current revision also has several limitations that may affect model predictions. The efficacy of antiviral regimens represented in the treatment pattern data are based on randomized clinical trials identified via a comprehensive search of main medical databases as well as proceedings from top liver-related conferences. However, the identified clinical trials are unable to provide all estimates needed in the model. For example, we have to assume that HIV co-infection has the same impact on SVR rates associated with new antiviral regimens as that found in traditional PEG-IFN/RBV treatment due to the lack of trials assessing new antiviral treatments in patients with HIV co-infection. Additionally, the reported treatment efficacies associated with these new antiviral regimens are determined based on SVR at 12 weeks, which is only half the time conventionally used to assess SVR following treatment. Even though both Health Canada and US FDA accept SVR at 12 weeks as the main outcome measure to assess treatment efficacies of new antivirals, there is no clinical evidence confirming that SVR at 12 weeks represents a clinical cure. Thus, current model predictions may require further adjustment if SVR rates associated with new antiviral regimens change appreciably given longer follow-up. Finally, the current revision doesn't take into account the prognosis of small number of claimants (33 claimants, 0.86% of total surviving claimants as of August 31, 2013) who were categorized into compensation level 6 because of liver-unrelated complications, such as lymphoma (8 claimants), cryoglobulinemia (14 claimants), and glomerulonephritis (11 claimants). Because cryoglobulinemia and glomerulonephritis can be substantially improved after eradication of HCV,[97] the new treatment patterns could make their impact on model prediction totally ignorable.

Also, more and more convincing evidence suggest that successful antiviral therapy improves cure rate of HCV-related lymphoma.[98] We believe that this small group of patients only have modest effects on the future mortality of the compensation cohort.

In summary, the HCV prognostic model has been revised by including future treatment pattern data which takes into account new antiviral regimens that are likely to be available in Canada within the next two years. The much improved treatment rate and cure rate associated with sofosbuvir-based doublets and 3D antiviral regimen plus RBV would reduce the lifetime risks of liver-related complications and mortality by half in current surviving hemophilic and non-hemophilic claimants. Additionally, hemophilic claimants are predicted to continue to have a worse prognosis than non-hemophilic claimants likely due to a higher initial proportion of cirrhosis and HIV co-infection. Thus, future compensation funds are definitely needed to be adjusted by taking into account the changes of treatment patterns, expected reductions of liver-related complications and mortality, and reduced indirect costs to claimants due to substantially improved cure rate.

10. References

1. The hepatitis C prevention, support and research program: Health Canada Initiatives on hepatitis C. Health Canada. Can J Public Health 2000;9:S27-31
2. Remis RS, Hogg RS, Krahn MD, Preiksaitis JK, Sherman M, Palmer RWH. Estimating the number of blood transfusion recipients infected by hepatitis C virus in Canada, 1960-85 and 1990-92: Report to Health Canada; 1998.
3. Zou S, Tepper M, Giulivi A. Current status of hepatitis C in Canada. Can J Public Health 2000;91 Suppl 1:S10-15, S10-16.
4. Scully LJ, Mitchell S, Gill P. Clinical and epidemiologic characteristics of hepatitis C in a gastroenterology/hepatology practice in Ottawa. CMAJ 1993;148(7):1173-7.
5. Stevens CE, Taylor PE, Pindyck J, Choo QL, Bradley DW, Kuo G, et al. Epidemiology of hepatitis C virus. A preliminary study in volunteer blood donors. JAMA 1990;263:49-53.
6. Comeau P. Hepatitis C compensation may be extended. CMAJ 2005;172:25.

7. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. Ann Intern Med 1997;127:855-865.
8. Wong JB. Interferon treatment for chronic hepatitis B or C infection: costs and effectiveness. Acta Gastroenterol Belg 1998;61:238-242.
9. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update.Hepatology 2009;49(4):1335-74.
10. Venkatraman S, Bogen SL, Arasappan A, et al. Discovery of (1R,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino] carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo [3.1.0]hexan-2(S)-carboxamide (SCH 503034), a selective, potent, orally bioavailable hepatitis C virus NS3 protease inhibitor: a potential therapeutic agent for the treatment of hepatitis C infection. J Med Chem. 2006; 49:6074–86.
11. Lin C, Kwong AD, Perni RB. Discovery and development of VX-950, a novel, covalent, and reversible inhibitor of hepatitis C virus NS3.4A serine protease. Infect Disord Drug Targets 2006; 6: 3-16.
12. Maylin S, Martinot-Peignoux M, Ripault MP, et al. Sustained virological response is associated with clearance of hepatitis C virus RNA and a decrease in hepatitis C virus antibody. Liver Int 2009;29(4):511-7.
13. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial.Lancet 2010;376(9742):705-16.
14. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364(25):2405-16.
15. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364(13):1207-17.
16. McHutchison JG, Manns MP, Muir AJ, et al.Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010;362(14):1292-303.
17. RK Chaudhary, M Tepper, S Eisaadany, Paul R Gully.Distribution of hepatitis C virus genotypes in Canada: Results from the LCDC Sentinel Health Unit Surveillance System. Can J Infect Dis 1999; 10(1): 53–56.
18. Lin TI, Lenz O, Fanning G, et al. In vitro activity and preclinical profile of TMC435350, a potent hepatitis C virus protease inhibitor. Antimicrob Agents Chemother 2009;53(4):1377-85.
19. Herbst DA Jr, Reddy KR. Sofosbuvir, a nucleotide polymerase inhibitor, for the treatment of chronic hepatitis C virus infection.Expert Opin Investig Drugs 2013;22(4):527-36.
20. Ira M. Jacobson, Reem H. Ghalib, Maribel Rodriguez-Torres, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naïve and prior null responder patients: The COSMOS study. 2013 AASLD annual meeting.
21. Sulkowski MS, Asselah T, Lalezari J, et al. Faldaprevir combined with pegylated interferon alfa-2a and ribavirin in treatment-naïve patients with chronic genotype 1 HCV: SILEN-C1 trial.Hepatology 2013;57(6):2143-54.
22. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection.N Engl J Med (published online on April 11, 2014)
23. Afdhal N, Reddy KR, Nelson DR, et al.Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection.N Engl J Med 2014;370(16):1483-93.
24. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al.Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection.N Engl J Med 2014;370(3):211-21.
25. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin.N Engl J Med 2014;370(17):1594-603.

26. Dore GJ. The changing therapeutic landscape for hepatitis C. Med J Aust. 2012;196:629-632.
27. Aleman S et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C–associated liver cirrhosis. Clin Infect Dis 2013; 57:230-6.
28. Franchini M, Mengoli C, Veneri D, Mazzi R, Lippi G, Cruciani M. Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis. J Antimicrob Chemother 2008;61(6):1191-200.
29. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998; 352: 1426–32.
30. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001; 358: 958–65.
31. Seeger JD, Walker AM, Williams PL, Saperia GM, Sacks FM. A propensity score-matched cohort study of the effect of statins, mainly fluvastatin, on the occurrence of acute myocardial infarction. Am J Cardiol 2003;92:1447-1451.
32. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265-2281.
33. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2011_victrelis_141556-eng.php
34. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm255413.htm
35. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2012_incivek_142482-eng.php
36. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm256328.htm
37. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_sovaldi_165043-eng.php
38. http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377920.htm
39. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_galexos_164021-eng.php
40. http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377234.htm
41. Pearlman BL and Ehleben C. Hepatitis C Genotype 1 Virus With Low Viral Load and Rapid Virologic Response to Peginterferon/Ribavirin Obviates a Protease Inhibitor. Hepatology 2014;59(1): 71-77.
42. Poordad F, Bronowicki JP,Gordon SC, et al.Factors That Predict Response of Patients With Hepatitis C Virus Infection to Boceprevir.GASTROENTEROLOGY 2012;143:608–618
43. Kwo PY, Lawitz EJ, McCone J et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet 2010; 376(9742): 705-716.
44. Lawitz E, Zeuzem S, Nyberg L, et al. Boceprevir(BOC) combined with peginterferon alfa 2b/ribavirin (P/RBV) in treatment-naïve chronic HCV genotype 1 patients with compensated cirrhosis: sustained virologic response(SVR) and safety subanalyses from the anemia management study.Hepatology 2012;56(4):216A.
45. Poordad F, McCone J, Bacon B, et al. Boceprevir for Untreated Chronic HCV Genotype 1 Infection.New England Journal of Medicine 2011;364(13): 1195-1206.
46. Basu P,Siriki R,Shah N, et al.Telaprevir with adjusted dose of ribavirin in naïve CHC-G1:efficacy and treatment in CHC in hemodialys is population. target c(RCT). Journal of Hepatology 2013;58:S30-S31.
47. Basu P, Shah N, Farhat S, et al. Pegylated interferon alfa,nitazaxanide,telapravir and ribavirin in prior experienced chronic hepatitis C genotype 1 patients-a randomized placebo control clinical pilot trial(INTRIGUE-C). Hepatology 2012;56(4):1035A.

48. Horsmans Y, Brown Jr R, Buti M, et al.Safety and efficacy of twice daily versus every 8 hour telaprevir with peginterferon/ribavirin (pr) in patients with cirrhosis.Journal of Hepatology 2013;58:S338-S339.
49. Mathurin P, Sarrazin C,Reesink H,et al.Treatment with telaprevir-based therapy after exposure to PEG-IFN/RBV in the realize study: results from the phase iiib c219 rollover study. Journal of Hepatology 2013;58:S356-S357.
50. McHutchison J, Everson G, Gordon S, et al. Telaprevir with Peginterferon and Ribavirin for Chronic HCV Genotype 1 Infection. New England Journal of Medicine 2009;360(18): 1827-1838.
51. Sherman K, Flamm S, Afdhal N, et al.Response-Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection.New England Journal of Medicine 2011;365(11): 1014-1024.
52. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for Retreatment of HCV Infection. New England Journal of Medicine 2011;364(25): 2417-2428.
53. Buti M, Agarwal K, Horsmans Y, et al.Telaprevir Twice Daily Is Noninferior to Telaprevir Every 8 Hours for Patients With Chronic Hepatitis C.Gastroenterology 2014;146(3):744-753
54. Hézode C, Forestier N, Dusheiko G, et al.Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009; 360:1839-1850.
55. Kumada H, Toyota J, Okanoue T, et al. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan.J Hepatol 2012;56(1):78-84.
56. Benhamou Y, Moussalli J, Ratziu V, et al.Telaprevir Activity in Treatment-Naive Patients Infected Hepatitis C Virus Genotype 4: A Randomized Trial. Journal of Infectious Diseases 2013; 208(6): 1000-1007.
57. Foster G, Hezode C, Bronowicki J, et al.Telaprevir Alone or With Peginterferon and Ribavirin Reduces HCV RNA in Patients With Chronic Genotype 2 but Not Genotype 3 Infections. Gastroenterology 2011;141(3): 881-889.
58. Jacobson I, McHutchison J, Dusheiko G, et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. New England Journal of Medicine 2011;364(25): 2405-2416.
59. Marcellin P, Forns X, Goeser T, et al.Telaprevir Is Effective Given Every 8 or 12 Hours With Ribavirin and Peginterferon Alfa-2a or-2b to Patients With Chronic Hepatitis C.Gastroenterology 2011;140(2): 459-468.
60. Rizzetto M, Andreone P, Colombo M, et al. ADVANCE study: Final results of the phase III trial with telaprevir in combination with PEG-IFN and RBV in treatment-naive genotype 1 HCV. Digestive and Liver Disease 2011;43: S69-S69.
61. Rockstroh J, Nelson M, Soriano V,et al. Startverso 4 phase III trial of faldaprevir plus peginterferon alfa-2a and ribavirin(PR) in patients with HIV and HCV genptype 1 coinfection:end of treatment response.Hepatology 2013;58(4):741A-742A.
62. Ferenci P, Asselah T, Foster G, et al.Faldaprevir plus pegylated interferon alfa-2a and ribavirin in chronic hcv genotype-1 treatment-na¨ive patients: final results from startverso1, a randomised, double-blind, placebo-controlled phase iii trial. Journal of Hepatology 2013; 58:S569–570.
63. Sulkowski M, Asselah T, Lalezari J, et al. Faldaprevir combined with pegylated interferon alfa-2a and ribavirin in treatment-naive patients with chronic genotype1 HCV: SILEN-C1 trial. Hepatology 2013;57(6): 2143-2154.
64. Sulkowski M, Pol S, Mallolas 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(7):597-605.
65. Sulkowski M, Sherman K, Dieterich D, et al. Combination Therapy With Telaprevir for Chronic Hepatitis C Virus Genotype 1 Infection in Patients With HIV A Randomized Trial. Annals of Internal Medicine 2013;159(2): 86-W35.
66. Sulkowski M, Sherman K, Soriano V,et al. Telaprevir in combination with peginterferon alfa-2a/ribavirin in HCV/HIV co-infected patients:SVR24 final study results.Hepatology 2012; 56(4):219A-220A.

67. Poordad F, Bronowicki J, Gordon S, et al. Factors That Predict Response of Patients With Hepatitis C Virus Infection to Boceprevir. Gastroenterology 2012;143:608–618
68. Bacon B, Gordon S, Lawitz E, et al. Boceprevir for Previously Treated Chronic HCV Genotype 1 Infection.N Engl J Med 2011; 364(13): 1207–1217.
69. Hézode C, Fontaine H, Dorival C, et al.Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) – NCT01514890.Journal of Hepatology 2013; 59:434–441
70. Flamm S, Lawitz E, Jacobson I, et al. Boceprevir With Peginterferon Alfa-2a–Ribavirin Is Effective for Previously Treated Chronic Hepatitis C Genotype 1 Infection.Clinical Gastroenterology and Hepatology 2013; 11:81–87
71. Pockros P, Zeuzem S, Lawitz E, et al.Telaprevir-Based Regimen in Genotype 1 Hepatitis C Virus-Infected Patients With Prior Null Response, Partial Response or Relapse to Peginterferon/Ribavirin: REALIZE Trial Final Results. Gastroenterology 2011;140(5): S898-S898.
72. Hayashi N, Okanoue T, Tsubouchi H, et al. Efficacy and safety of telaprevir, a new protease inhibitor, for difficult-to-treat patients with genotype 1 chronic hepatitis C.Journal of Viral Hepatitis 2012; 19:e134–e142.
73. Foster G, Zeuzem S, Andreone P, et al. Sustained virologic response rates with telaprevir by response after 4 weeks of lead-in therapy in patients with prior treatment failure. Journal of Hepatology 2013; 58:488–494.
74. Hézode C, Fontaine H, Dorival C, et al.Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) – NCT01514890.Journal of Hepatology 2013; 59:434–441
75. McHutchison J, Manns M, Muir A, et al.Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010; 362(14):1292-303.
76. Sulkowski M, Bourliere M, Bronowicki J. et al.Faldaprevir combined with peginterferon alfa-2a and ribavirin in chronic hepatitis C virus genotype-1 patients with prior nonresponse: SILEN-C2 trial. Hepatology 2013;57(6): 2155-2163.
77. Sulkowski M, Sherman K, Dieterich D, et al. Combination Therapy With Telaprevir for Chronic Hepatitis C Virus Genotype 1 Infection in Patients With HIV A Randomized Trial. Annals of Internal Medicine 2013; 159(2): 86-W35.
78. Jacobson I, Ghalib R, Rodriguez-Torres M, et al. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: The COSMOS study.Hepatology 2013;58(6): 1379A-1380A.
79. Lawitz E, Poordad F, Pang P,et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial.Lancet. 2014;383(9916):515-23.
80. Sulkowski M, Gardiner D, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370(3):211-21.
81. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin.N Engl J Med 2014;370(17):1604-14.
82. http://liver.ca/liver-education-liver-research/resources-health-professionals/Physician_Directories.aspx
83. Yi Q, Wang PP, Krahn M. Improving the accuracy of long-term prognostic estimates in hepatitis C virus infection. J Viral Hepat. 2004;11:166-174.
84. 2009 to 2011 Canada life tables. http://www.statcan.gc.ca/pub/84-537-x/2013005/tbl-eng.htm
85. Mohsen AH, Easterbrook PJ, Taylor C, et al. Impact of human immunodeficiency virus (HIV) infection on the progression of liver fibrosis in hepatitis C virus infected patients. Gut. 2003;52(7):1035-40.

86. Franchini M, Mengoli C, Veneri D, et tal. Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis. J Antimicrob Chemother 2008;61(6):1191-200.
87. Yee TT, Griffioen A, Sabin CA, Dusheiko G, Lee CA. The natural history of HCV in a cohort of haemophilic patients infected between 1961 and 1985. Gut 2000;47(6):845-51.
88. Estimating the Prognosis of Canadians Infected With the Hepatitis C Virus Through the Blood Supply, 1986-1990 (fourth revision)
89. Barrett S, Goh J, Coughlan B, Ryan E, Stewart S, Cockram A, O'Keane JC, Crowe J. The natural course of hepatitis C virus infection after 22 years in a unique homogenous cohort: spontaneous viral clearance and chronic HCV infection. Gut. 2001;49(3):423-30.
90. Yatsuhashi H, Yano M. Natural history of chronic hepatitis C. J Gastroenterol Hepatol 2000;15:E111-116.
91. Braks RE, Ganne-Carrie N, Fontaine H, et al. Effect of sustained virological response on long-term clinical outcome in 113 patients with compensated hepatitis C-related cirrhosis treated by interferon alpha and ribavirin. World J Gastroenterol. 2007;13:5648-5653.
92. Ly KN, Xing J, Klevens RM, Jiles RB, Holmberg SD. Causes of death and characteristics of decedents with viral hepatitis, United States, 2010. Clin Infect Dis. 2014;58:40-49.
93. Vezali E, Aghemo A, Colombo M. A review of the treatment of chronic hepatitis C virus infection in cirrhosis.Clin Ther. 2010;32(13):2117-38.
94. Federico CA, Hsu PC, Krajden M, et al. Patient time costs and out-of-pocket costs in hepatitis C. Liver Int. 2012;32:815-825.
95. Bova C, Ogawa LF, Sullivan-Bolyai S. Hepatitis C treatment experiences and decision making among patients living with HIV infection. J Assoc Nurses AIDS Care. 2010;21:63-74.
96. Niederau C, Huppe D, Zehnter E, et al. Chronic hepatitis C: treat or wait? Medical decision making in clinical practice. World J Gastroenterol. 2012;18:1339-1347.
97. Alric L, Plaisier E, Thebault S, et al. Influence of antiviral therapy in hepatitis C virus-associated cryoglobulinemic MPGN. Am J Kidney Dis. 2004;43:617-623.
98. Takahashi K, Nishida N, Kawabata H, Haga H, Chiba T. Regression of Hodgkin lymphoma in response to antiviral therapy for hepatitis C virus infection. Intern Med. 2012;51:2745-2747.

11. Tables

Table 1. Baseline clinical and serological features of post-transfusion claimant cohort as of August 31, 2013: comparisons between hemophilics and non-hemophilics.

	Total	Hemophilics		non-Hemophilics		Statistical test	
Characteristics	N=5368	N=1345		N=4023			
	N	N	%*	N	%*	Chi	P
Sex							
Male	3303	1189	88.4	2114	52.5	547.423	*<0.001*
Female	2061	155	11.5	1906	47.4	547.815	*<0.001*
Missing	4	1	0.1	3	0.1	0.000	0.998

Survival status as of August 31, 2013							
Alive	3832	884	65.7	2948	73.3	27.789	*<0.001*
Dead	1536	461	34.3	1075	26.7	27.789	*<0.001*
Compensation level based on biopsy							
Yes	1053	232	17.3	821	20.4	6.378	*0.012*
No	4315	1113	82.7	3202	79.6	6.378	*0.012*
Level of compensation							
Level 1	872	155	11.5	717	17.8	29.390	*<0.001*
Level 2	1442	211	15.7	1231	30.6	114.078	*<0.001*
Level 3	1322	347	25.8	975	24.2	1.328	0.249
Level 4	292	84	6.3	208	5.2	2.265	0.132
Level 5	361	112	8.3	249	6.2	7.344	*0.007*
Level 6	610	148	11.0	462	11.5	0.231	0.631
Missing	469	288	21.4	181	4.5	361.636	*<0.001*
HCV therapy							
Yes	1342	378	28.1	964	24.0	9.223	*0.002*
No	4026	967	71.9	3059	76.0	9.223	*0.002*
HIV Positive							
Yes	537	412	30.6	125	3.1	848.248	*<0.001*
No	4339	847	63.0	3492	86.8	369.331	*<0.001*
Indeterminate	38	3	0.2	35	0.9	6.002	*0.014*
Missing	454	83	6.2	371	9.2	12.119	*0.001*
Age at first blood transfusion (yr)							
0-9	286	0	0.0	286	7.1	0.078	0.780
10-19	252	0	0.0	252	6.3	0.068	0.794
20-29	694	1	0.1	693	17.2	4.687	*0.030*
30-39	747	0	0.0	747	18.6	0.234	0.629
40-49	596	0	0.0	596	14.8	0.178	0.673
50-59	590	0	0.0	590	14.7	0.176	0.675
60-69	571	0	0.0	571	14.2	0.169	0.681
70+	203	0	0.0	203	5.1	0.054	0.816
Missing	7	0	0.0	7	0.2	0.002	0.966
Year at first blood transfusion							
<1986	567	0	0.0	567	14.1	0.168	0.682
1986	793	1	0.1	792	19.7	3.977	*0.046*
1987	805	0	0.0	805	20.0	0.256	0.613
1988	737	0	0.0	737	18.3	0.230	0.632
1989	751	0	0.0	751	18.7	0.235	0.628
1990	292	0	0.0	292	7.3	0.080	0.777
Missing	1	0	0.0	1	0.0	0.000	0.987

Number of transfusions, 1986-1990							
1	1385	1	0.1	1384	34.4	1.850	0.174
2	348	0	0.0	348	8.7	0.097	0.756
3	183	0	0.0	183	4.6	0.049	0.825
4	272	0	0.0	272	6.8	0.074	0.786
5	100	0	0.0	100	2.5	0.026	0.872
>5	1653	0	0.0	1653	41.1	0.721	0.396
Missing	5	0	0.0	5	0.1	0.001	0.972
Among alive cohort	N=3832	N=884		N=2948			
HIV Positive							
Yes	326	227	25.7	99	3.4	435.296	*<0.001*
No	3160	595	67.3	2565	87.0	182.516	*<0.001*
Indeterminate	24	2	0.2	22	0.8	2.955	0.086
Missing	322	60	6.8	262	8.9	3.897	*0.048*
Sex							
Male	2173	749	84.7	1424	48.3	367.526	*<0.001*
Female	1655	134	15.2	1521	51.6	367.967	*<0.001*
Current age, mean (SD) years	5362	883	49.7 (13.7)	2944	61.8 (18.5)	17.970	*<0.001*

*Percentages were calculated based on available observations excluding missing and unknown categories.
HCV, hepatitis C virus; RNA, ribonucleic acid; SD, standard deviation.

Table 2.1. Baseline characteristics and SVR among previously treated compensation claimants.

Hemophilic status	Hemophilics		Non-hemophilics		P value
Sample size	118		354		
Demography	N	Mean±SD/%	N	Mean±SD/%	
Age (years)	118	51.3±10.7	354	57.0±13.7	*<0.001*
Male gender (%)	103	87.3	176	49.72	*<0.001*
Viral genotype (%)					
1a	34	28.8	95	26.8	0.721
1b	13	11.0	28	7.9	0.345

2 or 3	21	17.8	58	16.4	0.776
others	3	2.5	4	1.1	0.374
Unknown	47	39.8	169	47.7	0.165
Compensation level (%)					
2	21	17.8	42	11.9	0.118
3	41	34.8	196	55.4	*<0.001*
4	18	15.3	41	11.6	0.335
5	23	19.5	43	12.2	0.065
6	8	6.8	12	3.4	0.119
Unknown	7	5.9	20	5.7	1.000
HIV co-infection (%)	24	20.3	5	1.4	*<0.001*
Treatment outcome					
SVR (%)	55	46.6	218	61.6	*0.001*

SVR, sustained viral response; SD, standard deviation; HIV, human immunodeficiency virus

Table 2.2. Characteristics of surveyed compensation claimants with successful antiviral treatment (SVR).

Hemophilic status	Hemophilics		Non-hemophilics		P value
Sample size	55		218		
Demography	N	Mean±SD/%	N	Mean±SD/%	
Age (years)	55	50.0±11.2	218	56.1±14.0	*0.003*
Male gender (%)	49	89.1	109	50.0	*<0.001*
Viral genotype (%)					
1a	8	14.6	58	26.6	0.077

1b	7	12.7	12	5.5	0.075
2 or 3	13	23.6	40	18.4	0.445
others	2	3.6	3	1.4	0.265
Unknown	25	45.5	105	48.2	0.764
Compensation level (%)					
2	8	14.6	24	11.0	0.484
3	24	43.6	137	62.8	***0.014***
4	10	18.2	29	13.3	0.389
5	6	10.9	15	6.9	0.393
6	4	7.3	3	1.4	***0.032***
Unknown	3	5.5	10	4.6	0.729
HIV co-infection (%)	8	14.6	2	0.9	***<0.001***

Table 2.3. Characteristics of surveyed compensation claimants with unsuccessful antiviral treatment (no SVR).

Hemophilic status	Hemophilics		Non-hemophilics		P value
Sample size	62		119		
Demography	N	Mean±SD/%	N	Mean±SD/%	
Age (years)	62	52.5±10.2	119	58.4±13.1	***0.002***
Male gender (%)	53	85.5	60	50.4	***<0.001***
Vrial genotype (%)					
1a	26	41.9	35	29.4	0.1
1b	6	9.7	15	12.6	0.632

2 or 3	8	12.9	18	15.1	0.824
others	1	1.6	1	0.8	1
Unknown	21	33.9	50	42.0	0.337
Compensation level (%)					
2	12	19.4	17	14.3	0.398
3	17	27.4	48	40.3	0.103
4	8	12.9	11	9.2	0.453
5	17	27.4	25	21.0	0.357
6	4	6.5	8	6.7	1
Unknown	4	6.5	10	8.4	0.774
HIV co-infection (%)	16	25.8	2	1.7	***<0.001***

Table 3. Initial distribution of disease stages in the surviving compensation claimants stratified by their hemophilic status.

Hemophilic status			Hemophilics			Non-hemophilics		
Disease stage			Distribution (%)	initial age (years)	Male proportion (%)	Distribution (%)	initial age (years)	Male proportion (%)
SVC (level 1)			21.8	47.8	84.5	28.4	64.5	39.0
Responders to previous treatment	without HIV	level 2	2.7	41.4	89.3	2.0	59.8	46.0
		level 3	5.7	47.2	84.6	11.8	51.8	49.8
		level 4	3.5	49.0	83.2	2.4	59.7	41.2
		level 5	1.5	54.8	100.0	1.2	64.8	59.8
		missing	1.7	60.0	100.0	0.2	70.7	66.5
	with HIV	level 2	0.5	74.4	100.0	NA	NA	NA

		level 3	2.4	43.5	100.0	0.2	46.7	0.0
		level 4	0.0	NA	NA	NA	NA	NA
		level 5	0.3	49.0	100.0	NA	NA	NA
		missing	0.0	NA	NA	NA	NA	NA
Non-responders to previous treatment	Without HIV	level 2	2.8	50.1	68.6	1.4	63.6	64.8
		level 3	4.4	53.3	80.0	4.2	57.2	46.3
		level 4	1.6	52.1	100.0	0.9	61.8	55.1
		level 5	4.0	50.9	77.8	2.1	52.3	43.6
		missing	0.0	NA	NA	NA	NA	NA
		decompensated cirrhosis	0.9	48.9	100.0	0.6	57.2	72.8
		HCC	0.3	56.4	100.0	0.2	54.1	100.0
		post-transplant	0.0	NA	NA	0.1	64.4	0.0
	With HIV	level 2	1.1	63.3	100.0	NA	NA	NA
		level 3	1.5	50.2	100.0	NA	NA	NA
		level 4	0.9	45.6	100.0	NA	NA	NA
		level 5	1.2	54.8	100.0	NA	NA	NA
		missing	0.0	NA	NA	NA	NA	NA
		decompensated cirrhosis	0.5	36.5	100.0	NA	NA	NA
		HCC	0.0	NA	NA	NA	NA	NA
		post-transplant	0.0	NA	NA	NA	NA	NA
Treatment-naïve	without HIV	level 2	13.2	45.5	85.5	27.5	65.2	48.1
		level 3	10.0	59.0	73.9	11.7	60.4	47.1
		level 4	3.3	55.1	86.2	1.4	64.4	45.3
		level 5	1.6	50.9	85.7	2.0	71.1	53.4
		missing	0.1	79.1	100.0	NA	NA	NA
		decompensated cirrhosis	0.7	57.4	66.7	0.9	70.3	46.4
		HCC	0.3	52.8	100.0	0.2	72.5	60.0
		post-transplant	0.3	71.1	100.0	0.2	64.4	60.0
	with HIV	level 2	5.4	48.7	97.9	0.0	54.4	0.0
		level 3	3.8	44.2	100.0	NA	NA	NA
		level 4	0.6	46.0	100.0	0.0	50.9	100.0
		level 5	1.4	45.0	100.0	NA	NA	NA
		missing	0.1	71.5	100.0	NA	NA	NA
		decompensated cirrhosis	0.1	44.1	100.0	NA	NA	NA
		HCC	0.0	NA	NA	NA	NA	NA
		post-transplant	0.1	42.3	100.0	NA	NA	NA

SVC, spontaneous viral clearance; HIV, human immunodeficiency virus

Table 4.1. Estimated initial distribution of disease stages in surviving hemophilic claimants as of August 31, 2013.

Age strata	20 to 29		30 to 39		40 to 49		50 to 59		60 to 69		70 to 79		80 to 89		90 or above		All age	
Sample size	22		192		265		206		107		49		24		7		872	
Disease stage	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
F0, HCV RNA-	6	27.3	51	26.6	40	15.1	21	10.2	10	9.3	7	14.3	3	12.5	0	0.0	138	15.8
F0, HCV RNA+	4	18.2	38	19.8	48	18.1	39	18.9	14	13.1	12	24.5	16	66.7	6	85.7	177	20.3
F1/2	3.6	16.4	30.5	15.9	50.1	18.9	41	19.9	21.7	20.3	7.2	14.7	1.2	5.0	0.3	4.3	156	17.8
F3	4.7	21.4	39.7	20.7	65.3	24.6	53.5	26.0	28.3	26.4	9.4	19.2	1.6	6.7	0.4	5.7	203	23.3
F4, compensated cirrhosis	3.7	16.8	30.8	16.0	50.6	19.1	41.5	20.1	22	20.6	7.3	14.9	1.2	5.0	0.3	4.3	157	18.1
F4, decompensated cirrhosis	0	0.0	2	1.0	7	2.6	6	2.9	7	6.5	2	4.1	1	4.2	0	0.0	25	2.9
HCC	0	0.0	0	0.0	3	1.1	4	1.9	1	0.9	3	6.1	0	0.0	0	0.0	11	1.3
Post-transplant	0	0.0	0	0.0	1	0.4	0	0.0	3	2.8	1	2.0	0	0.0	0	0.0	5	0.6

Table 4.2. Estimated initial distribution of disease stages in surviving non-hemophilic claimants as of August 31, 2013.

Age strata	20 to 29		30 to 39		40 to 49		50 to 59		60 to 69		70 to 79		80 to 89		90 or above		All age	
Sample size	196		112		397		693		494		409		354		227		2882	
Disease stage	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
F0, HCV RNA-	31	15.8	23	20.5	71	17.9	128	18.5	77	15.6	70	17.1	67	18.9	38	16.7	505	17.5
F0, HCV RNA+	69	35.2	35	31.3	97	24.4	179	25.8	123	24.9	146	35.7	165	46.6	146	64.3	960	33.3
F1/2	54.7	27.9	30.8	27.5	129.8	32.7	213.6	30.8	158.9	32.2	100.1	24.5	64.6	18.2	23.3	10.3	775	26.9
F3	21.8	11.1	12.3	11.0	51.7	13.0	85.1	12.3	63.3	12.8	39.9	9.8	25.8	7.3	9.3	4.1	309	10.7
F4, compensated cirrhosis	17.5	8.9	9.9	8.8	41.5	10.5	68.3	9.9	50.8	10.3	32	7.8	20.6	5.8	7.4	3.3	248	8.6
F4, decompensated cirrhosis	1	0.5	1	0.9	3	0.8	11	1.6	9	1.8	16	3.9	7	2.0	1	0.4	49	1.7
HCC	0	0.0	0	0.0	1	0.3	2	0.3	5	1.0	3	0.7	3	0.8	1	0.4	15	0.5
Post-transplant	1	0.5	0	0.0	2	0.5	6	0.9	7	1.4	2	0.5	1	0.3	1	0.4	20	0.7

Table 5.1. Summary of synthesized SVR rates associated with selected four antiviral regimens in patients with CHC stratified by previous treatment status and HIV co-infection status.

Treatment regimen	Treatment duration	Treatment-naïve without HIV		Treatment-naïve with HIV		Previously treated without HIV		Previously treated with HIV	
		SVR	95% CI	SVR	95% CI	SVR	95% CI	SVR	95% CI
PEG-IFN/RBV	24 to 48 weeks	0.455	0.433 to 0.478	0.371	0.260 to 0.498	0.374	0.323 to 0.428	0.305	0.263 to 0.349
PEG-IFN/RBV-based triple therapy	24 to 48 weeks	0.7	0.670 to 0.728	0.735	0.644 to 0.809	0.538	0.452 to 0.623	0.538	0.452 to 0.623
Sofosbuvir-based doublet	12 weeks	0.946	0.885 to 0.976	0.802	0.751 to 0.828	0.954	0.866 to 0.985	0.809	0.734 to 0.783
3D regimen plus RBV	12 weeks	0.962	0.944 to 0.975	0.816	0.800 to 0.826	0.963	0.938 to 0.977	0.817	0.795 to 0.829

Table 5.2. Summary of synthesized AE-related treatment discontinuation rates associated with selected four antiviral regimens in patients with CHC stratified by previous treatment status and HIV co-infection status.

Anregimen	Treatment duration	Treatment-naïve without HIV		Treatment-naïve with HIV		Previously treated without HIV		Previously treated with HIV	
		Treatment discontinuation	95% CI	Treatment discontinuation	95% CI	Treatment discontinuation	95% CI	Treatment discontinuation	95% CI
PEG-IFN/RBV	24 to 48 weeks	0.1	0.05 to 0.16	0.18	0.02 to 0.33	0.131	0.07 to 0.21	0.236	0.126 to 0.378
PEG-IFN/RBV-based triple therapy	24 to 48 weeks	0.127	0.103 to 0.154	0.2	0.119 to 0.316	0.166	0.111 to 0.242	0.261	0.175 to 0.381
Sofosbuvir-based doublet	12 weeks	0.022	0.006 to 0.084	0.0396	0.011 to 0.151	0.022	0.006 to 0.084	0.0396	0.011 to 0.151
3D regimen plus RBV	12 weeks	0.006	0.001 to 0.018	0.0108	0.002 to 0.032	0.01	0.002 to 0.029	0.018	0.004 to 0.052

Table 6.1. Summary of baseline characteristics associated with surviving compensation claimants with ongoing CHC stratified by previous treatment status and HIV co-infection status.

Type of claimants	Treatment naive without HIV	Treatment naive without HIV	Previously treated without HIV	Previously treated with HIV
Age (years)	62.8 ± 20.2	47.6 ± 11.2	54.3 ± 14.0	50.2 ± 8.2
Male gender	53.3%	96.3%	58.0%	93.3%
Duration of HCV infection (years)	26.7 ± 4.8	25.0 ± 1.0	26.4 ± 5.2	26.0 ± 1.7
Hemophilics	16.2%	97.3%	27.3%	93.0%
Previous blood transfusion	81.9%	2.8%	71.4%	7.0%
Distribution of fibrosis stage				
F0	63.5%	39.4%	0.0%	0.0%
F1/F2	27.8%	39.4%	71.0%	53.5%
F3	3.8%	5.5%	15.2%	16.3%
F4	4.9%	15.6%	13.8%	30.2%
Distribution of viral genotype				
1	74.4%	75.0%	74.4%	75.0%
2 or 3	24.4%	16.7%	24.4%	16.7%
4, 5 or 6	1.2%	8.3%	1.3%	8.3%

Table 6.2. Summary of the treatment pattern based on 14 surveyed physicians for surviving compensation claimants with ongoing CHC over the next five years.

Treatment patterns	Treatment rate (%)		Treatment options							
			PEG/RBV		PEG/RBV-based triple therapy		Sofosbuvir-based doublet		3D regimen plus RBV	
Type of claimant	Baseline	95% CI	N	%	N	%	N	%	N	%
Treatment-naïve without HIV	87.5	79.2 to 95.8	0	0	2	14.3	7	50	5	35.7
Treatment-naïve with HIV	65.8	42.3 to 89.3	0	0	1	8.3	3	25	8	66.7
Previously treated without HIV	91.0	86.0 to 96.1	0	0	1	7.1	5	35.7	8	57.1
Previously treated with HIV	61.7	39.5 to 84.0	0	0	1	8.3	1	8.3	10	83.4

Table 7. Uncalibrated and calibrated annual stage-specific fibrosis transition probabilities derived from non-hemophilic claimants using MMLE method in the fourth and fifth revisions.

Revision version	Fibrosis transition	F0 to F1		F1 to F2		F2 to F3		F3 to F4	
		Baseline	95% CI	Baseline	95% CI	Baseline	95% CI	Baseline	95% CI
The fourth revision (2010)	Uncalibrated	0.029	0.025,0.032	0.118	0.080,0.145	0.137	0.079,0.175	0.103	0.042,0.130
	Calibrated	0.057	0.051,0.084	0.145	0.082,0.153	0.15	0.130,0.202	0.12	0.133,0.253
The fifth revision (2014)	Uncalibrated	0.038	0.033,0.044	0.101	0.074,0.128	0.133	0.084,0.182	0.114	0.063,0.166
	Calibrated	0.054	0.046,0.062	0.12	0.088,0.152	0.135	0.085,0.185	0.138	0.076,0.200

Table 8. Prognosis of cirrhosis derived from approved compensation claimants for the current revision and derived from literature in the fourth revision.

Transition between health states	Sample size	Cumulative events	Follow-up time (years)		Annual transition probability (fifth revision)		Annual transition probability (fourth revision)	
			Baseline	95% CI	Baseline	95% CI	Baseline	95% CI
Compensated cirrhosis to decompensated cirrhosis	98	64	13.05	12.22, 13.89	0.078	0.073,0.083	0.065	0.053,0.092
Compensated cirrhosis to HCC	98	28	13.05	12.22, 13.89	0.025	0.024,0.027	0.033	0.024,0.046
Decompensated cirrhosis to death	414	343	10.72	10.26, 11.19	0.152	0.146,0.158	0.186	0.137,0.250
HCC to death	130	110	9.32	8.50, 10.13	0.182	0.169,0.198	0.35	0.316,0.699
Decompensated cirrhosis or HCC to liver transplantation	515	21	10.29	9.87, 10.71	0.004	0.0039,0.0042	0.1	0.050,0.180
Mortality after liver transplantation (first year)	58	5			0.086	0.037,0.186	0.146	0.127,0.210
Mortality after liver transplantation (subsequent year)	53	24	15.06	13.73, 16.39	0.039	0.036,0.043	0.044	0.035,0.053

Table 9.1. Canadian age- and sex-related life table, 2009 to 2011.

Age	Male	Female	Age	Male	Female
1 year	0.0003	0.00021	56 years	0.00533	0.00336
2 years	0.00022	0.00016	57 years	0.00586	0.00368
3 years	0.00017	0.00013	58 years	0.00645	0.00403
4 years	0.00013	0.0001	59 years	0.00709	0.00442
5 years	0.00011	0.00009	60 years	0.0078	0.00485
6 years	0.0001	0.00008	61 years	0.00859	0.00533
7 years	0.00009	0.00007	62 years	0.00945	0.00586
8 years	0.00008	0.00007	63 years	0.0104	0.00645
9 years	0.00008	0.00007	64 years	0.01145	0.0071
10 years	0.00009	0.00008	65 years	0.0126	0.00782
11 years	0.0001	0.00008	66 years	0.01387	0.00862
12 years	0.00012	0.00009	67 years	0.01528	0.00951
13 years	0.00015	0.00011	68 years	0.01682	0.01051
14 years	0.0002	0.00014	69 years	0.01852	0.01161
15 years	0.00028	0.00018	70 years	0.0204	0.01284
16 years	0.00039	0.00022	71 years	0.02247	0.0142
17 years	0.00051	0.00026	72 years	0.02475	0.01573
18 years	0.00059	0.00028	73 years	0.02726	0.01743
19 years	0.00066	0.00029	74 years	0.03004	0.01934
20 years	0.00071	0.0003	75 years	0.0331	0.02146
21 years	0.00075	0.0003	76 years	0.03647	0.02384
22 years	0.00076	0.00031	77 years	0.04019	0.02649
23 years	0.00076	0.00031	78 years	0.0443	0.02947
24 years	0.00074	0.0003	79 years	0.04883	0.0328
25 years	0.00071	0.0003	80 years	0.05383	0.03654
26 years	0.0007	0.0003	81 years	0.05935	0.04074
27 years	0.00069	0.00031	82 years	0.06543	0.04545
28 years	0.0007	0.00032	83 years	0.07215	0.05074
29 years	0.00071	0.00034	84 years	0.07957	0.05669
30 years	0.00074	0.00037	85 years	0.08776	0.06338
31 years	0.00078	0.0004	86 years	0.0968	0.07091
32 years	0.00082	0.00043	87 years	0.10678	0.0794
33 years	0.00086	0.00047	88 years	0.1178	0.08897
34 years	0.00091	0.00051	89 years	0.12997	0.09977
35 years	0.00096	0.00056	90 years	0.14341	0.11196
36 years	0.00102	0.0006	91 years	0.15794	0.12542
37 years	0.00108	0.00066	92 years	0.17326	0.13991
38 years	0.00115	0.00071	93 years	0.18931	0.15541
39 years	0.00123	0.00077	94 years	0.20604	0.1719
40 years	0.00132	0.00084	95 years	0.21839	0.18849
41 years	0.00142	0.00092	96 years	0.23536	0.20653
42 years	0.00153	0.001	97 years	0.2529	0.22549
43 years	0.00165	0.00109	98 years	0.27092	0.24526
44 years	0.00179	0.00118	99 years	0.28933	0.26571
45 years	0.00194	0.00129	100 years	0.30802	0.28671
46 years	0.00211	0.0014	101 years	0.32687	0.3081
47 years	0.00229	0.00153	102 years	0.34576	0.3297
48 years	0.00251	0.00166	103 years	0.36457	0.35132
49 years	0.00275	0.00181	104 years	0.38319	0.3728
50 years	0.00301	0.00197	105 years	0.40149	0.39395
51 years	0.00331	0.00215	106 years	0.41937	0.41461
52 years	0.00364	0.00235	107 years	0.43673	0.43462
53 years	0.00401	0.00257	108 years	0.4535	0.45386
54 years	0.00441	0.0028	109 years	0.4696	0.47222
55 years	0.00484	0.00307	110 years and over	1	1

Table 9.2. Annual risk of non-liver-related mortality based on the 10-year follow-up (2003 to 2013) of hemophilic claimants stratified by age strata and gender.

Gender	Males			Females		
Age strata	Sample size	Non-liver-related death	Annual non-liver-related mortality rate	Sample size	Non-liver-related death	Annual non-liver-related mortality rate
20 to 29	139	0	0.0000	14	0	0.0000
30 to 39	170	5	0.0029	39	0	0.0000
40 to 49	133	3	0.0022	31	1	0.0032
50 to 59	70	3	0.0046	32	2	0.0062
60 to 69	49	4	0.0093	13	1	0.0078
70+	28	4	0.0170	10	1	0.0127

Table 9.3. Annual risk of non-liver-related mortality based on the 10-year follow-up (2003 to 2013) of non-hemophilic claimants stratified by age strata and gender.

Gender	Male			Female		
Age strata	Sample size	Non-liver-related death	Annual non-liver-related mortality rate	Sample size	Non-liver-related death	Annual non-liver-related mortality rate
20 to 29	59	1	0.0017	53	0	0.0000
30 to 39	217	5	0.0023	227	3	0.0013
40 to 49	293	18	0.0063	428	8	0.0019
50 to 59	248	19	0.0079	273	13	0.0049
60 to 69	238	30	0.0134	217	11	0.0052
70+	352	51	0.0155	272	26	0.0100

Table 10. Annual risk of non-liver-related mortality based on the 10-year follow-up (2003 to 2013) of claimants with HIV co-infection stratified by age strata and gender.

Gender	Male			Female		
Age strata	Sample size	Non-liver-related death	Annual non-liver-related mortality rate	Sample size	Non-liver-related death	Annual non-liver-related mortality rate
20 to 29	52	4	0.0083	0	0	-
30 to 39	89	3	0.0036	4	0	-
40 to 49	63	3	0.0051	3	0	-
50 to 59	18	0	-	0	0	-
60 to 69	3	0	-	1	0	-
70+	1	1	1	1	0	-

Table 11. Model predicted and observed prognosis of non-hemophilic claimants over 10-year follow-up from 2003 to 2013.

Outcome measure	2003 (observed)	2013 (observed)	2013 (predicted)
Cumulative rate (%)			
Cirrhosis	10.4	12.1	13.6
Decompensated cirrhosis	2.9	7.4	6.1
Liver transplantation	0.6	0.7	0.7
HCC	0.4	1.8	1.9
Liver-related mortality	0	7.4	4.1
Non-liver-related mortality	0	4.5	6.5
Proportion of disease stage among surviving claimants (%)			
F_0 with HCV RNA-	23.1	24.8	25.1
F_0 with HCV RNA+	46.9	46.7	29.3
F_1	6.8	10.2	19.7
F_2	6.8	10	9.1
F_3	5.9	2.2	7
Compensated cirrhosis	7.5	3.8	6.3
Decompensated cirrhosis	1.9	1.5	2.2
Post-transplant	0.6	0.5	0.5
HCC	0.4	0.4	0.9

Table 12. Summary of model variables applied to the HCV prognostic model in the current revision.

Model variables	Baseline value	Lower limit of 95% CI	Upper limit of 95% CI	Data source
Prevalence of hemophilia in the survival claim cohort on August 31, 2014	0.231			Table 1
Initial distribution of disease stage in survival hemophilia claimants				
F0 with HCV RNA-	0.158			Table 4.1
F0 with HCV RNA+	0.203			Table 4.1
F1/2	0.178			Table 4.1
F3	0.233			Table 4.1
F4, compensated cirrhosis	0.181			Table 4.1
F4, decompensated cirrhosis	0.029			Table 4.1
HCC	0.013			Table 4.1
Post-transplant	0.006			Table 4.1
Initial distribution of disease stage in survival non-hemophilia claimants				
F0 with HCV RNA-	0.175			Table 4.2
F0 with HCV RNA+	0.333			Table 4.2
F1/2	0.269			Table 4.2
F3	0.107			Table 4.2

F4 (compensated cirrhosis)	0.086			Table 4.2
Decompensated cirrhosis	0.017			Table 4.2
HCC	0.005			Table 4.2
Post-transplant	0.007			Table 4.2
Natural history of CHC				
Annual incidence rate of SVC for F0 and F1	0.017	0.011	0.022	The fourth revision report
Annual incidence rate of SVC for F2	0.01			The fourth revision report
Annual incidence rate of SVC for F3	0.005			The fourth revision report
Annual transition from F0 to F1	0.054	0.046	0.062	Table 7
Annual transition from F1 to F2	0.12	0.088	0.152	Table 7
Annual transition from F2 to F3	0.135	0.085	0.185	Table 7
Annual transition from F3 to F4	0.138	0.076	0.200	Table 7
Annual transition between fibrosis stages in treatment naïve or previously treated claimants with SVR	0			Model assumption
Annual risk of decompensated cirrhosis associated with compensated cirrhosis	0.078	0.073	0.083	Table 8
Annual risk of decompensated cirrhosis associated with compensated cirrhosis after successful antiviral treatment	0.039			Model assumption
Annual risk of HCC associated with F1 to F2	0.0001			The fourth revision report
Annual risk of HCC associated with F3	0.001			The fourth revision report
Annual risk of HCC associated with compensated cirrhosis	0.025	0.024	0.027	Table 8
Annual risk of mortality associated with decompensated cirrhosis	0.152	0.146	0.158	Table 8
Annual risk of mortality associated with HCC	0.182	0.169	0.198	Table 8
Annual risk of liver transplantation associated with decompensated cirrhosis or HCC	0.004	0.004	0.004	Table 8
Risk of mortality in the first year after liver transplantation	0.086	0.037	0.186	Table 8
Annual risk of mortality in subsequent years after liver transplantation	0.039	0.036	0.043	Table 8
Proportion of previous treatments in hemophilic claimants	0.38			Claims data
Proportion of previous treatments in non-hemophilic claimants	0.29			Claims data
SVR rate of previous antiviral treatment in hemophilic claimants	0.466			Table 2.1
SVR rate of previous antiviral treatment in non-hemophilic claimants	0.616			Table 2.1
Treatment pattern				
Treatment rate in treatment-naïve claimants without HIV	0.875	0.792	0.958	Table 6.3
Treatment rate in treatment-naïve claimants with HIV	0.658	0.423	0.893	Table 6.3
Treatment rate in previously treated claimants without HIV	0.91	0.86	0.961	Table 6.3
Treatment rate in previously treated claimants with HIV	0.617	0.395	0.84	Table 6.3
Distribution of antiviral regimens used in treatment-naïve claimants without HIV				
PEG-IFN/RBV	0			Table 6.3
PEG-IFN/RBV-based triple therapy	0.143			Table 6.3
Sofosbuvir-based doublet	0.5			Table 6.3
3D regimen plus RBV	0.357			Table 6.3
Distribution of antiviral regimens used in treatment-naïve claimants with HIV				

PEG-IFN/RBV	0			Table 6.3
PEG-IFN/RBV-based triple therapy	0.083			Table 6.3
Sofosbuvir-based doublet	0.250			Table 6.3
3D regimen plus RBV	0.667			Table 6.3
Distribution of antiviral regimens used in previously treated claimants without HIV				
PEG-IFN/RBV	0			Table 6.3
PEG-IFN/RBV-based triple therapy	0.071			Table 6.3
Sofosbuvir-based doublet	0.357			Table 6.3
3D regimen plus RBV	0.571			Table 6.3
Distribution of antiviral regimens used in previously treated claimants with HIV				
PEG-IFN/RBV	0			Table 6.3
PEG-IFN/RBV-based triple therapy	0.083			Table 6.3
Sofosbuvir-based doublet	0.083			Table 6.3
3D regimen plus RBV	0.834			Table 6.3
Treatment efficacy of antiviral regiments in treatment-naïve patients without HIV				
PEG-IFN/RBV	0.455	0.433	0.478	Table 6.1
PEG-IFN/RBV-based triple therapy	0.7	0.67	0.728	Table 6.1
Sofosbuvir-based doublet	0.946	0.885	0.976	Table 6.1
3D regimen plus RBV	0.962	0.944	0.975	Table 6.1
Treatment efficacy of antiviral regiments in treatment-naïve patients with HIV				
PEG-IFN/RBV	0.371	0.26	0.498	Table 6.1
PEG-IFN/RBV-based triple therapy	0.735	0.644	0.809	Table 6.1
Sofosbuvir-based doublet	0.802	0.751	0.828	Table 6.1
3D regimen plus RBV	0.816	0.8	0.826	Table 6.1
Treatment efficacy of antiviral regiments in previously treated patients without HIV				
PEG-IFN/RBV	0.374	0.323	0.428	Table 6.1
PEG-IFN/RBV-based triple therapy	0.538	0.452	0.623	Table 6.1
Sofosbuvir-based doublet	0.954	0.866	0.985	Table 6.1
3D regimen plus RBV	0.963	0.938	0.977	Table 6.1
Treatment efficacy of antiviral regiments in previously treated patients with HIV				
PEG-IFN/RBV	0.305	0.263	0.349	Table 6.1
PEG-IFN/RBV-based triple therapy	0.538	0.452	0.623	Table 6.1
Sofosbuvir-based doublet	0.809	0.734	0.783	Table 6.1
3D regimen plus RBV	0.817	0.795	0.829	Table 6.1
Annual risk of non-liver-related mortality in male hemophilics				
20 to 29	Canadian life table			Table 9.1
30 to 39	0.003			Table 9.2
40 to 49	0.002			Table 9.2
50 to 59	0.005			Table 9.2
60 to 69	0.009			Table 9.2
70+	Canadian life table			Table 9.1

Annual risk of non-liver-related mortality in female hemophilics				
20 to 29	Canadian life table			Table 9.1
30 to 39	Canadian life table			Table 9.1
40 to 49	Canadian life table			Table 9.1
50 to 59	Canadian life table			Table 9.1
60 to 69	Canadian life table			Table 9.1
70+	Canadian life table			Table 9.1
Annual risk of non-liver-related mortality in male non-hemophilics				
20 to 29	0.002			Table 9.3
30 to 39	0.002			Table 9.3
40 to 49	0.006			Table 9.3
50 to 59	0.008			Table 9.3
60 to 69	0.013			Table 9.3
70+	Canadian life table			Table 9.1
Annual risk of non-liver-related mortality in female non-hemophilics				
20 to 29	Canadian life table			Table 9.1
30 to 39	0.001			Table 9.3
40 to 49	0.002			Table 9.3
50 to 59	0.005			Table 9.3
60 to 69	0.005			Table 9.3
70+	Canadian life table			Table 9.1
Annual risk of non-liver-related mortality in male claimants with HIV co-infection				
20 to 29	0.0083			Table 10
30 to 39	0.0036			Table 10
40 to 49	0.0051			Table 10
RR of fibrosis progression associated with HIV co-infection	2.122	1.518	2.967	The fourth revision report
Excess mortality associated with HIV co-infection	6.24	5.43	7.18	The fourth revision report

Table 13.1. Model outputs by calendar year: All surviving claimants as of August 31, 2013.

Calendar year	2013	2020	2030	2040	2050	2060	2070

Cumulative proportion (%)*							
Cirrhosis	14.1	16.9	18.3	19.3	19.7	19.8	19.9
Decompensated cirrhosis	3.3	6.5	9.5	11.0	11.8	12.0	12.1
HCC	0.7	1.8	3.1	3.8	4.1	4.3	4.3
Liver transplantation	0.7	0.7	0.8	0.9	0.9	0.9	0.9
Non-liver-related mortality	0.0	14.9	32.6	48.5	63.5	75.1	81.2
Liver-related mortality	0.0	3.3	8.5	11.7	13.5	14.4	14.7
All-cause mortality	0.0	18.3	41.1	60.4	77.1	89.4	95.8
Sex distribution (%)							
Female	59.3	44.6	46.6	48.1	47.9	46.2	44.2
Age distribution (%)							
<30 yr	5.7						
30- yr	8.0	6.9					
40- yr	17.8	8.9	8.9				
50- yr	23.8	19.9	10.5	12.3			
60- yr	16.4	27.4	23.8	13.3	19.3		
70- yr	12.1	17.9	32.1	29.4	18.7	36.6	
80- yr	10.1	11.6	17.3	33.5	35.5	26.8	62.4
95- yr	6.1	7.5	7.3	11.4	26.5	36.5	37.6
Stage distribution (%)†							
F_0 with HCV RNA-	17.1	20.2	25.6	30.3	34.1	37.3	40.8
F_0 with HCV RNA+	30.3	25.1	20.7	18.0	15.7	13.6	10.8
F_1	12.4	13.8	14.1	14.0	14.4	14.7	15.2
F_2	12.4	12.7	13.4	13.6	13.9	14.2	14.5
F_3	13.6	13.6	14.6	15.2	15.3	15.3	15.6
Compensated cirrhosis	10.8	9.7	7.0	5.0	3.3	2.1	1.4
Decompensated cirrhosis	2.0	3.2	2.7	2.2	2.0	1.5	0.9
Post-transplant	0.7	0.7	0.7	0.6	0.6	0.5	0.4
HCC	0.7	1.1	1.1	1.0	0.8	0.7	0.5

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 13.2. Model outputs by calendar year: Hemophilics vs. Non-hemophilics.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	22.9	27.7	29.8	30.7	31.1	31.2	31.2	11.5	13.6	14.9	15.9	16.3	16.4	16.5
Decompensated cirrhosis	4.8	11.0	16.6	19.2	20.3	20.6	20.7	2.9	5.2	7.3	8.5	9.2	9.4	9.5
HCC	1.3	3.3	5.4	6.6	7.0	7.2	7.3	0.5	1.4	2.4	2.9	3.2	3.4	3.4
Liver transplantation	0.6	0.7	0.8	1.0	1.0	1.0	1.0	0.7	0.7	0.8	0.9	0.9	0.9	0.9
Non-liver-related mortality		8.3	20.4	34.4	49.4	62.6	71.4		16.9	36.3	52.8	67.8	78.8	84.1
Liver-related mortality		5.5	14.9	20.5	23.2	24.5	24.9		2.7	6.6	9.1	10.6	11.3	11.6
All-cause mortality		13.8	35.2	54.9	72.6	87.1	96.3		19.6	42.9	62.0	78.5	90.1	95.6
Sex distribution (%)														
Female	84.8	15.8	16.3	16.2	16.0	16.2	14.4	51.6	53.3	55.7	57.7	57.5	55.2	53.2
Age distribution (%)														
<30 yr	2.5							6.6						
30- yr	21.7	2.7						3.9	8.1					
40- yr	31.0	23.3	3.1					13.8	4.5	10.7				
50- yr	23.5	32.3	26.2	3.8				23.9	16.2	5.8	14.8			
60- yr	12.3	24.2	35.1	31.4	5.4			17.6	28.3	20.4	7.9	23.5		
70- yr	5.6	11.9	24.0	39.1	40.9	9.2		14.1	19.7	34.6	26.5	12.0	44.8	
80- yr	2.7	4.2	9.5	20.4	41.2	54.9	20.1	12.3	13.8	19.6	37.5	33.8	18.4	75.1
95- yr	0.8	1.4	2.2	5.3	12.6	35.9	79.9	7.7	9.3	8.9	13.2	30.7	36.7	24.9
Stage distribution (%)†														
F_0 with HCV RNA-	15.8	18.9	23.8	28.0	31.1	33.7	34.8	17.5	20.6	26.2	31.0	35.0	38.4	42.6
F_0 with HCV RNA+	20.3	16.3	14.1	12.7	11.4	9.8	9.3	33.3	27.8	22.7	19.6	17.0	14.8	11.2
F_1	8.9	10.0	10.5	11.1	11.7	12.3	13.4	13.5	14.9	15.2	14.9	15.2	15.4	15.7
F_2	8.9	9.2	10.0	10.5	10.6	10.9	9.9	13.5	13.7	14.4	14.5	14.9	15.2	15.9
F_3	23.3	21.7	23.6	25.3	26.5	27.4	28.5	10.7	11.2	11.9	12.2	11.9	11.7	11.7
Cirrhosis	18.1	15.8	10.5	6.8	4.3	2.6	1.9	8.6	7.9	6.0	4.5	3.0	1.9	1.3
Decompensated cirrhosis	2.9	5.7	4.9	3.5	2.6	1.8	1.2	1.7	2.4	2.1	1.8	1.8	1.4	0.8
Post-transplant	0.6	0.6	0.6	0.7	0.7	0.7	0.4	0.7	0.7	0.7	0.6	0.6	0.5	0.4
HCC	1.3	1.9	1.8	1.5	1.1	0.9	0.7	0.5	0.8	0.9	0.8	0.7	0.6	0.4

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.1. Model outputs for claimants with ages 20 to 29.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	16.8	21.2	23.7	25.0	25.6	25.9	26.0	9.9	12.0	14.0	15.6	16.7	17.4	17.7
Decompensated cirrhosis		5.9	12.3	15.7	17.4	18.4	18.8	1.0	3.5	6.6	9.0	10.7	11.8	12.4
HCC		1.8	4.0	5.3	6.1	6.5	6.7	0	0.9	2.2	3.3	4.1	4.6	4.9
Liver transplantation		0.1	0.2	0.4	0.5	0.5	0.5	0.5	0.5	0.6	0.7	0.7	0.8	0.8
Non-liver-related mortality		0.9	5.6	9.4	15.4	24.7	42.8		0.7	2.8	6.6	11.9	19.1	36.3
Liver-related mortality		2.6	10.7	16.8	20.4	22.4	23.5		1.6	5.7	9.5	12.3	14.2	15.5
All-cause mortality		3.6	16.3	26.2	35.8	47.1	66.3		2.3	8.5	16.1	24.2	33.4	51.8
Alive	100	96.4	83.7	73.8	64.2	52.9	33.7	100	97.7	91.5	83.9	75.8	66.6	48.2
Stage distribution (%)†														
F_0 with HCV RNA-	27.3	29.4	34.3	38.9	42.5	44.7	46.5	15.8	19.5	25.0	29.8	34.1	37.6	40.9
F_0 with HCV RNA+	18.2	14.2	11.9	10.3	8.8	7.7	6.6	35.2	28.8	23.6	19.9	16.9	14.5	12.1
F_1	8.2	9.0	9.3	9.7	10.1	10.3	10.3	14.0	15.2	15.5	15.8	15.9	16.2	16.4
F_2	8.2	8.4	8.9	9.1	9.3	9.6	9.9	14.0	14.2	14.7	15.0	15.2	15.3	15.4
F_3	21.4	19.9	21.0	22.2	23.1	23.7	23.9	11.1	11.8	12.3	12.6	12.6	12.6	12.5
Compensated cirrhosis	16.8	14.1	9.1	5.7	3.6	2.3	1.5	8.9	7.8	5.8	4.3	3.0	2.0	1.3
Decompensated cirrhosis		3.8	4.1	2.9	1.7	1.0	0.7	0.5	1.9	1.9	1.6	1.3	1.0	0.7
Post-transplant		0.0	0.2	0.3	0.4	0.3	0.2	0.5	0.4	0.3	0.3	0.3	0.3	0.3
HCC		1.2	1.3	1.0	0.6	0.5	0.3	0	0.6	0.8	0.7	0.5	0.4	0.3

*Proportion computed with reference to the number of patients who were alive in year 2013.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).

Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.2. Model outputs for claimants with ages 30 to 39.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	17	21.2	23.5	24.7	25.3	25.6	25.6	9.7	11.7	13.7	15.2	16.3	16.7	16.9
Decompensated cirrhosis	1	6.7	12.5	15.7	17.3	18.0	18.2	0.9	3.2	6.3	8.6	10.1	11.0	11.3
HCC		1.7	3.7	4.9	5.6	6.0	6.1	0.0	1.0	2.2	3.1	3.8	4.3	4.5
Liver transplantation		0.1	0.2	0.4	0.4	0.5	0.5	0.0	0.0	0.1	0.2	0.3	0.3	0.3
Non-liver-related mortality		3.4	7.6	14.1	24.2	43.1	64.5	0.0	1.5	5.5	11.2	18.9	36.2	64.7
Liver-related mortality		3.1	11.0	16.6	19.9	21.6	22.5	0.0	1.7	5.6	9.0	11.7	13.5	14.4
All-cause mortality		6.5	18.6	30.7	44.1	64.7	87.0	0.0	3.2	11.1	20.3	30.6	49.7	79.1
Alive	100	93.5	81.4	69.3	55.9	35.3	13.1	100	96.8	88.9	79.7	69.4	50.3	20.9
Stage distribution (%)†														
F_0 with HCV RNA-	26.6	29.2	34.4	39.0	42.3	44.2	46.5	20.5	23.7	28.8	33.5	37.5	40.7	43.7
F_0 with HCV RNA+	19.8	15.7	13.1	11.4	10.1	8.9	7.4	31.3	25.6	20.9	17.5	14.8	12.6	10.5
F_1	7.9	9.1	9.3	9.5	9.9	9.9	9.7	13.8	14.7	14.8	15.0	15.3	15.6	15.5
F_2	7.9	8.1	8.6	8.8	9.0	9.2	9.1	13.8	14.2	14.7	14.8	15.0	15.0	14.7
F_3	20.7	19.2	20.4	21.6	22.4	23.1	23.6	11.0	11.6	12.0	12.3	12.2	12.4	12.4
Compensated cirrhosis	16	13.5	8.7	5.6	3.7	2.4	1.5	8.8	7.8	5.9	4.4	3.1	2.0	1.2
Decompensated cirrhosis	1	4.2	4.0	2.9	1.8	1.4	1.3	0.9	1.8	1.9	1.7	1.3	1.1	1.1
Post-transplant	0	0.1	0.2	0.3	0.3	0.3	0.3	0.0	0.0	0.1	0.2	0.2	0.2	0.3
HCC	0	1.0	1.3	0.9	0.6	0.6	0.6	0.0	0.6	0.7	0.7	0.5	0.4	0.5

*Proportion computed with reference to the number of patients who were alive in year 2013.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).

Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.3. Model outputs for claimants with ages 40 to 49.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	23.2	28.6	31.3	32.4	32.9	33.0	33.0	12.1	14.7	16.9	18.4	19.2	19.5	19.5
Decompensated cirrhosis	4.1	11.0	17.8	21.2	22.6	23.1	23.1	1.6	4.5	8.2	10.8	12.2	12.8	12.9
HCC	1.1	3.3	5.9	7.4	8.1	8.3	8.3	0.3	1.4	2.9	3.9	4.6	4.9	5.0
Liver transplantation	0.4	0.5	0.8	0.9	1.0	1.0	1.0	0.5	0.6	0.7	0.7	0.8	0.8	0.8
Non-liver-related mortality		3.0	10.0	20.1	38.3	59.2	70.7	0.0	2.7	8.3	15.7	33.6	62.2	81.4
Liver-related mortality		5.4	15.8	22.4	26.0	27.7	28.2	0.0	2.1	7.1	11.3	14.2	15.8	16.5
All-cause mortality		8.4	25.8	42.5	64.3	86.9	98.9	0.0	4.8	15.4	26.9	47.8	78.0	97.9
Alive	100	91.6	74.2	57.5	35.7	13.1	1.1	100	95.2	84.6	73.1	52.2	22.0	2.1
Stage distribution (%)†														
F_0 with HCV RNA-	15.1	18.0	22.6	26.5	29.4	31.7	33.9	17.9	20.6	25.1	29.1	32.4	34.9	33.9
F_0 with HCV RNA+	18.1	14.7	12.8	11.5	10.4	9.2	6.3	24.4	20.3	16.7	14.1	11.9	10.1	9.1
F_1	9.5	10.3	10.9	11.5	11.7	12.0	11.2	16.3	16.1	16.6	16.9	17.5	18.0	18.9
F_2	9.5	9.9	10.6	11.1	11.6	11.5	11.9	16.3	16.3	16.7	17.2	17.4	17.3	17.9
F_3	24.6	22.6	24.4	26.4	27.7	28.6	28.5	13.0	13.7	14.3	14.5	14.7	14.9	15.1
Compensated cirrhosis	19.1	16.7	11.2	7.2	4.6	2.8	2.3	10.5	9.4	6.8	4.8	3.2	2.0	1.1
Decompensated cirrhosis	2.6	5.6	5.0	3.8	2.8	2.6	3.4	0.8	2.3	2.5	2.1	1.7	1.6	1.9
Post-transplant	0.4	0.4	0.6	0.6	0.7	0.8	0.5	0.5	0.5	0.4	0.4	0.5	0.6	0.7
HCC	1.1	1.9	1.8	1.4	1.1	0.8	1.8	0.3	0.8	0.9	0.8	0.7	0.7	1.4

*Proportion computed with reference to the number of patients who were alive in year 2013.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).

Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.4. Model outputs for claimants with ages 50 to 59.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	24.9	31.0	33.5	34.3	34.6	34.6	34.6	12.7	15.2	17.2	18.5	19.1	19.2	19.2
Decompensated cirrhosis	4.8	12.0	18.6	21.3	22.3	22.4	22.4	2.8	5.6	9.0	11.1	12.1	12.3	12.3
HCC	1.9	4.3	6.7	7.9	8.4	8.5	8.5	0.3	1.3	2.8	3.7	4.2	4.3	4.3
Liver transplantation	0	0.1	0.3	0.4	0.5	0.5	0.5	0.9	0.9	1.1	1.1	1.2	1.2	1.2
Non-liver-related mortality		6.4	18.9	38.9	60.3	71.9	72.9	0.0	3.9	11.6	30.4	61.3	82.5	84.7
Liver-related mortality		6.4	16.9	23.2	25.9	27.0	27.1	0.0	2.7	7.6	11.6	14.1	15.1	15.3
All-cause mortality		12.8	35.9	62.1	86.3	98.9	100.0	0.0	6.6	19.2	41.9	75.4	97.6	100.0
Alive	100	87.2	64.1	37.9	13.7	1.1	0.0	100	93.4	80.8	58.1	24.6	2.4	0.0
Stage distribution (%)†														
F_0 with HCV RNA-	10.2	12.8	17.0	20.6	23.7	24.0	.	18.5	21.6	26.3	30.1	33.4	34.2	.
F_0 with HCV RNA+	18.9	15.3	13.4	12.2	10.6	9.6	.	25.8	21.7	17.9	15.3	12.9	9.1	.
F_1	10	10.9	11.6	12.0	12.7	10.7	.	15.4	15.4	15.9	16.4	16.9	19.0	.
F_2	10	10.4	11.2	11.8	12.3	11.8	.	15.4	15.4	15.8	16.1	15.8	15.4	.
F_3	26	23.9	26.1	28.1	28.4	29.5	.	12.3	12.9	13.4	13.6	13.7	12.8	.
Compensated cirrhosis	20.1	18.1	12.6	8.5	5.3	3.1	.	9.9	9.0	6.5	4.7	3.2	2.8	.
Decompensated cirrhosis	2.9	6.2	5.8	4.5	4.3	5.6	.	1.6	2.5	2.4	2.2	2.4	2.9	.
Post-transplant	0	0.1	0.3	0.5	0.6	0.7	.	0.9	0.7	0.7	0.8	0.9	1.4	.
HCC	1.9	2.3	2.0	1.7	2.0	4.9	.	0.3	0.7	0.9	0.9	0.8	2.5	.

*Proportion computed with reference to the number of patients who were alive in year 2013.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).

Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.5. Model outputs for claimants with ages 60 to 69.

Hemophilic status	Hemophilics							Non-hemophilics						
	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	30.8	36.8	38.6	39.0	39.1	39.1		14.5	16.9	18.9	19.8	19.9	19.9	
Decompensated cirrhosis	10.2	17.1	22.3	24.0	24.2	24.2		4.2	7.1	10.3	11.7	12.0	12.0	
HCC	0.9	3.5	5.8	6.6	6.7	6.8		1.0	2.1	3.5	4.2	4.3	4.3	
Liver transplantation	2.8	3.0	3.2	3.4	3.4	3.4		1.4	1.5	1.6	1.7	1.7	1.7	
Non-liver-related mortality		10.5	33.6	56.9	70.6	71.9		0.0	6.0	27.4	61.1	83.4	85.5	
Liver-related mortality		8.6	19.8	25.5	27.9	28.1		0.0	3.5	8.9	12.4	14.2	14.5	
All-cause mortality		19.1	53.4	82.4	98.4	100.0		0.0	9.5	36.3	73.5	97.6	100.0	
Alive	100	80.9	46.7	17.6	1.6	0.0		100	90.5	63.7	26.5	2.4	0.0	
Stage distribution (%)†														
F_0 with HCV RNA-	9.3	11.4	14.6	16.9	16.8	.	.	15.6	18.8	23.1	26.5	27.1	.	.
F_0 with HCV RNA+	13.1	11.3	10.2	8.9	8.5	.	.	24.9	20.7	17.4	14.3	12.0	.	.
F_1	10.1	10.1	11.0	11.3	12.6	.	.	16.1	16.2	16.5	16.7	17.1	.	.
F_2	10.1	10.6	11.4	12.4	11.4	.	.	16.1	16.3	16.7	16.4	16.9	.	.
F_3	26.4	24.9	27.1	29.0	29.8	.	.	12.8	13.9	14.3	14.9	14.2	.	.
Compensated cirrhosis	20.6	18.9	13.2	8.2	5.1	.	.	10.3	9.2	6.8	4.7	3.1	.	.
Decompensated cirrhosis	6.5	7.8	6.8	6.9	7.0	.	.	1.8	2.6	2.9	3.3	5.3	.	.
Post-transplant	2.8	2.7	3.1	3.5	4.1	.	.	1.4	1.3	1.3	1.6	2.0	.	.
HCC	0.9	2.3	2.7	2.7	4.6	.	.	1.0	1.0	1.1	1.5	2.4	.	.

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.6. Model outputs for claimants with ages 70 to 79.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	27.1	30.4	31.1	31.3	31.3			7.8	14.4	15.3	15.5	15.5		
Decompensated cirrhosis	12.2	16.2	18.5	18.8	18.8			5.1	7.0	8.5	8.8	8.9		
HCC	6.1	7.8	8.9	9.1	9.1			0.7	1.7	2.4	2.6	2.6		
Liver transplant	2	2.3	2.4	2.5	2.5			0.5	0.6	0.6	0.7	0.7		
Non-liver-related death		27.5	60.5	77.7	79.2			0.0	18.6	60.7	87.4	89.9		
Liver-related death		9.4	17.4	20.5	20.8			0.0	4.0	8.0	9.9	10.1		
All cause death		36.9	77.9	98.2	100.0			0.0	22.6	68.6	97.2	100.0		
Alive	100	63.1	22.1	1.8	0.0			100	77.4	31.4	2.8	0.0		
Stage distribution (%)†														
F0 RNA-	14.3	17.6	22.3	26.6	.	.	.	17.1	21.1	26.6	30.4	.		
F0 RNA+	24.5	20.7	17.3	13.5	.	.	.	35.7	30.3	24.6	20.4	.		
Fibrosis 1	7.4	9.1	9.6	10.0	.	.	.	12.2	14.0	14.0	13.4	.		
Fibrosis 2	7.4	8.0	8.5	8.5	.	.	.	12.2	12.8	13.2	13.9	.		
Fibrosis 3	19.2	18.5	20.0	19.5	.	.	.	9.8	10.3	11.1	11.3	.		
Compensated cirrhosis	14.9	13.4	9.0	5.2	.	.	.	7.8	6.9	5.1	3.5	.		
Decompensated cirrhosis	4.1	5.7	6.8	8.8	.	.	.	3.9	3.1	3.3	4.3	.		
Post-transplant	2	2.3	3.0	2.8	.	.	.	0.5	0.5	0.8	0.9	.		
HCC	6.1	4.5	3.5	5.0	.	.	.	0.7	1.1	1.2	2.0	.		

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.7. Model outputs for claimants with ages 80 to 89.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	7.7	9.5	9.6	9.7				8.9	9.7	9.9	9.9			
Decompensated cirrhosis	4.2	4.9	5.2	5.2				3.1	4.3	4.7	4.7			
HCC	0	0.5	0.7	0.8				0.8	1.4	1.6	1.6			
Liver transplantation	0	0.1	0.1	0.1				0.3	0.4	0.4	0.4			
Non-liver-related mortality		56.1	91.4	94.5				0.0	45.7	90.5	94.8			
Liver-related mortality		3.0	5.3	5.5				0.0	2.6	5.0	5.2			
All-cause mortality		59.0	96.6	100.0				0.0	48.4	95.5	100.0			
Alive	100	41.0	3.4	0.0				100	51.6	4.5	0.0			
Stage distribution (%)†														
F_0 with HCV RNA-	12.5	18.9	28.3	.	.	.	.	18.9	24.2	31.6	.			
F_0 with HCV RNA+	66.7	54.3	41.9	.	.	.	.	46.6	37.7	29.6	.			
F_1	2.5	7.5	8.3	.	.	.	.	9.1	12.1	12.6	.			
F_2	2.5	3.4	4.4	.	.	.	.	9.1	9.5	10.1	.			
F_3	6.7	6.6	6.4	.	.	.	.	7.3	7.7	7.6	.			
Compensated cirrhosis	5	4.0	3.3	.	.	.	.	5.8	4.7	3.0	.			
Decompensated cirrhosis	4.2	4.5	4.9	.	.	.	.	2.0	2.5	3.0	.			
Post-transplant	0	0.1	0.4	.	.	.	.	0.3	0.4	0.3	.			
HCC	0	0.8	1.9	.	.	.	.	0.8	1.1	2.1	.			

*Proportion computed with reference to the number of patients who were alive in year 2013.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).

Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 14.8. Model outputs for claimants with ages 90 or above.

Hemophilic status	Hemophilics							Non-hemophilics						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	4.3	4.5	4.5					4.5	4.9	4.9				
Decompensated cirrhosis	0	0.4	0.5					1.2	1.7	1.8				
HCC	0	0.2	0.2					0.4	0.6	0.6				
Liver transplantation	0	0.0	0.0					0.4	0.5	0.5				
Non-liver-related mortality		86.9	99.4					0.0	80.9	98.1				
Liver-related mortality		0.4	0.6					0.0	1.4	1.9				
All-cause mortality		87.2	100.0					0.0	82.3	100.0				
Alive	100	12.8	0.0					100	17.7	0.0				
Stage distribution (%)†														
F_0 with HCV RNA-	0	8.5	.	.	.	.	.	16.7	23.4	.				
F_0 with HCV RNA+	85.7	69.2	.	.	.	.	.	64.3	51.4	.				
F_1	2.1	8.9	.	.	.	.	.	5.1	9.5	.				
F_2	2.1	3.2	.	.	.	.	.	5.1	5.9	.				
F_3	5.7	5.4	.	.	.	.	.	4.1	4.5	.				
Compensated cirrhosis	4.3	3.3	.	.	.	.	.	3.3	2.8	.				
Decompensated cirrhosis	0	1.1	.					0.4	1.2	.				
Post-transplant	0	0.0	.					0.4	0.5	.				
HCC	0	0.4	.					0.4	0.7	.				

*Proportion computed with reference to the number of patients who were alive in year 2013.

†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).

Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 15. Comparing model outputs for the fourth (2010) and current (2014) revisions.

Revision version	The fourth revision (2010)					The current revision (2014)				
Calendar year	2020	2030	2040	2050	2060	2020	2030	2040	2050	2060
Cumulative proportion (%)*										
Cirrhosis	24.3	32.2	36.3	37.9	38.5	16.9	18.3	19.3	19.7	19.8
HCC	4	7	9.1	10.1	10.5	1.8	3.1	3.8	4.1	4.3
Liver transplantation	2.9	3.6	3.9	4.1	4.2	0.7	0.8	0.9	0.9	0.9
Non-liver-related mortality	21.9	38.3	52.3	63.4	70.3	14.9	32.6	48.5	63.5	75.1
Liver-related mortality	7	14.6	20	22.8	24	3.3	8.5	11.7	13.5	14.4
All-cause mortality	29	52.9	72.2	86.3	94.3	18.3	41.1	60.4	77.1	89.4
Stage distribution (%)†										
F_0 with HCV RNA-	22.2	27.4	32.6	37.4	42	20.2	25.6	30.3	34.1	37.3
F_0 with HCV RNA+	15.8	8.4	4.5	2.4	1.3	25.1	20.7	18.0	15.7	13.6
F_1	12.2	10.3	9.2	9	8.2	13.8	14.1	14.0	14.4	14.7
F_2	13.2	12.3	11.8	11.8	11.8	12.7	13.4	13.6	13.9	14.2
F_3	16.4	17.1	16.8	16.7	17	13.6	14.6	15.2	15.3	15.3
Compensated cirrhosis	14.1	16.2	16.2	14.1	11.6	9.7	7.0	5.0	3.3	2.1
Decompensated cirrhosis	3.5	4.3	4.1	3.4	2.9	3.2	2.7	2.2	2.0	1.5
Post-transplant	1.5	2.5	3.2	3.9	4.1	0.7	0.7	0.6	0.6	0.5
HCC	1.2	1.5	1.5	1.3	1	1.1	1.1	1.0	0.8	0.7

Table 16.1. Comparing model estimates derived from claims data in the current revision and literature review in the fourth revision.

Data source	Claim cohort data based estimations			Literature based estimations		
Model variables (annual transition probability)	Baseline	95% CI		Baseline	95% CI	
Compensated cirrhosis to decompensated cirrhosis	0.078	0.073	0.083	0.065	0.033	0.092
Compensated cirrhosis to HCC	0.025	0.024	0.027	0.033	0.024	0.046
Decompensated cirrhosis to death	0.152	0.146	0.158	0.186	0.137	0.25
HCC to death	0.182	0.169	0.198	0.35	0.316	0.699
Decompensated cirrhosis or HCC to liver transplantation	0.004	0.004	0.004	0.1	0.05	0.18
First year mortality after liver transplantation	0.086	0.037	0.186	0.146	0.127	0.21
Subsequent year mortality after liver transplantation	0.039	0.036	0.043	0.044	0.035	0.053

Table 16.2. Comparing model outputs for non-hemophilic claimants using model variables derived from different data sources: Literature review vs. Claims data.

Model data source	Literature review							Claims data						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	11.5	13.3	14.7	15.5	16.0	16.1	16.2	11.5	13.6	14.9	15.9	16.3	16.4	16.5
Dec. Cirrhosis	2.9	4.7	6.5	7.6	8.1	8.3	8.4	2.9	5.2	7.3	8.5	9.2	9.4	9.5
HCC	0.5	1.6	2.6	3.3	3.6	3.7	3.8	0.5	1.4	2.4	2.9	3.2	3.4	3.4
Liver transplant	0.7	1.5	2.3	2.8	3.1	3.2	3.2	0.7	0.7	0.8	0.9	0.9	0.9	0.9
Non-liver-related mortality		16.8	36.5	53.1	68.3	79.2	84.6		16.9	36.3	52.8	67.8	78.8	84.1
Liver-related mortality		3.1	6.4	8.6	10.0	10.8	11.1		2.7	6.6	9.1	10.6	11.3	11.6
All-cause mortality		19.9	42.9	61.7	78.3	89.9	95.7		19.6	42.9	62.0	78.5	90.1	95.6
Sex distribution (%)														
Female	48.4	53.9	56.6	58.4	58.9	55.9	53.6	51.6	53.3	55.7	57.7	57.5	55.2	53.2
Age distribution (%)														
<30 yr	6.6							6.6						
30- yr	3.9	8.1						3.9	8.1					
40- yr	13.8	4.6	10.7					13.8	4.5	10.7				
50- yr	23.9	16.0	5.9	14.8				23.9	16.2	5.8	14.8			
60- yr	17.6	28.4	20.1	7.9	23.4			17.6	28.3	20.4	7.9	23.5		
70- yr	14.1	19.8	34.8	26.2	12.2	44.7		14.1	19.7	34.6	26.5	12.0	44.8	
80- yr	12.3	13.6	19.7	37.7	33.7	18.9	75.5	12.3	13.8	19.6	37.5	33.8	18.4	75.1
95- yr	7.7	9.6	8.8	13.5	30.7	36.4	24.5	7.7	9.3	8.9	13.2	30.7	36.7	24.9
Stage distribution (%)†														
F_0 with HCV RNA-	17.5	21.2	26.5	31.1	34.8	38.8	42.8	17.5	20.6	26.2	31.0	35.0	38.4	42.6
F_0 with HCV RNA+	33.3	27.8	22.9	19.0	15.7	13.2	11.5	33.3	27.8	22.7	19.6	17.0	14.8	11.2
F_1	13.5	14.9	15.2	15.3	15.6	16.0	15.7	13.5	14.9	15.2	14.9	15.2	15.4	15.7
F_2	13.5	13.7	14.1	14.1	14.4	14.4	13.9	13.5	13.7	14.4	14.5	14.9	15.2	15.9
F_3	10.7	11.4	11.8	12.3	12.4	11.9	12.3	10.7	11.2	11.9	12.2	11.9	11.7	11.7
Compensated cirrhosis	8.6	7.9	6.1	4.5	3.4	2.0	1.3	8.6	7.9	6.0	4.5	3.0	1.9	1.3
Decompensated cirrhosis	1.7	1.4	1.0	0.8	0.8	0.6	0.2	1.7	2.4	2.1	1.8	1.8	1.4	0.8
Post-transplant	0.7	1.3	2.0	2.5	2.7	2.8	2.3	0.7	0.7	0.7	0.6	0.6	0.5	0.4
HCC	0.5	0.5	0.4	0.3	0.2	0.3	0.1	0.5	0.8	0.9	0.8	0.7	0.6	0.4

*Proportion computed with reference to the number of patients who were alive in year 2013.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2020, 2030, ...).
Stage distribution of the living patients in year 2013 is taken from the post-transfusion claimant cohort data with the adjustment for non-biopsy.

Table 17.1. Estimates of non-liver-related mortality derived from the claimant cohort and the 2009 to 2011 Canada life tables.

Gender	Male			Female	
Age stratum	Hemophilics	Non-hemophilics	Canada life table	Non-hemophilics	Canada life table
20 to 29	0.00000	0.00171	0.00071	0.00000	0.00030
30 to 39	0.00290	0.00233	0.00096	0.00133	0.00056
40 to 49	0.00220	0.00632	0.00194	0.00189	0.00129
50 to 59	0.00464	0.00794	0.00484	0.00487	0.00307
60 to 69	0.00933	0.01338	0.01260	0.00519	0.00782

Table 17.2. Comparing model outputs for non-hemophilic claimants using non-liver-related mortality derived from different data sources: claims data vs. 2009 to 2011 Canada life tables.

Data source	Claims data							2009 to 2011 Canada life tables						
Calendar year	2013	2020	2030	2040	2050	2060	2070	2013	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*														
Cirrhosis	11.5	13.6	14.9	15.9	16.3	16.4	16.5	11.5	13.1	14.5	15.4	15.8	16.0	16.0
Dec. Cirrhosis	2.9	5.2	7.3	8.5	9.2	9.4	9.5	2.9	5.1	7.3	8.6	9.2	9.4	9.5
HCC	0.5	1.4	2.4	2.9	3.2	3.4	3.4	0.5	1.4	2.3	2.9	3.2	3.3	3.4
Liver transplantation	0.7	0.7	0.8	0.9	0.9	0.9	0.9	0.7	0.8	0.8	0.9	0.9	0.9	0.9
Non-liver-related mortality		16.9	36.3	52.8	67.8	78.8	84.1		16.6	35.8	52.3	67.2	78.5	84.1
Liver-related mortality		2.7	6.6	9.1	10.6	11.3	11.6		2.7	6.5	9.1	10.5	11.2	11.5
All-cause mortality		19.6	42.9	62.0	78.5	90.1	95.6		19.2	42.3	61.3	77.8	89.7	95.6
Sex distribution (%)														
Female	51.6	53.3	55.7	57.7	57.5	55.2	53.2	51.6	53.2	55.4	57.1	56.7	53.7	51.2
Age distribution (%)														
<30 yr	6.6							6.6						
30- yr	3.9	8.1						3.9	8.1					
40- yr	13.8	4.5	10.7					13.8	4.6	10.7				
50- yr	23.9	16.2	5.8	14.8				23.9	16.4	6.1	15.0			
60- yr	17.6	28.3	20.4	7.9	23.5			17.6	28.7	20.9	8.3	24.3		
70- yr	14.1	19.7	34.6	26.5	12.0	44.8		14.1	19.3	34.5	26.9	12.4	44.8	
80- yr	12.3	13.8	19.6	37.5	33.8	18.4	75.1	12.3	13.5	19.4	37.1	33.6	19.1	76.6
95- yr	7.7	9.3	8.9	13.2	30.7	36.7	24.9	7.7	9.3	8.4	12.7	29.8	36.1	23.4
Stage distribution (%)†														
F_0 with HCV RNA-	17.5	20.6	26.2	31.0	35.0	38.4	42.6	17.5	20.7	26.4	31.2	35.1	38.3	40.6
F_0 with HCV RNA+	33.3	27.8	22.7	19.6	17.0	14.8	11.2	33.3	27.8	22.5	19.2	16.4	13.4	11.1
F_1	13.5	14.9	15.2	14.9	15.2	15.4	15.7	13.5	14.8	15.2	15.2	15.8	16.9	18.1
F_2	13.5	13.7	14.4	14.5	14.9	15.2	15.9	13.5	14.0	14.6	14.7	14.9	15.1	14.7
F_3	10.7	11.2	11.9	12.2	11.9	11.7	11.7	10.7	11.3	11.9	12.0	11.9	11.7	12.1
Compensated cirrhosis	8.6	7.9	6.0	4.5	3.0	1.9	1.3	8.6	7.4	5.7	4.2	3.1	2.2	1.5
Decompensated cirrhosis	1.7	2.4	2.1	1.8	1.8	1.4	0.8	1.7	2.5	2.2	2.0	1.6	1.4	1.0
Post-transplant	0.7	0.7	0.7	0.6	0.6	0.5	0.4	0.7	0.7	0.7	0.6	0.5	0.5	0.4
HCC	0.5	0.8	0.9	0.8	0.7	0.6	0.4	0.5	0.8	0.8	0.7	0.6	0.5	0.5

Table 18. Comparing model outputs for non-hemophilic claimants using treatment patterns in the current revision and the fourth revision.

Treatment pattern	The current revision in 2014						The fourth revision in 2010					
Calendar year	2020	2030	2040	2050	2060	2070	2020	2030	2040	2050	2060	2070
Cumulative proportion (%)*												
Cirrhosis	13.6	14.9	15.9	16.3	16.4	16.5	19.1	27.5	32.1	34.1	34.8	35.0
Dec. Cirrhosis	5.2	7.3	8.5	9.2	9.4	9.5	6.9	12.7	16.7	18.7	19.4	19.7
HCC	1.4	2.4	2.9	3.2	3.4	3.4	2.1	4.7	6.7	7.7	8.2	8.3
Liver transplantation	0.7	0.8	0.9	0.9	0.9	0.9	0.8	0.9	1.1	1.2	1.2	1.2
Non-liver-related mortality	16.9	36.3	52.8	67.8	78.8	84.1	16.8	34.9	48.8	60.3	68.1	71.8
Liver-related mortality	2.7	6.6	9.1	10.6	11.3	11.6	3.3	11.0	17.7	22.0	24.1	24.9
All-cause mortality	19.6	42.9	62.0	78.5	90.1	95.6	20.1	45.8	66.5	82.3	92.2	96.7
Sex distribution (%)												
Female	53.3	55.7	57.7	57.5	55.2	53.2	53.9	56.6	58.0	58.4	55.7	53.5
Age distribution (%)												
<30 yr		.	.	.	.	.						
30- yr	8.1						8.3	.	.	.	.	.
40- yr	4.5	10.7	.	.	.	.	4.7	10.8	.	.	.	.
50- yr	16.2	5.8	14.8	.	.	.	16.1	6.0	14.9	.	.	.
60- yr	28.3	20.4	7.9	23.5	.	.	27.8	20.2	8.1	23.5	.	.
70- yr	19.7	34.6	26.5	12.0	44.8	.	19.6	33.9	26.4	12.5	43.4	.
80- yr	13.8	19.6	37.5	33.8	18.4	75.1	13.7	19.5	36.9	33.0	19.2	72.1
95- yr	9.3	8.9	13.2	30.7	36.7	24.9	9.8	9.5	13.7	31.0	37.4	27.9
Stage distribution (%)†												
F_0 with HCV RNA-	20.6	26.2	31.0	35.0	38.4	42.6	20.9	25.8	30.7	34.6	36.8	39.1
F_0 with HCV RNA+	27.8	22.7	19.6	17.0	14.8	11.2	22.2	11.8	6.5	3.4	1.9	0.6
F_1	14.9	15.2	14.9	15.2	15.4	15.7	13.7	12.8	11.1	10.8	10.3	10.7
F_2	13.7	14.4	14.5	14.9	15.2	15.9	13.5	13.3	13.7	13.8	15.2	14.2
F_3	11.2	11.9	12.2	11.9	11.7	11.7	12.1	13.3	13.9	14.8	15.7	17.5
Compensated cirrhosis	7.9	6.0	4.5	3.0	1.9	1.3	11.6	13.9	13.4	11.7	10.1	7.7
Decompensated cirrhosis	2.4	2.1	1.8	1.8	1.4	0.8	3.9	5.9	6.7	6.5	6.0	6.3
Post-transplant	0.7	0.7	0.6	0.6	0.5	0.4	0.6	0.8	1.0	1.1	1.1	1.3
HCC	0.8	0.9	0.8	0.7	0.6	0.4	1.5	2.4	3.1	3.3	2.8	2.6

Table 19. Monte Carlo simulation projecting the 95% CI of the model predictions on cumulative rates of liver-related clinical outcomes.

Calendar year	2020		2030		2040		2050		2060		2070	
Cumulative rates of clinical outcomes (%)	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Cirrhosis	16.9	14.6 -19.2	18.3	14.7 -21.9	19.3	15.0 -23.6	19.7	14.8 -24.6	19.8	14.6 -25.0	19.9	14.7 -25.1
Decompensated cirrhosis	6.5	5.5 -7.5	9.5	7.5 -11.5	11	8.4 -13.6	11.8	8.6 -15.0	12	8.7 -15.3	12.1	8.7 -15.5
HCC	1.8	1.4 -2.2	3.1	2.3 -3.9	3.8	2.8 -4.8	4.1	2.9 -5.3	4.3	3.1 -5.6	4.3	3.1 -5.5
Liver-related mortality	3.3	2.8 -3.8	8.5	7.0 -10.0	11.7	9.3 -14.1	13.5	10.3 -16.7	14.4	10.8 -18.0	14.7	11.0 -18.4

Table 20. Reported mean cost to HCV patients and their caregivers by disease stage in a recent Canadian survey study.

Disease stage	Patient time costs	Caregiver time costs	Out-of-pocket costs
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Chronic (N = 326)	$1411 ($931–1891)	$60 ($23–98)	$1150 ($615–1686)
Treatment (N = 61)	$1481 ($851–2111)	$152 ($18–285)	$2496 ($677–4316)
Viral clearance (N = 148)	$281 ($175–387)	$31 ($0–72)	$427 ($73–780)
Cirrhosis (N = 135)	$3588 ($1766–5411)	$766 ($173–1359)	$1667 ($766–2568)
HCC (N = 21)	$2739 ($972–4507)	$1050 ($45–2345)	$2837 ($178–5495)
Transplant (N = 47)	$9416 ($2987–15 844)	$2460 ($1–4982)	$2204 ($1103–3305)
Total (N = 738)	$2136 ($1554–2719)	$372 ($174–570)	$1326 ($979–1673)

Table 21. Coefficients associated with patient baseline characteristics for annual patient time and caregiver time costs and out-of-pocket costs in a Canadian HCV survey study.

Predictor	Annual patient and caregiver time cost				Annual out-of-pocket cost			
	Coefficient	SE	t	P-value	Coefficient	SE	t	P-value
(Constant)	5291.14	2329.15	2.27	0.02	1012.71	1217.99	0.83	0.41
Treatment	184.66	1281.15	0.14	0.89	1511.28	669.89	2.26	<0.05
Viral clearance	-893.79	916.62	-98	0.33	-626.31	479.33	-1.31	0.19
Cirrhosis	2758.79	950.32	2.9	0.004	369.4	496.95	0.74	0.46
HCC	1992.02	2234.15	0.89	0.37	1594.62	1168.31	1.36	0.17
Transplantation	10028.23	1449.33	6.92	<0.0001	1013.5	757.9	1.34	0.18
Age	-73.51	40.08	-1.83	0.07	17.58	20.96	0.84	0.4
Gender	394.75	708.36	0.56	0.58	-628.3	370.43	-1.7	0.09
Marital status	363.69	710.33	0.51	0.61	143.24	371.45	0.39	0.7
Education	-198.53	724.06	-0.27	0.78	54.6	378.64	0.14	0.89
Ln income	-188.38	90.88	-2.07	0.04	-121.61	47.53	-2.56	<0.05
ICED	281	325.44	0.86	0.39	1511.28	669.89	0.18	<0.05

ICED, Index of Co-Existent Disease; SE, standard error.

12. Figures.

Figure 1. Simplified Markov model structure for simulating prognosis of HCV in the current revision.

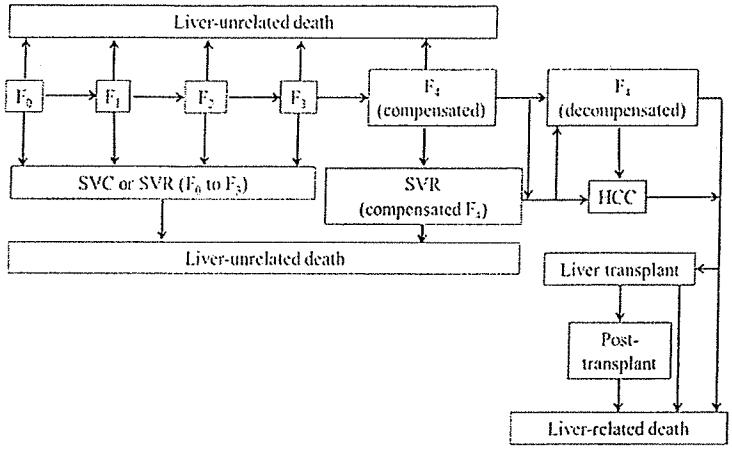


Figure 2. Subtree for health state "Fibrosis stage 0 with negative HCV RNA".

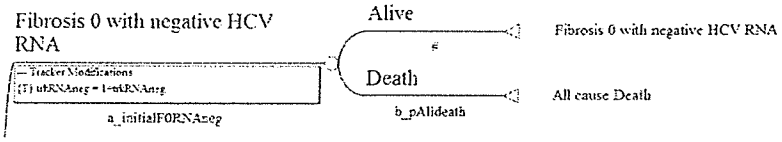


Figure 3. Subtree for health state "Fibrosis stage 0 with positive HCV RNA".

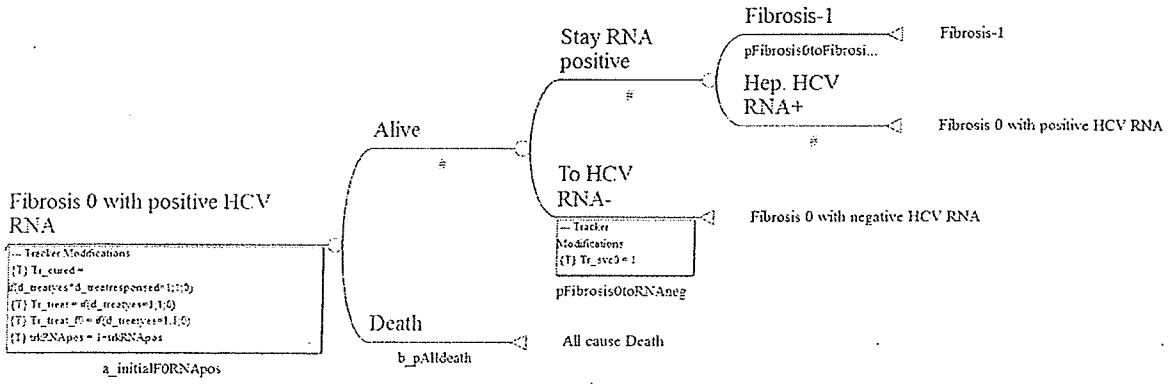


Figure 4. Subtree for health state "Fibrosis stage 1".

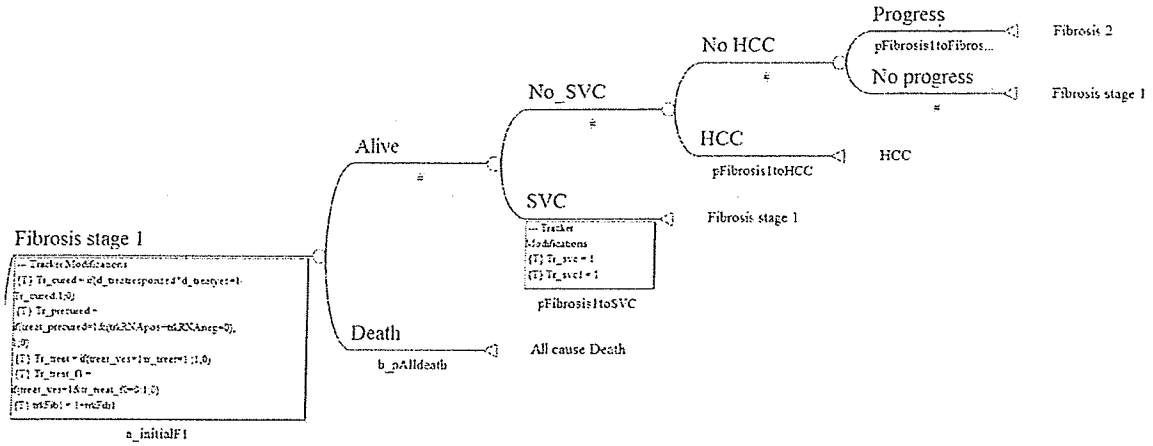


Figure 5. Subtree for health state "Fibrosis stage 2".

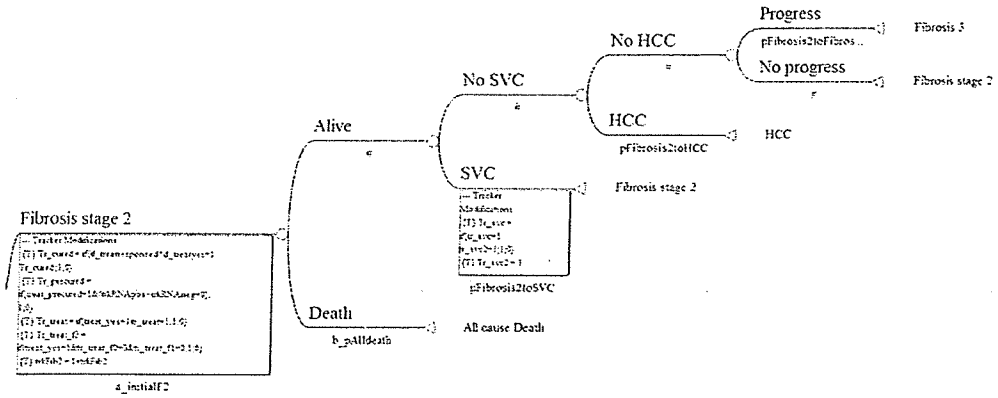


Figure 6. Subtree for health state "Fibrosis stage 3".

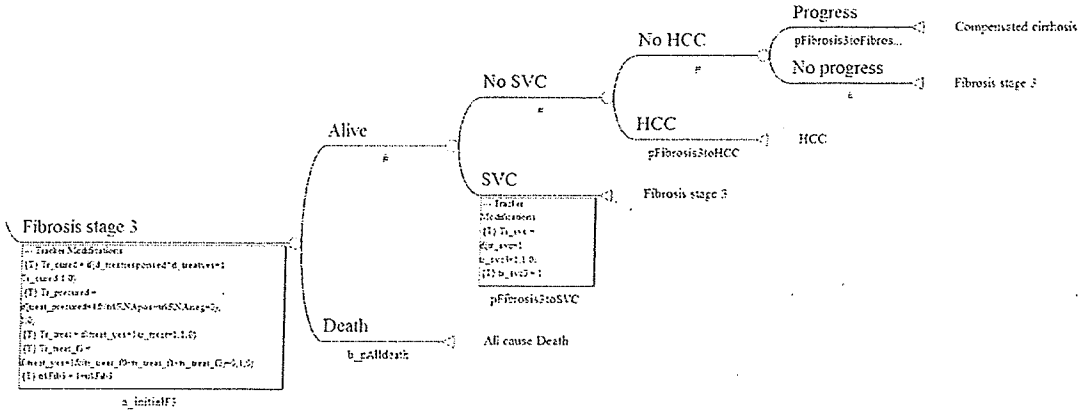


Figure 7. Subtree for health state "Compensated cirrhosis".

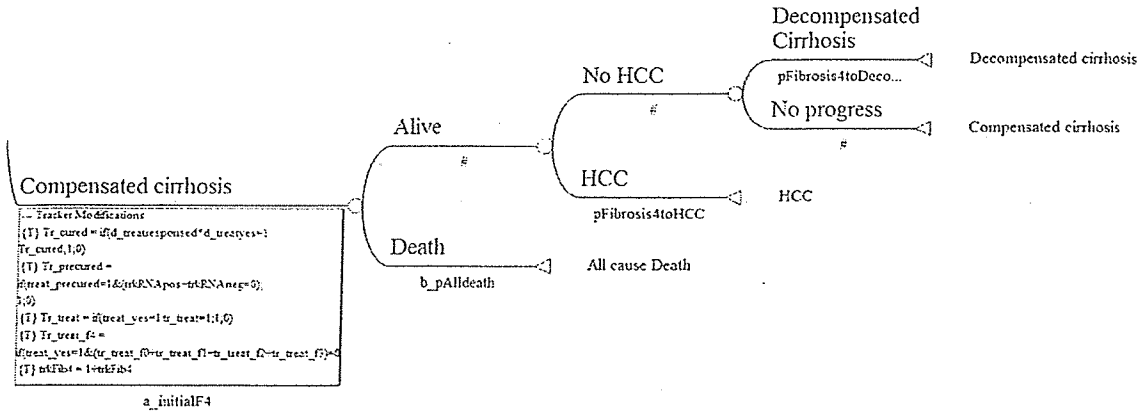


Figure 8. Subtree for health state "Decompensated cirrhosis".

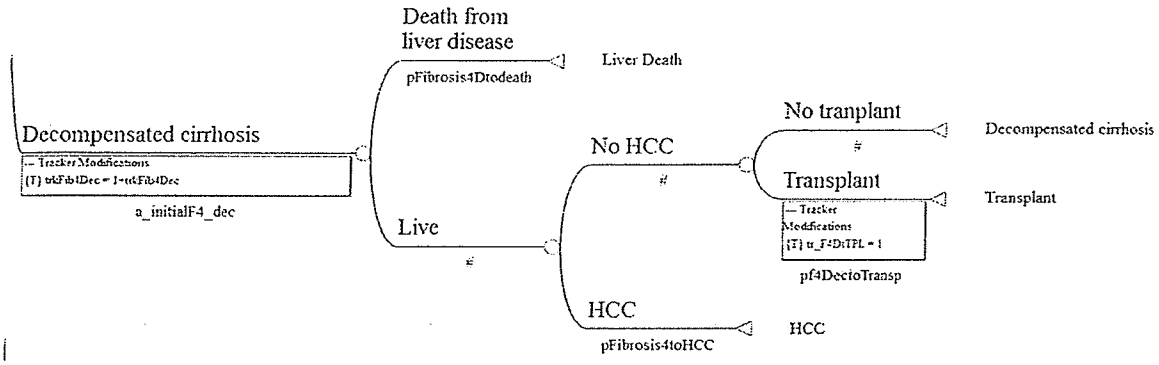


Figure 9. Subtree for health state "HCC".

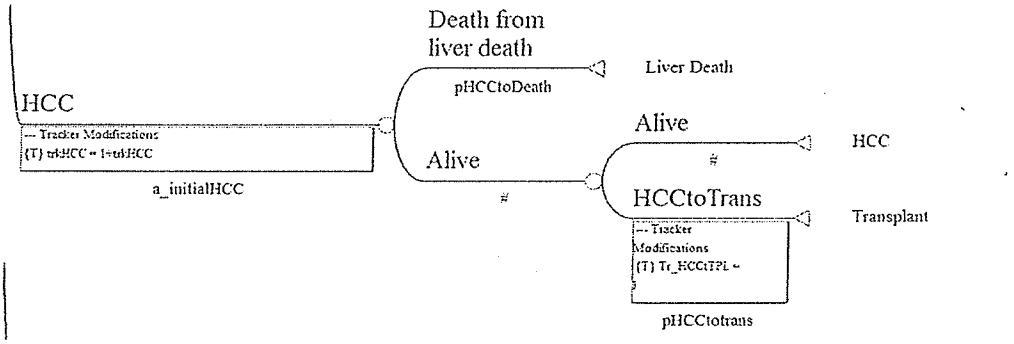
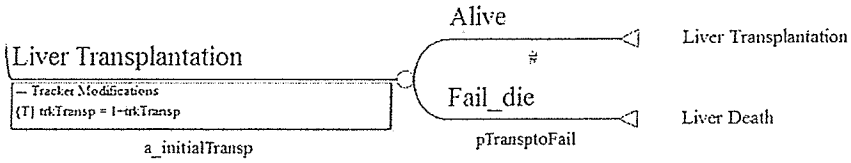


Figure 10. Subtree for health state "Liver transplantation".



Appendix 1. The study ethics approval letter for the fifth revision of HCV prognostic model for 1986-1990 HCV compensation claimants.

UNIVERSITY OF TORONTO

OFFICE OF THE VICE-PRESIDENT, RESEARCH AND INNOVATION

PROTOCOL REFERENCE # 29618

January 6, 2014

Dr. Murray Krahn
DEPT OF MEDICINE
FACULTY OF MEDICINE

Dear Dr. Krahn,

Re: Your research protocol entitled, "The fifth revision plan on estimating the prognosis of Canadians infected with the Hepatitis C virus through the blood supply, 1986-1990"

ETHICS APPROVAL	Original Approval Date: January 6, 2014 Expiry Date: January 5, 2015 Continuing Review Level: 1

We are writing to advise you that the Health Sciences Research Ethics Board (REB) has granted approval to the above-named research protocol under the REB's delegated review process. Your protocol has been approved for a period of one year and ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events in the research should be reported to the Office of Research Ethics as soon as possible.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your current ethics approval. Note that annual renewals for studies cannot be accepted more than 30 days prior to the date of expiry.

If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

OFFICE OF RESEARCH ETHICS
McMurrich Building, 12 Queen's Park Crescent West, 2nd Floor, Toronto, ON M5S 1S8 Canada
Tel: +1 416 946-3273 • Fax: +1 416 946-5763 • ethics.review@utoronto.ca • http://www.research.utoronto.ca/for-researchers/administration/ethics/

Appendix II. The survey package measuring clinical physicians' treatment preferences for survival compensation claimants with CHC.

I. INFORMED CONSENT FORM

I volunteer to participate in a research project conducted by Dr. Murray Krahn from the Toronto Health Economics and Technology Assessment (THETA) Collaborative at the University of Toronto.

I understand that this project is designed to gather information to predict long-term health outcomes in a cohort of patients who have acquired chronic hepatitis C (CHC) through blood transfusion or blood products from 1986 to 1990 in Canada and who are currently qualified to receive compensation for antiviral therapy for CHC-related complications from a trust fund set by the Canadian Federal, Provincial, and Territory governments.

I understand that this survey will assess physician's preferences regarding the use of new antiviral regimens in this CHC compensation cohort.

I understand that my participation in this survey is voluntary and that I may refuse to volunteer, decline to answer any questions and withdraw from the survey at any time without giving any reasons.

I understand that my participation in this survey is unlikely to cause any risks, harm or inconvenience to me or my patients.

I understand that the generated outcomes of this survey will be included in the study final report and might be published in a relevant medical journal.

I understand that my personal information and generated data will be strictly protected in a secured computer and locked in a safe box in the administrative office at THETA.

I understand that all information from this survey will be considered confidential and access to this data will be limited to the principal investigator, study coordinator and data analyst.

I understand that my personal information will be encrypted as codes in the survey and data analysis and the final report and manuscript will not include any identifiable information.

Certificate of consent:

I have read the foregoing information or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction. I consent voluntarily to be a participant in this study.

Print Name of Participant: _____

Signature of Participant: _____

Date (DD/MM/YYYY): _____

Please fax back the signed consent form to 416-946-3719 with attention to Dr. Murray Krahn.

II. CHARACTERISTICS OF SURVEY PATICIPANT

1. **Please provide the following personal information:**

   Birth year: _____Gender: ☐ Male / ☐ Female

2. **Please outline your educational background**

   MD completed year: _____

   Master's degree completed year: _____

   PhD completed year: _____

3. **Please describe your university affiliations**

   Position: _____

   Faculty/Department: _____

   Institution: _____

4. **Please describe your clinical practice**

   Type of clinical setting:

   - ☐ Tertiary care hospital
   - ☐ Community medical center
   - ☐ Ambulatory care (physician's office) not attached to hospital
   - ☐ Other: (please specify) _____

   Clinical specialty:

   - ☐ Hepatology
   - ☐ Gastroenterology
   - ☐ Infectious diseases
   - ☐ Internal medicine
   - ☐ Other: (please specify) _____

   Duration of clinical practice in your current specialty (years): _____

5. **Please provide information regarding chronic hepatitis C patients**

   Monthly number of patient visits for chronic hepatitis C in 2013:_____

Monthly number of patients receiving antiviral therapy for chronic hepatitis C in 2013: _____

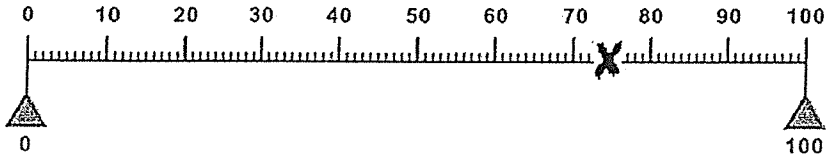
III. INSTRUCTIONS TO COMPLETE THIS SURVEY

This survey aims to understand how patients within the HCV compensation cohort are likely to be treated with antiviral therapy. In formulating your response, please consider how you are likely to treat HCV patients OVER THE NEXT TWO YEARS. We ask you to think ahead, because some of these regimens are not available in every jurisdiction at present. We will be considering the following treatment regimens:

a. Pegylated interferon plus ribavirin (PEG/RBV) (24 to 48 weeks)
b. PEG/RBV-based triple therapy with bocepreivr, telaprevir, or faldaprevir (24 to 48 weeks)
c. PEG-free therapy including the combination of ribavirin and three direct antiviral agents (12 weeks)
d. PEG/RBV-free therapy including sofosbuvir-based doublet with daclatasvir, ledipasvir or simeprevir (12 weeks)

Because HIV co-infection and previous failed antiviral treatment will affect treatment decisions, the CHC compensation cohort will be divided into four subgroups. You will read a brief description of baseline characteristics associated with the subgroup and the estimated clinical efficacy (sustained viral response (SVR)) and treatment discontinuation associated with antiviral regimens for the subgroup.

1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



2. If you decide to treat this subgroup, please indicate which regimen you are likely to use most frequently in this group: a

a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

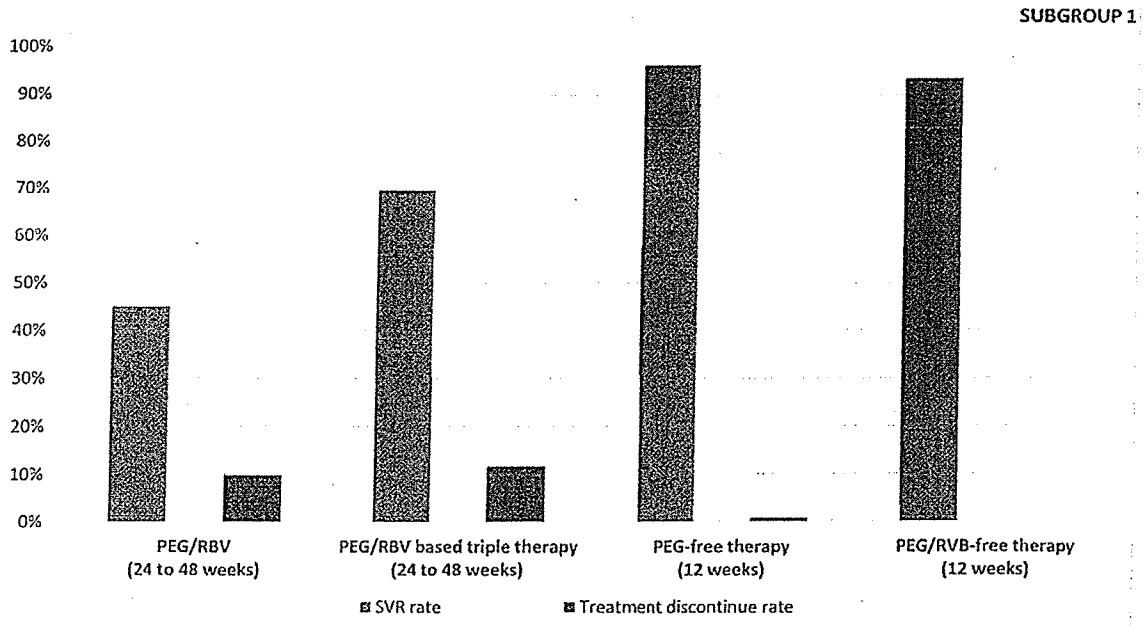
IV. QUESTIONNAIRES FOR THE FOUR PATIENT SUBGROUPS

Patient subgroup 1: Naïve patients without HIV co-infection

1. Baseline characteristics of patient subgroup 1

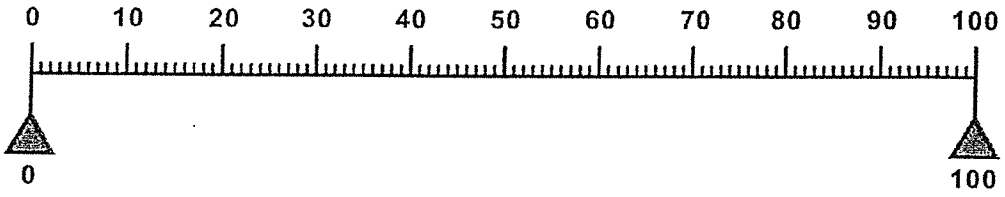
Baseline variable	%/mean ±SD
Age (years)	62.8 ± 20.2
Male gender	53.3%
Duration of HCV infection (years)	26.7 ± 4.8
Hemophilics	16.2%
Previous blood transfusion	81.9%
Distribution of fibrosis stage	
F0	63.5%
F1/F2	27.8%
F3	3.8%
F4	4.9%
Distribution of viral genotype	
1	74.4%
2 or 3	24.4%
4, 5 or 6	1.2%

2. Estimated clinical efficacies and toxicities associated with antiviral regimens in the patient subgroup 1 (naïve patients without HIV co-infection).



3. Survey questions for patient subgroup 1 (naïve patients ***without*** HIV co-infection).

3.1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup (naïve patients ***without*** HIV co-infection) that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



3.2. If you decide to treat this subgroup (naïve patients ***without*** HIV co-infection), please indicate which regimen you are likely to use most frequently in this group:

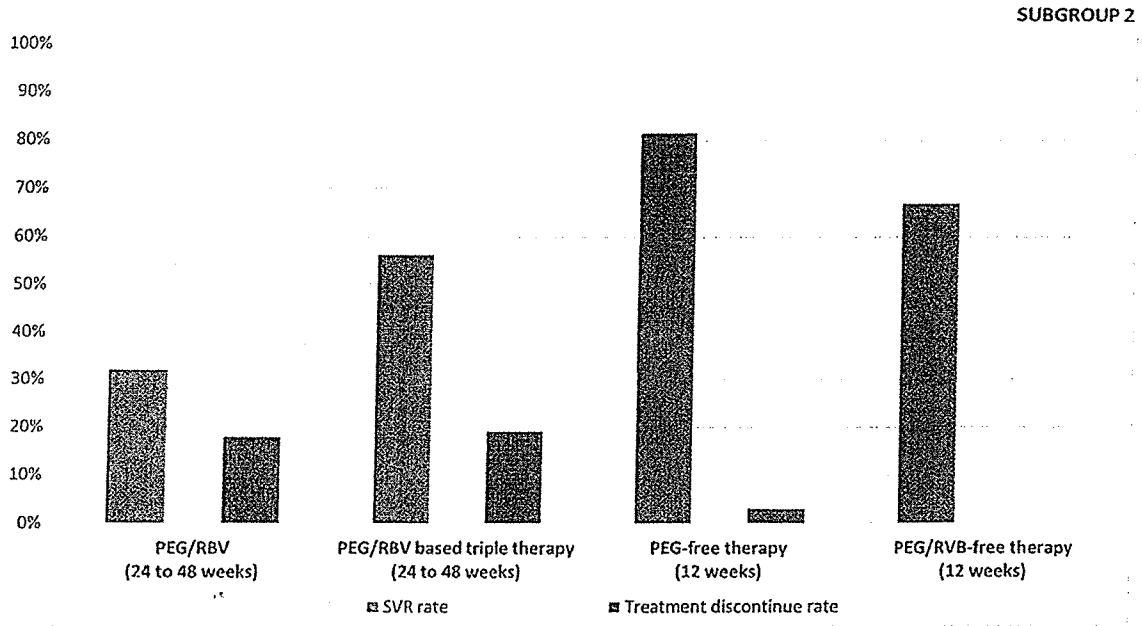
a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

Patient subgroup 2: Naïve patients with HIV co-infection

1. Baseline characteristics of patient subgroup 2.

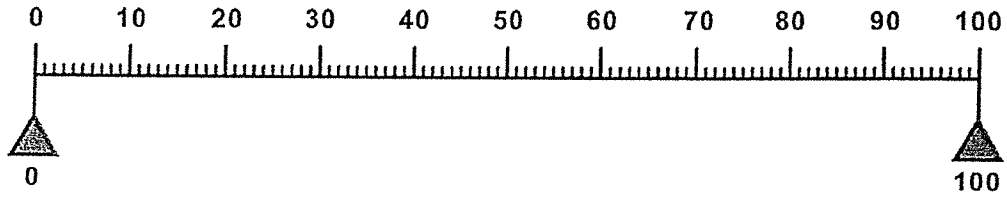
Baseline variable	%/mean ±SD
Age (years)	47.6 ± 11.2
Male gender	96.3%
Duration of HCV infection (years)	25.0 ± 1.0
Hemophilics	97.3%
Previous blood transfusion	2.8%
Distribution of fibrosis stage	
F0	39.4%
F1/F2	39.4%
F3	5.5%
F4	15.6%
Distribution of viral genotype	
1	75.0%
2 or 3	16.7%
4, 5 or 6	8.3%

2. Estimated clinical efficacies and toxicities associated with antiviral regimens in the patient subgroup 2.



3. Survey questions for patient subgroup 2 (naïve patients ***with*** HIV co-infection).

3.1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup (naïve patients ***with*** HIV co-infection) that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



3.2. If you decide to treat this subgroup (naïve patients ***with*** HIV co-infection), please indicate which regimen you are likely to use most frequently in this group:

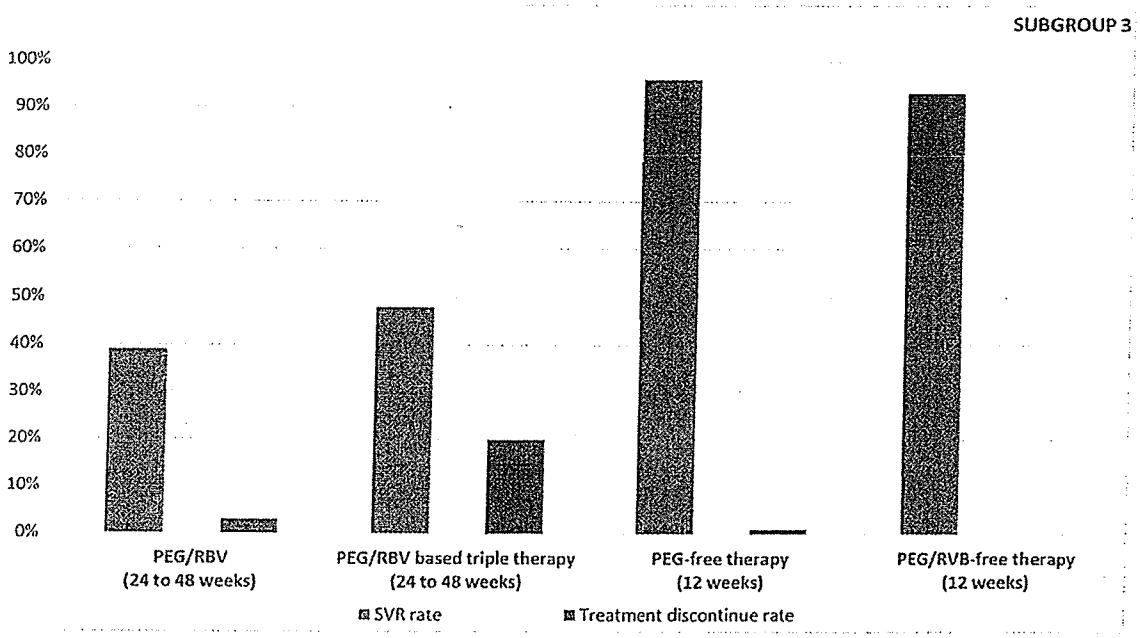
a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

Patient subgroup 3: Previously treated patients without HIV co-infection

1. Baseline characteristics of patient subgroup 3.

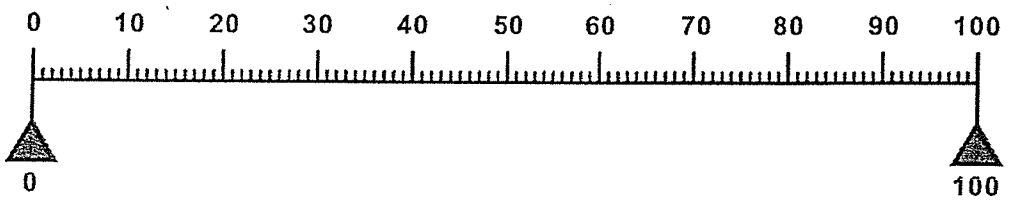
Baseline variable	%/mean ±SD
Age (years)	54.3 ± 14.0
Male gender	58.0%
Duration of HCV infection (years)	26.4 ± 5.2
Hemophilics	27.3%
Previous blood transfusion	71.4%
Distribution of fibrosis stage	
F0	0.0%
F1/F2	71.0%
F3	15.2%
F4	13.8%
Distribution of viral genotype	
1	74.4%
2 or 3	24.4%
4, 5 or 6	1.3%

2. Estimated clinical efficacies and toxicities associated with antiviral regimens in the patient subgroup 3.



3. Survey questions for patient subgroup 3 (previously treated patients ***without*** HIV co-infection)

3.1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup (previously treated patients ***without*** HIV co-infection) that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



3.2. If you decide to treat this subgroup (previously patients ***without*** HIV co-infection), please indicate which regimen you are likely to use most frequently in this group:

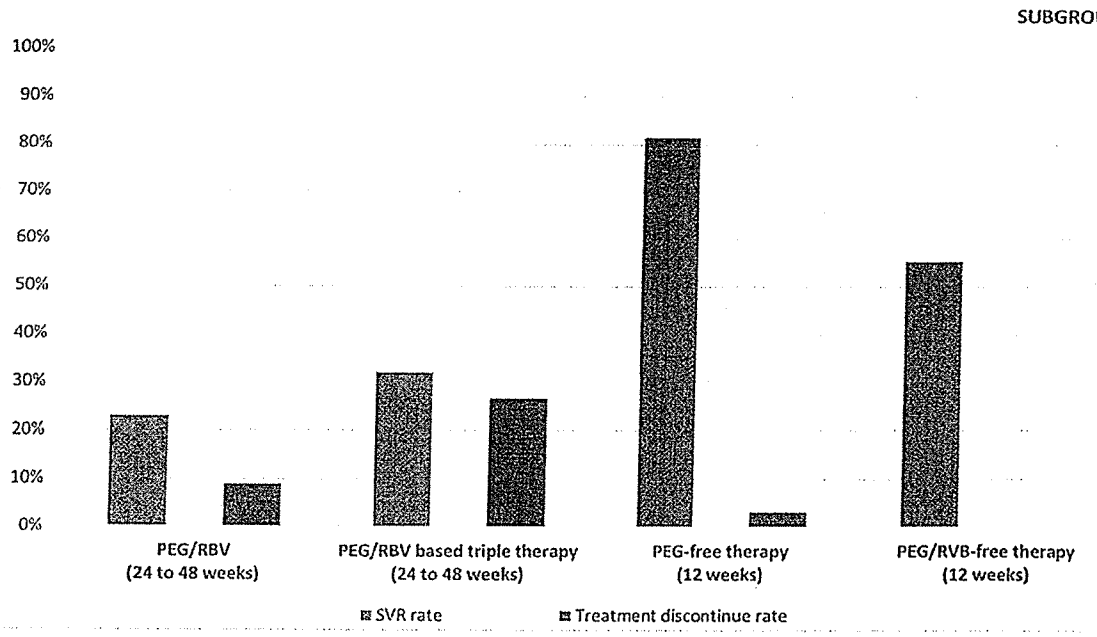
a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

Patient subgroup 4: Previously treated patients with HIV co-infection

1. Baseline characteristics of patient subgroup 4.

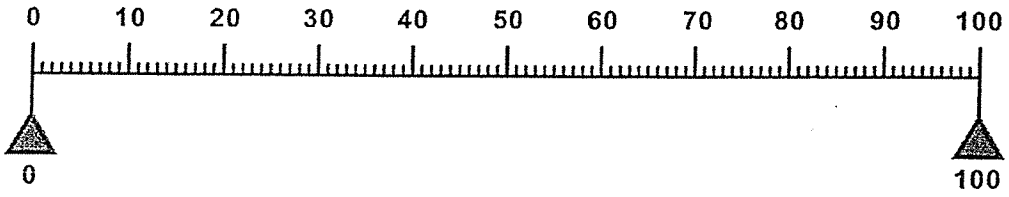
Baseline variable	%/mean ±SD
Age (years)	50.2 ± 8.2
Male gender	93.3%
Duration of HCV infection (years)	26.0 ± 1.7
Hemophilics	93.0%
Previous blood transfusion	7.0%
Distribution of fibrosis stage	
F0	0.0%
F1/F2	53.5%
F3	16.3%
F4	30.2%
Distribution of viral genotype	
1	75.0%
2 or 3	16.7%
4, 5 or 6	8.3%

2. Estimated clinical efficacies and toxicities associated with antiviral regimens in the patient subgroup 4.



3. Survey questions for patient subgroup 4 (previously treated patients *with* HIV co-infection)

3.1. Please mark on the following 0-100 scale to indicate the percentage of patients within this subgroup (previously treated patients *with* HIV co-infection) that would likely be treated within your practice, if antiviral therapy is reimbursed by the compensation trust fund and patient's willingness to be treated is fully taken into account. "100" means you would treat 100% of patients. "0" means you would treat no patients.



3.2. If you decide to treat this subgroup (previously patients *with* HIV co-infection), please indicate which regimen you are likely to use most frequently in this group:

a. PEG/RBV
b. PEG/RBV-based triple therapy
c. PEG-free therapy
d. PEG/RBV-free therapy

Many thanks for completing the survey questions for our study. You can fax back the signed information consent form and completed survey with attention to Dr. Murray Krahn.

Fax number is 416-946-3719.