This is Exhibit "P" 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

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

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List of Abbreviations

ALT, alanine aminotransferase

β, coefficient

BMI, body mass index

CASL, Canadian Association for the study of the Liver

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 three subsequent revisions. This document describes the third 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.

This third revision includes 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.

For the overall living patients, our model predicts that the prevalence of cirrhosis in August 2007 is 9.8%. The cumulative lifetime incidence of cirrhosis is 39.3%, and 23.5% will ultimately die of liver disease. Our model also predicts that 34.8% of non-hemophilic patients alive in 2007 will ultimately develop cirrhosis, and 20.0% 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 HCV death (53.4% and 34.6%, respectively).

Predictions of the current model relative to those of the earlier two models are reported in Tables 7.2 and 7.3. Prognostic projections of the current model, in general, fall between those of the latter two models (2002 and 2004). The differences between recent revisions (2004 and 2007) and 2002 revision are attributable to several factors. First, there are now more claimants in early HCV stages (F0) than when the last simulation (2002) was performed (44.4% in 2004 and 51.8% in 2007 vs. 30.9%). Second, the stage transition probabilities used in current 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.

The current 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 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 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 10% from 2004 data. The number of outstanding claims is believed to be very 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 current practice patterns among Canadian hepatologists. 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.

This 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 includes 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 expert.

2. Model Structure and Assumptions

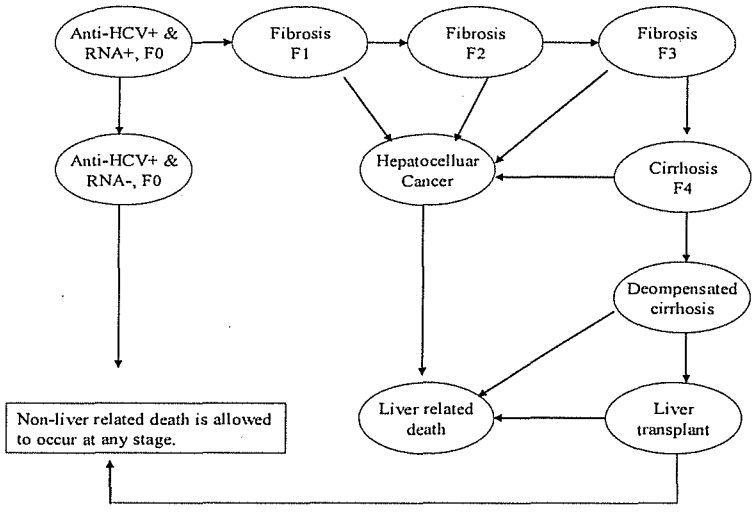
2.1. Model Structure

The proposed model (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 DATA PRO is shown in Figure 2.1). The 2004 and 2007 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. 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.

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



Transitions between fibrosis stages (F0 to F4) are explicitly represented in the current version of the model (all three revisions). For patients with F0 disease, 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).

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. 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 26.1% of HCV patients in our cohort (as of 2007), and had very different age and sex distributions (significantly younger and more males), and a high rate of coinfection with HIV (41.0% vs. 0.4% in non-hemophilics). Thus, non-hemophilic patients and hemophilic patients were modeled separately.

2.3. Analytic Method

Prognostic results were generated using first order Monte Carlo simulation, as implemented in TREEAGE PRO.[12] 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, 50,000 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 50,000, 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, liver transplantation to death and decompensation to liver-related death). After reviewing studies published in the last few years, we were convinced that these transition probabilities derived in our last reports remain valid, in particular for late stage HCV infection. Our estimates are not substantially different from those used by Hutchinson *et al.*[13] and Sweeting *et al.*[14] to predict the burden of hepatitis C in England and Scotland (transition from decompensation to liver transplant: 0.033 vs. 0.02; liver transplant to death, first year: 0.169 vs. 0.146; liver transplant to death, after first year: 0.034 vs. 0.044; decompensated cirrhosis to death: 0.138 vs. 0.186). Thus,

they were incorporated without amendment in the current model. Similarly, the excess mortality ratios attributable to transfusion itself were derived from Vamvakas.[15,16] 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 2007 (baseline) model, that begin on August 31, 2007, used the actual stage distributions derived from the compensation cohort.

3.1.2. Data from the literature

We performed new comprehensive literature reviews on the following:

(1) Seroconversion from HCV RNA+ to HCV RNA- status (spontaneous HCV clearance, Table 4.1);

(2) Transition probabilities for stages up cirrhosis, i.e. from F0 to F4 (Tables 4.2.1-4.2.5);

(3) Transition probabilities for stages after cirrhosis, i.e. from cirrhosis to HCC (Table 4.4.1);

(4) Effect of HIV on liver fibrosis progression/cirrhosis (Figure 4.3.3); and

(5) Effectiveness of pegylated interferon (PEG-IFN) and ribavirin combination therapy in HCV-infected individuals (Tables 4.3.1.1-4.3.1.3).

We updated data regarding excess mortality associated with HIV infection (Table 4.3.4.2). For other data relating to late stages of HCV (i.e. transition from F4 to decompensated cirrhosis and from HCC to liver death), we referred to Hutchinson *et al's*[13] report. In their analysis for the transition from F4 to decompensated cirrhosis, the authors included five studies involving 904 subjects with approximately 4,720 years of follow-up. The pooled estimate reported was 0.065

(95% CI, 0.04-0.092). For the transition from HCC to liver-related death, two studies were included in their analysis involving 130 patients. The follow-up period was 0.7 years for one study and not reported for another study. The pooled estimate was 0.605 (95% CI, 0.545-0.676).

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).[17]

3.1.3. Data from the post-transfusion compensation claimant cohort

Data compiled from compensation claim files were also used to calculate transition probabilities, which were compared and also combined with literature-based transition probabilities.

3.2. Synthesizing published data

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 histor". 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.

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.[18] 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.*[19] 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.[18] Variation across individuals has also been convincingly demonstrated. Poynard *et al.*,[20] 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 "th 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

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

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.*[21] 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.*[17] and in Appendix B.

In this third revision, 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 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[21-28] 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.[29] In a prospective study of 43 hepatitis C patients with a

history of illicit drug use, Villano *et al.*[27] 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,[29] 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.[23] Alter *et al.*[22] 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.*[30] 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.*[31] 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.*[28] 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. 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 after the acute infection.

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 20 years post-transfusion. Except for young women cohorts (assumed 20% seroconversion),[21,30,31] we assumed that 15% of individuals seroconvert within the first 6 months, based on the published estimate of Hoofnagle.[29] 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 therefore 0.0042 (Table 4.3.1). When published data are pooled with our own data from the compensation cohort, the weighted transition rate is 0.018 (95% CI, 0.011-0.024) (Table 4.3.1). We used this new data in the current prediction model. In the simulation study by Salomon *et al.*[1] the transition rate range used was 0-0.01. In our 2002 and 2004 simulation studies, 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.[32] 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[33] 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.[19] 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.*[34] 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[35-37] reported annual rates of fibrosis progression similar to that reported by Poynard *et al.*[19] 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.[19] In addition, we used MMLE method to derive stage-specific transition probabilities for studies[19,34,38-41] 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[40] 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.[38,41]

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[21] and Wiese *et al.*[30,31] 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[21] and Wiese *et al's*[30] 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,[32,42-44] 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[43] fibrosis stages (S0-S6) were converted to the well-validated METAVIR scoring system,[32] 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)[45,46] 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.[47,48] Effective treatment of HCV infection also seems to prevent the complications of chronic infection such as liver failure.[49]

However, not every patient responds to treatment. According to Sobesky *et al.*,[35] 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,[50] and to 60-65% with PEG-IFN alfa-2a and ribavirin combination therapy.[51,52] Results from a large international randomized clinical trial[45] 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.[53-56]

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. 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). The response rate for F0-F1 is somewhat higher than that used in the previous model (60% vs. 42%). 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.*[35] 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.*[57] 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. We used the same treatment effect in the current model.

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 current models as it has a larger sample size (Table 4.3.2).

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.[58] Based on a large retrospective data set, Poynard *et al.*[19] 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.[19] 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[59-65] irrespective of study design or definition of alcohol abuse.

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.[66] Studies have also suggested that HCV patients with HIV coinfection are more likely to develop end-stage liver disease (ESLD). Ragni and co-workers[67] 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.*[59] 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.*[59] 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.[67-75] 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[68] or the HIV/HCV coinfected group,[76] 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.*[77] 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 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 current model (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.[78] 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.*[39] 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 (≥50 units). Hui *et. al.*[79] 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.*[80] 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.*[81] 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.[19,34,82] 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.*[83] 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.[84,85] (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.[86,87] 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.[86,87] The primary reason for this decline was the increased wide application of clotting factor replacement products for treating life-threatening bleeding episodes.[88]

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.*[88] 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.[88] These findings were corroborated by other studies. Based on a survey study of 919 male hemophilics, Triemstra and colleagues[89] 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.*[67] 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.*[75] 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.*[90] 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[91] 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.[92] 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.[92,93] Obesity is also likely to be associated with poorer response to IFN treatment.[94] However, the link between HCV progression and obesity is not consistent. In a study of 148 clinical patients, Fiore and co-workers[95] 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.*[63] 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[96] 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.*[97] 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.[97]

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 numbers 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[60] 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.[98] Statistical analysis was performed with SAS version 9.1 and Proc Mixed ML procedure[99] 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.[100] In our 1998 model, the weighted annual probability of progression to HCC given cirrhosis was 1.7% per year.[101-103] Additional references were included in the 2002 study. In a cohort study of 252 patients with HCV-related cirrhosis, Kato *et al.*[104] 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.*[105] 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%[106] and 5%[107]. del Olmo *et al.*[108] 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 current study, 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.*[14] Therefore, in our current model, we used our new weighted mean annual HCC rate of 3.1%.

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.*[109] 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[110] 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.[15] 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] Because little has been published in

recent years describing the prognosis of late stage patients, we adopted transition probabilities from the 2002 model.

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 2007, 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 5,004 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, 2007, 1,231 (24.6%) of the 5,004 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 5,004 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. Overall, the mean$\pm$SD age (current) of the PTCC cohort was 55.6$\pm$18.8 years, age at transfusion was 40.8$\pm$19.3 years, and the duration of infection was 20.3$\pm$5.6 years. There were 3,112 (62%) males and 1,892 (38%) females (Table 5.3.1). Among living patients, males were younger, on average, than females (52.5 vs. 56.1 years). Overall,

males were more likely to be in a higher compensation category (i.e. level 5/6, 19.5% vs. 12.8%). 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, 1,231 (25%) 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.

All except 230 individuals (with 1,379 missing) were positive for serum antibody to HCV based on the last available testing results. Among 2,676 with HCV RNA testing records, 93% were HCV RNA positive. Just less than half (47%) of the individuals did not have HCV RNA test results. History of blood transfusion was available for 3,615 non-hemophilic patients, of whom 556 (15%) indicated that they received a blood transfusion before 1986. Among those with blood transfusion records, 66% were multiple blood transfusion recipients. A total of 2,311 (64%) 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 77% 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 7.1% of claimants, and decompensated cirrhosis, liver transplant, and HCC in 1.9%, 0.6%, and 0.5% 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 (22% vs. 3%), but appear not substantially different in the more advanced disease stages.

5.3.2. Hemophilia and other underlying conditions for blood transfusion

There were 1,305 (26%) hemophilic patients, of which 1,157 (89%) were males (Table 5.3.2). Few (11%) 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 (44.3 vs. 57.1 years, $P<0.0001$). Although the two groups had similar distributions of serologic status (anti-HCV, HCV RNA), hemophilics had higher compensation levels ($\geq$level 3: 61% vs. 45%, $P<0.0001$) and higher proportion of previous HCV treatment (24% vs. 21%, $P=0.009$). A higher proportion of claims came from estates of deceased patients among hemophilics than non-hemophilics (31% vs. 22%, $P<0.0001$). 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 this current 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)[32]

Level 4: Bridging fibrosis: F3 (numerous septa without cirrhosis)[32]

Level 5: Cirrhosis: F4

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, nearly 80% 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[111,112] 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 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).
- Based on the propensity score (predicted probability of having biopsy), patients were then classified into three groups: propensity score <0.4, 0.4-0.6, and ≥0.6).

- 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, 2007. 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,[17] we derived the fibrosis progression rates from stage distributions in our adjusted non-hemophilic PTCC data. The derived rates are 0.032, 0.137, 0.150 and 0.097 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 2004 estimates except for transition from F1→F2. The corresponding rates used in the 2004 revision are 0.041, 0.088, 0.327, and 0.384, respectively. In comparison with the rates derived from the PTCC data available in 2002, our 2007 transition rates are somewhat lower for all stages. 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 both 2004 and 2007 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 2007 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 and F2→F3 (Table 4.2.5). In addition, the estimated number of years (55.5 years=1/0.032+1/0.137+1/0.150+1/0.097) required to progress from infection (F0) to cirrhosis are somewhat longer than our 2004 report (41.5 years) and the 30 years (4/0.133) reported by Poynard *et al.*[19]

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 this current report, the PTCC data showed a different pattern: increased rates from F0→F1,...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 were used to estimate transition probabilities, HCV treatment (PEG-IFN and ribavirin) efficacy, general population and post-transfusion mortality rates, and the effect of HIV and hemophilia on long-term prognosis. Our clinician survey provided data regarding current treatment patterns among Canadian liver specialists. Finally, we used our previous models 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[17] 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, 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 13 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,[15] 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 2007 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. The observed distribution has slightly less patients in the early stages compared to predicted distribution (F0-F2, 77.4% vs. 82.2%), and more patients in the later stages (F3-F4: 18.2% vs. 16.1%; advanced stages: 2.9% vs. 1.7%).

Both the 2004 and 2007 models fit the data considerably better than the 2002 model. 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 second and third revisions than those in the first revision.

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 2004 and 2007 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 four models. The 2007 model projections fall between those of the 2002 model and the 2004 model.

The 2004 and 2007 predictions are lower than 2002 for several reasons: i) the proportion of hemophilics that are HIV positive has fallen (25-26% vs. 39%); ii) transition rates between fibrosis stages are lower; iii) the starting distribution of patients with cirrhosis is considerably lower (7-8% vs. 15.5%); iv) 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); v) 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).

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.

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.[12] 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. Table 8.1.5 for

prognosis of age group 10-19 years among hemophilic patients is not created as there is only a single patient in this group.

Each table displays the cumulative incidence rate of cirrhosis, decompensated cirrhosis, HCC, liver transplantation, non-liver and liver 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 39.3%, starting from a point prevalence rate of 9.8% in August 2007. 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 nine (10.9%) will develop liver cancer, and about one in four (23.5%) 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, and all other cirrhosis-related events are relatively higher than non-hemophilics. 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 triangle 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 2010 to 2060 are reported in Table 8.2.1.

Table 8.2.1 suggests that the error in lifetime cirrhosis incidence rate (39%) is about +/- 12% in absolute terms (27%-51% and about +/- 31% in relative terms. Similar errors: +/- 6% in absolute terms and ~52% in relative terms in the lifetime HCC incidence rate (11%); and +/- ~8% in absolute terms and ~32% in relative terms in the lifetime incidence of liver-related death (24%). These values reflect the overall uncertainty in our prediction 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. Though, 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 2007, 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 2007 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.

As the observed number of patients with HCC and liver transplant are 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 2007 results suggest that many more individuals would be in stages F0-F2 and F4, and few in F3 and later stages (e.g. decompensated cirrhosis, HCC and liver transplant) 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 third 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 5,004 individuals whose claims for compensation had been approved as of August 2007. Close to two-thirds (62%) of claimants were male, and 25% 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 (78%) of claimants were compensated at level 3 or below. Just more than one-fifth (22%) had received prior HCV therapy. Less than a quarter (23%, 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 2007 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 (53% and 35%, respectively). Compared with the results in the 2002 and 2004 revisions, the current long-term projections for cumulative proportions of cirrhosis (non-hemophilics: 35% vs. 37% vs. 33%; hemophilics: 53% vs. 46% vs. 57%) and liver-related deaths (non-hemophilics: 20% vs. 22% vs. 17%; hemophilics: 35% vs. 27% and 37%) fall between the two. Since the current 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 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.

Finally, this 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.

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 direct estimation of current practice patterns among Canadian hepatologists, 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 2007, 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.

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11. Tables

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

ıuthor	opulation	?isk	Sample size	Years o follow-up	Total vira clearance	Chronic HCV	Clearance ir chronic stage	Clearance rate in chronic stage	Est person-y	Clearance rate/yr
Mattsson,1993[24]	Acute	Non-A, Non-B	24	13	8 (33%)	20	4	0.216	265	0.017
Barrera,1995[113]	Acute	Transfusion	41	6	5 at 6 wks 5 at 6 yrs (24%)	36	5	0.139	216	0.023
Kenny-Walsh,1999[21]	Acute	Contaminated anti-D	704	17	314 (45%)	563	173	0.308	9574	0.018
Villano,1999[27]	Acute	IDU	34	6	6 (18%)	29	1	0.031	173	0.005
Vogt,1999[114]	Acute	Pediatric, surgical	67	19.8	30 (45%)	57	20	0.350	1128	0.018
Wiese,2000[30]	Acute	Contaminated anti-D	917	20	412 (45%)	734	229	0.312	14672	0.016
Barrett,2001[115]	Acute	Contaminated anti-D	155	22	68 (44%)	124	37	0.298	2728	0.014
Lehmann,2004[116]	Acute	IDU	84	0.5-1	19 (23%)	71	6	0.090	71	0.090
Spada,2004[117]	Acute	IDU, surgical	34	0.5-1	10 (29%)	29	5	0.170	29	0.170
Wiese,2005[31]	Acute	Contaminated anti-D	1811	25	836 (46%)	1449	362	0.327	36220	0.013
Micallef,2005[28]	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[118]	Acute	Community-acquired	203	1.2	73 (36%)	173	43	0.247	207	0.205
Alter,1992[119]	Chronic	Community-acquired		3.75		25	1	0.040	94	0.011
Seeff,1997[33]	Chronic			25		129		0.23	3225	0.009
Thomas,2000[26]	Chronic	IDU		8.8		919	90	0.098	8087	0.011
Messick,2001[120]	Chronic	Hemophilics		24		49	12	0.245	1176	0.010
Mazzeo,2003[107]	Chronic	General population		10		63	7	0.111	630	0.011
Bortolotti,2005[121]	Chronic	Pediatric, transfusion, maternal infection		8		522	24	0.046	4176	0.006
Grebely,2006[122]	Chronic	IDU		5.2		658	152	0.231	3422	0.044
Posthouwer,2006[123]	Chronic	Pediatric, transfusion		15		68	24	0.353	1020	0.024
Scott,2006[124]	Chronic	IDU, transfusion, sporadic		7		139	11	0.079	943	0.012
Harris,2007[125]	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[126]	Chronic	Pediatric, transfusion		11.9		55	11	0.200	655	0.017
Yeung,2007[126]	Chronic	Pediatric, nontransfusion		7.4		20	6	0.300	148	0.041
Krahn,2005[127§]	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).[21,30,31]

[§]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[128]	1991-1994	USA	Blood donors	Non-clinical	R-P
Silva, 2004[129]	1997-2001	Brazil	Blood donors	Non-clinical	C-S/R
Dalgard, 2003[130]	2000-2001	Norway	Community	Non-clinical	C-S/R
Saadoun, 2006[131]		France	Community	Non-clinical	C-S/R
Serra, 2003[132]		Spain	Community	Non-clinical	C-S/R
Verma, 2006[133]	1994-2004	USA	Community	Non-clinical	C-S/R
Hu, 2005[134]	1999-2003	USA	Dialysis patients	Clinical	C-S/R
Martin, 2000[135]	1992-1997	USA	Dialysis patients	Clinical	C-S/R
Sezer, 2001[136]		Turkey	Dialysis patients	Clinical	C-S/R
Sterling, 1999[137]		USA	Dialysis patients	Clinical	C-S/R
Toz, 2002[138]	1996-2000	Turkey	Dialysis patients	Clinical	C-S/R
Varaut, 2005[139]	1999-2003	France	Dialysis patients	Clinical	C-S/R
Di Martino, 2004[140]	1993-2001	France	Females	Clinical	C-S/R
Kenny-Walsh,1999[21]	1970-1994	Ireland	Females	Non-clinical	R-P
Levine, 2006[141]	1977-2004	Ireland	Females	Non-clinical	R-P
Wiese, 2005[31,142]	1978-2003	Germany	Females	Non-clinical	R-P
Benhamou, 1999[59]		France	Injecting drug users	Clinical	C-S/R
Cournot, 2004[143]	1990-2000	France	Injecting drug users	Clinical	C-S/R
Grando-Lemaire, 2001[144]	1997-2000	France	Injecting drug users	Non-clinical	C-S/R
Puoti, 2001[145]	1988-1996; 1993-1996	Italy+USA	Injecting drug users	Clinical	C-S/R
Rai, 2002[146]	1996-1998	USA	Injecting drug users	Non-clinical	C-S/R
Wilson, 2006[147]	2001-2003	USA	Injecting drug users	Non-clinical	R-P
Allory, 2000[148]		France	Liver clinic	Clinical	C-S/R
Asselah, 2003[149]	2000-2001	France	Liver clinic	Clinical	C-S/R
Bedossa, 2007[150]	2005-2006	France	Liver clinic	Clinical	C-S/R
Cheung, 2005[151]	1999-2000	USA	Liver clinic	Clinical	C-S/R
Cholet, 2004[152]	1992-2001	France	Liver clinic	Clinical	C-S/R
Costa, 2002[153]	1994-2000	Brazil	Liver clinic	Clinical	C-S/R
Cournot, 2004[143]	1990-2000	France	Liver clinic	Clinical	C-S/R
Erhardt, 2003[154]		Germany	Liver clinic	Clinical	C-S/R
Fernandez-Rodriguez, 2004[155]	1998-2003	Spain	Liver clinic	Clinical	C-S/R
Fernandez-Salazar, 2004[156]	2000-2002	Spain	Liver clinic	Clinical	C-S/R
Fontaine, 2001[157]		France	Liver clinic	Clinical	C-S/R
Fontana, 2006[158]		USA	Liver clinic	Clinical	C-S/R
Forrest, 2005[159]		UK	Liver clinic	Clinical	C-S/R
Freeman, 2003[160]		UK	Liver clinic	Clinical	C-S/R
Gaslightwala & Bini, 2006[161]		USA	Liver clinic	Clinical	C-S/R
Geier, 2004[162]	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[38]	1980-2000	USA	Liver clinic	Clinical	R-P
Gonzalez, 2006[163]		USA	Liver clinic	Clinical	C-S/R
Haber, 1995[164]	1990-1992	USA	Liver clinic	Clinical	C-S/R
Hezode, 2005[165]	2003-2005	France	Liver clinic	Clinical	C-S/R
Hofer, 2005[166]		Austria	Liver clinic	Clinical	C-S/R
Hollander, 2004[167]	1997-1998; 1999-2000	Sweden	Liver clinic	Clinical	C-S/R
Hu, 2005[134]	1999-2003	USA	Liver clinic	Clinical	C-S/R
Huang, 2006[168]		USA	Liver clinic	Clinical	C-S/R
Huang, 2006[168]		USA	Liver clinic	Clinical	C-S/R
Hui, 2003[79]	1991-1998	USA	Liver clinic	Clinical	R-P
Imazeki, 2005[169]	1986-1998	Japan	Liver clinic	Clinical	C-S/R
Khan, 2000[170]	1982-1996	Australia	Liver clinic	Clinical	R-P
Kryczka, 2003[171]		Poland	Liver clinic	Clinical	C-S/R
Lagging, 2002[172]	1971-1996	Sweden	Liver clinic	Clinical	C-S/R
Leroy, 2004[173]	1999-2000	France	Liver clinic	Clinical	C-S/R
Macias, 2005[174]		Spain	Liver clinic	Clinical	C-S/R
Marine-Barjoan, 2002[175]	1997-1998	France	Liver clinic	Non-clinical	C-S/R
Martinez-Sierra, 2003[176]		Spain	Liver clinic	Clinical	C-S/R
Metwally, 2004[177]	1998-1999	USA	Liver clinic	Clinical	C-S/R
Mohsen, 2003[178]		UK	Liver clinic	Clinical	C-S/R
Monto, 2002[179]	1997-2000	USA	Liver clinic	Clinical	C-S/R
Monto, 2004[180]	1997-2002	USA	Liver clinic	Clinical	C-S/R
Monto, 2004[180]	1997-2002	USA	Liver clinic	Clinical	C-S/R
Monto, 2004[180]	1997-2002	USA	Liver clinic	Clinical	C-S/R
Monto, 2005[181]		USA	Liver clinic	Clinical	C-S/R
Muller, 2003[182]	2001-2002	France	Liver clinic	Clinical	C-S/R
Myers, 2001[183]	1995-1999	Canada	Liver clinic	Clinical	C-S/R
Myers, 2002[184]	1997-2000	France	Liver clinic	Clinical	C-S/R
Myers, 2003[185]		France	Liver clinic	Clinical	C-S/R
Nguyen, 2002[186]	1992-2000	USA	Liver clinic	Clinical	C-S/R
Ong, 2001[187]	1997-1999	USA	Liver clinic	Clinical	C-S/R
Oritz, 2002[188]	2000-2001	Spain	Liver clinic	Clinical	C-S/R
Patel, 2006[189]	1992-2001	USA+UK	Liver clinic	Clinical	C-S/R
Patton, 2004[190]	1992	USA	Liver clinic	Clinical	C-S/R
Pohl, 2001[191]		USA	Liver clinic	Clinical	C-S/R
Poujol-Robert, 2006[192]	2000-2003	France	Liver clinic	Clinical	C-S/R
Poynard, 1997 DOSVIRC[19]		France	Liver clinic	Clinical	C-S/R
Poynard, 1997 METAVIR[19]		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[19]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 DOSVIRC-1[84]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 DOSVIRC-2[84]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 HITG[84]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 IHIT[84]		France	Liver clinic	Clinical	C-S/R
Poynard, 2001 OBSVIRC[84]		France	Liver clinic	Clinical	C-S/R
Poynard, 2002[46,50,193-195]	1996; 1997	France+USA	Liver clinic	Clinical	C-S/R
Poynard, 2002[46,50,193-195]	1996; 1997	USA	Liver clinic	Clinical	C-S/R
Poynard, 2002[46,50,193-195]	1996; 1997	USA	Liver clinic	Clinical	C-S/R
Poynard, 2002[46,50,193-195]	1996; 1997	Germany	Liver clinic	Clinical	C-S/R
Ratziu, 2003[196]	1993-2000	France	Liver clinic	Clinical	C-S/R
Renou, 2002[197]	1999-2000	France	Liver clinic	Clinical	C-S/R
Reynolds, 2002[198]	1994-1999	USA	Liver clinic	Clinical	C-S/R
Roger, 2005[199]		France	Liver clinic	Clinical	C-S/R
Romero-Gomez, 2003[200]		Spain	Liver clinic	Clinical	C-S/R
Ryder, 2004[40]	2000	UK	Liver clinic	Non-clinical	C-S/R
Sud, 2004[201]	1999-2002	Australia	Liver clinic	Clinical	C-S/R
Toccaceli, 2003[202]	1990-1997	Italy	Liver clinic	Clinical	C-S/R
Watt, 2004[203]		Canada	Liver clinic	Clinical	C-S/R
Wietzke-Braun, 2003[204]		Germany	Liver clinic	Clinical	C-S/R
Wilfredo Canchis, 2004[205]		USA	Liver clinic	Clinical	C-S/R
Wong, 1997[206]		UK	Liver clinic	Clinical	C-S/R
Wright, 2003[207]	1990-2001	Europe	Liver clinic	Clinical	C-S/R
Zarski, 2003[41]		France+USA	Liver clinic	Clinical	C-S/R
de Le'dinghen, 2002[208]	1998-2000	France	Liver clinic	Clinical	C-S/R
Castellino, 2004[209]	1995-2002	USA	Pediatric population	Clinical	R-P
Guido, 1998[210]	1990-1996	Italy	Pediatric population	Clinical	C-S/R
Guido, 2003[211]		Europe	Pediatric population	Clinical	C-S/R
Mohan, 2007[212]	1982-1992	USA	Pediatric population	Clinical	R-P
Hamada, 2002[213]	1980-2000	Japan	Post-transfusion	Clinical	R-P
Shin, 2005[214]	1992-2003	Canada	Post-transfusion	Clinical	C-S/R
Giordano, 2003[215]	1993-1995	Brazil	Renal transplant recipients	Clinical	C-S/R
Kamar, 2005[216]		France	Renal transplant recipients	Clinical	C-S/R
Toz, 2002[138]	1996-2000	Turkey	Renal transplant recipients	Clinical	C-S/R
Varaut, 2005[139]	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.*,[140] 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[128]	81	74	37.0	19.0	18.0	Conventional/unspecified	32	33	2	3	4†	1332.0
Silva, 2004[129]	142	142	38.7	19.9	18.8	METAVIR	9	66	32	25	10	2669.6
Dalgard, 2003[130]	72	38	42.5	20.5	22.0	Knodell	10	11	6	8	3†	836.0
Saadoun, 2006[131]	437	437	50.9	31.0	19.9	METAVIR	17	204	106	46	64	8696.3
Serra, 2003[132]	375	298	46.0	29.3	16.7	Batts-Ludwig	11	116	61	43	67	4976.6
Verma, 2006[133]	232	232	45.4	22.7	24.2	Ishak	16	51	51	41	73	5614.4
Hu, 2005[134]	91	91	46.4	25.7	20.7	Knodell	33	27	6	15	10	1883.7
Martin, 2000[135]	37	37	47.5	33.1	14.4	Scheuer	7	10	8	3	9	532.8
Sezer, 2001[136]	68	68	39.8	36.1	3.7	Scheuer/Desmet/Batts-Ludwig	8	13	27	16	4	250.2
Sterling, 1999[137]	50	50	42.3	26.7	15.6	Knodell	17	22	3	3	5	780.0
Toz, 2002[138]	40	40	42.0	38.2	3.8	Scheuer	7	14	14	4	1	153.2
Varaut, 2005[139]	50	50	48.0	29.0	17.0	METAVIR	1	28	11	7	3	850.0
Di Martino, 2004[140]	157	157	48.0	29.0	18.0	METAVIR	20	68	38	20	11	2826.0
Kenny-Walsh,1999[21]	376	363	45.0	28.0	17.0	Desmet	177	124	36	19	7	6171
Levine, 2006[141]	184	167	56.0	27.0	27.0	Ishak	50	53	34	26	4	4509.0
Wiese, 2005[31,142]	683	490	49.0	24.0	25.0	Ishak	164	173	97	43	13†	12250.0
Benhamou, 1999[59]	122	122	35.6	22.1	13.5	METAVIR	15	50	36	8	13	1647.0
Cournot, 2004[143]	225	122	31.9	20.6	11.3	METAVIR	36	36	20	21	9	1378.6
Grando-Lemaire, 2001[144]	225	88	33.0	19.5	13.4	METAVIR	3	38	27	6	14	1183.6
Puoti, 2001[145]	204	204	32.0	20.0	12.0	METAVIR	13	111	56	14	10	2448.0
Rai, 2002[146]	207	207	40.4	20.7	19.7	Ishak	74	65	47	18	3	4077.9
Wilson, 2006[147]	119	119	46.0	20.0	26.0	Ishak	32	30	34	15	8	3094.0
Allory, 2000[148]	58	58	35.0	20.0	12.0	METAVIR	6	27	14	5	6	696.0
Asselah, 2003[149]	290	290	46.0	25.0	21.0	METAVIR	4	177	73	21	15	6090.0
Bedossa, 2007[150]	278	278	47.0	24.0	23.0	METAVIR	54	54	101	40	29	6394.0
Cheung, 2005[151]	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[152]	314	314	40.8	26.8	13.7	METAVIR	72	72	82	42	46	4301.8
Costa, 2002[153]	59	59	43.0	29.0	14.0	Ludwig/Desmet	7	21	8	10	13	826.0
Cournot, 2004[143]	210	84	53.3	38.9	14.4	METAVIR	21	22	11	11	19	1209.6
Erhardt, 2003[154]	401	217	47.7	35.3	12.4	Knodell	42	93	27	27	28	2690.8
Fernandez-Rodriguez, 2004[155]	133	133	43.5	24.5	19.0	METAVIR	5	66	38	12	12	2527.0
Fernandez-Salazar, 2004[156]	50	50	40.7	21.0	19.8	Scheuer	1	17	18	10	4	987.5
Fontaine, 2001[157]	76	76	41.0	30.0	11.0	Knodell/METAVIR	9	46	8	7	6	836.0
Fontana, 2006[158]	399	399	48.5	22.5	26.0	Ishak	42	100	111	117	29	10374.0
Forrest, 2005[159]	195	195	38.6	24.1	14.5	Ishak	27	70	42	38	18	2827.5
Freeman, 2003[160]	87	87	44.9	35.4	9.5	Wong	8	13	27	24	15	826.5
Gaslightwala & Bini, 2006[161]	554	554	51.1	31.1	20.0	Scheuer	87	143	158	90	76	11080.0
Geier, 2004[162]	166	166	41.8	33.5	8.3	Batts-Ludwig	45	44	47	22	8	1377.8
Ghany, 2003[38]	123	123	44.7	27.0	17.7	Ishak	15	28	22	41	17	2177.1
Gonzalez, 2006[163]	117	117	48.6	27.7	20.9	Scheuer	13	38	37	22	7	2445.3
Haber, 1995[164]	90	90	40.9	26.4	14.5	Knodell	7	34	11	12	26	1305.0
Hezode, 2005[165]	270	270	43.2	24.4	18.8	METAVIR	13	154	46	21	36	5076.0
Hofer, 2005[166]	212	212	44.7	25.6	19.1	Ludwig	11	11	108	27	55	4051.3
Hollander, 2004[167]	323	323	45.0	24.0	21.0	METAVIR	51	52	98	76	46	6783.0
Hu, 2005[134]	159	159	46.3	24.9	21.4	Knodell	27	44	20	39	29	3402.6
Huang, 2006[168]	433	433	52.7	25.4	27.3	Knodell	93	109	110	73	48	11820.9
Huang, 2006[168]	483	483	50.8	28.9	21.9	Knodell	84	82	83	114	120	10577.7
Hui, 2003[79]	81	81	54.9	25.8	29.1	METAVIR	22	27	20	7	5	2357.1
Imazeki, 2005[169]	459	459	50.1	26.5	23.6	Desmet	19	238	76	58	68	10832.4
Khan, 2000[170]	455	432	37.0	25.0	12.0	Scheuer	29	96	143	73	91†	5184.0
Kryczka, 2003[171]	337	337	43.0	30.0	13.0	Ishak	132	82	28	56	39	4381.0
Lagging, 2002[172]	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[173]	194	188	43.0	25.0	18.0	METAVIR	32	72	48	22	14	3384.0
Macias, 2005[174]	100	100	42.0	21.0	21.0	Scheuer	22	17	21	24	16	2100.0
Marine-Barjoan, 2002[175]	924	924	44.9	30.9	14.0	METAVIR	100	496	147	136	45	12936.0
Martinez-Sierra, 2003[176]	147	147	38.1	21.7	17.9	Scheuer/Desmet	51	51	18	18	9	2631.3
Metwally, 2004[177]	100	100	45.5	22.5	22.6	METAVIR	21	13	31	10	25	2260.0
Mohsen, 2003[178]	153	153	39.8	23.0	15.0	METAVIR/Ishak	13	53	41	23	23	2295.0
Monto, 2002[179]	297	297	49.0	24.9	24.1	Batts-Ludwig	63	83	83	40	28	7157.7
Monto, 2004[180]	324	324	47.0	22.0	22.0	METAVIR	70	114	69	32	39	7128.0
Monto, 2004[180]	199	199	47.0	24.0	24.0	METAVIR	56	57	56	18	12	4776.0
Monto, 2004[180]	277	277	50.0	24.0	25.0	METAVIR	51	75	82	36	33	6925.0
Monto, 2005[181]	372	372	49.0	25.0	24.0	Batts-Ludwig	100	89	100	49	34	8928.0
Muller, 2003[182]	90	90	44.0	24.1	19.9	Knodell/METAVIR	14	27	18	13	18	1791.0
Myers, 2001[183]	106	106	42.0	23.0	19.0	METAVIR	26	36	16	12	16	2014.0
Myers, 2002[184]	211	211	42.0	28.0	17.0	METAVIR	34	93	49	15	20	3587.0
Myers, 2003[185]	132	132	45.9	28.5	15.4	METAVIR	2	46	42	21	21	2031.5
Nguyen, 2002[186]	206	206	46.5	22.5	24.0	METAVIR	17	61	62	35	31	4944.0
Ong, 2001[187]	170	170	48.7	30.9	17.8	Ishak	16	28	33	31	62	3026.0
Oritz, 2002[188]	114	114	41.0	23.0	18.0	Desmet	31	57	5	18	3	2052.0
Patel, 2006[189]	515	515	43.4	23.2	20.2	METAVIR	87	183	114	69	62	10403.0
Patton, 2004[190]	574	560	44.9	23.2	21.7	METAVIR	167	168	114	46	65	12152.0
Pohl, 2001[191]	211	153	45.0	24.1	20.9	METAVIR	61	38	18	13	23	3197.7
Poujol-Robert, 2006[192]	346	346	46.8	23.7	20.9	METAVIR	10	177	76	35	48	7231.4
Poynard, 1997 DOSVIRC[19]	607	607	46.2	32.0	14.2	METAVIR	36	229	159	79	104	8619.4
Poynard, 1997 METAVIR[19]	490	490	49.1	36.7	12.4	METAVIR	13	136	87	100	154	6076.0
Poynard, 1997 OBSVIRC[19]	1138	1138	43.8	32.5	11.3	METAVIR	178	441	216	161	142	12859.4
Poynard, 2001 DOSVIRC-1[84]	320	320	45.0	31.0	14.0	METAVIR	18	116	103	37	46	4480.0
Poynard, 2001 DOSVIRC-2[84]	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[84]	597	597	44.0	24.0	20.0	METAVIR	14	397	86	63	37	11940.0
Poynard, 2001 IHIT[84]	495	495	40.0	24.0	16.0	METAVIR	11	399	40	26	19	7920.0
Poynard, 2001 OBSVIRC[84]	546	546	43.0	31.0	12.0	METAVIR	94	213	99	84	56	6552.0
Poynard, 2002[46,50,193-195]	832	832	41.0	26.0	15.0	METAVIR	16	657	75	50	34	12480.0
Poynard, 2002[46,50,193-195]	912	912	44.0	25.0	19.0	METAVIR	18	627	127	91	49	17328.0
Poynard, 2002[46,50,193-195]	1219	1219	43.0	24.4	18.6	METAVIR	49	938	110	73	49	22673.4
Poynard, 2002[46,50,193-195]	1530	1530	43.0	23.7	19.3	METAVIR	15	1071	260	92	92	29529.0
Ratziu, 2003[196]	710	710	41.0	23.9	15.7	METAVIR	98	291	175	50	96	11147.0
Renou, 2002[197]	316	316	46.6	32.2	14.4	METAVIR	78	109	64	39	26	4550.4
Reynolds, 2002[198]	166	166	48.0	27.0	21.0	Knodell/METAVIR	30	86	14	15	21	3486.0
Roger, 2005[199]	28	28	46.5	28.5	18.0	METAVIR	1	9	12	4	2	504.0
Romero-Gomez, 2003[200]	131	131	38.0	22.0	16.0	Scheuer	4	58	47	12	10	2096.0
Ryder, 2004[40]	214	214	36.0	19.6	18.9	Knodell/Ishak	128	55	10	16	5	4044.6
Sud, 2004[201]	176	176	40.9	21.5	18.9	Scheuer	46	46	37	37	10	3326.4
Toccaceli, 2003[202]	112	112	46.4	36.4	10.0	Knodell	25	61	11	12	3	1120.0
Watt, 2004[203]	116	116	46.0	27.0	18.0	Desmet	45	32	21	3	15	2088.0
Wietzke-Braun, 2003[204]	72	72	46.8	31.4	15.4	Knodell/Desmet/Ishak	33	10	10	11	8	1108.8
Wilfredo Canchis, 2004[205]	156	156	49.0	26.0	23.0	METAVIR	14	44	32	45	21	3588.0
Wong, 1997[206]	140	140	36.0	24.0	12.0	Wong	14	15	58	43	10	1680.0
Wright, 2003[207]	352	352	41.8	27.1	14.7	Ishak	26	70	101	94	61	5174.4
Zarski, 2003[41]	180	180	45.3	26.2	18.0	METAVIR	48	69	28	26	9	3240.0
de Le'dinghen, 2002[208]	321	317	41.0	26.8	14.2	METAVIR	12	95	123	68	19	4501.4
Castellino, 2004[209]	122	60	29.0	5.0	19.5	Desmet	13	17	10	11	9†	1170.0
Guido, 1998[210]	80	80	9.1	5.7	3.5	Ishak	22	22	22	13	1	276.8
Guido, 2003[211]	112	112	8.6	0.6	8.0	METAVIR	25	57	24	5	1	900.5
Mohan, 2007[212]	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[213]	469	436	54.7	30.0	28.1	Desmet	72	72	87	69	136	12251.6
Shin, 2005[214]	65	63	33.0	15.6	26.9	METAVIR	4	17	17	11	14	1694.7
Giordano, 2003[215]	45	26	41.1	31.1	10.0	Knodell	9	11	2	3	1	260.0
Kamar, 2005[216]	51	42	38.0	27.8	10.2	METAVIR	6	16	9	8	3	428.4
Toz, 2002[138]	46	46	36.0	32.7	4.9	Scheuer	5	14	15	9	3	222.2
Varaut, 2005[139]	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:[32] 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[128]	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[129]	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[130]	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[131]	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[132]	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[133]	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[134]	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[135]	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[136]	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[137]	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[138]	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[139]	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[140]	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[21]	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[141]	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[31,142]	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[59]	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[143]	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[144]	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[145]	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[146]	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[147]	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[148]	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[149]	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[150]	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[151]	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[152]	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[153]	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[143]	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[154]	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[155]	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[156]	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[157]	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[158]	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[159]	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[160]	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[161]	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[162]	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[38]	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[163]	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[164]	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[165]	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[166]	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[167]	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[134]	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[168]	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[168]	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[79]	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[169]	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[170]	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[171]	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[172]	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[173]	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[174]	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[175]	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[176]	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[177]	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[178]	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[179]	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[180]	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[180]	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[180]	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[181]	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[182]	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[183]	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[184]	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[185]	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[186]	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[187]	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[188]	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[189]	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[190]	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[191]	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[192]	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[19]	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[19]	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[19]	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[84]	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[84]	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[84]	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[84]	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[84]	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[46,50,193-195]	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[46,50,193-195]	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[46,50,193-195]	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[46,50,193-195]	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[196]	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[197]	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[198]	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[199]	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[200]	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[40]	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[201]	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[202]	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[203]	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[204]	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[205]	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[206]	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[207]	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[41]	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[208]	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[209]	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[210]	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[211]	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[212]	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[213]	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[214]	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[215]	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[216]	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[138]	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[139]	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 2007 model

Data source	F0→F1	F1→F2	F2→F3	F3→F4
PTCC only*	0.032 (0.027-0.036)	0.137 (0.091-0.184)	0.150 (0.085-0.215)	0.097 (0.040-0.154)
Literature (unadjusted)[§]	0.117 (0.104-0.130)	0.085 (0.075-0.096)	0.120 (0.109-0.133)	0.116 (0.104-0.129)
Literature (adjusted)[±]	0.117 (0.107, 0.127)	0.085 (0.078, 0.093)	0.121 (0.112, 0.130)	0.115 (0.107, 0.123)
Literature and PTCC[†]	0.066 (0.051-0.084)	0.104 (0.082-0.133)	0.162 (0.130-0.202)	0.184 (0.133-0.253)

*Estimation based on non-hemophilic cohort without HIV infection and who had first blood transfusion between 1986 and 1990.
[§]Literature-derived pooled estimates based on data in Table 4.2.3.
[±]Literature-derived pooled stage-specific transition probabilities from 111 studies, adjusted for the effect of study design, setting and population, publication year, age at hepatitis C virus infection (mean 25.5 years), duration of infection (17.5 years), and mean proportions of male gender (62%), injecting drug use (41%), blood transfusion (31%), excess alcohol consumption (19%), HIV positivity (2%), HCV RNA positivity (95%), and genotype 1 (54%).
[†]Literature and PTCC cohort transition probabilities combined. PTCC cohort treated as a retrospective-prospective design and conducted in a non-clinical setting (literature-derived data); age at HCV infection, 41 years (PTCC cohort data); duration of infection, 20 years (PTCC cohort data); mode of HCV acquisition: injecting drug use, 0% and blood transfusion, 100%; (PTCC cohort data) excess alcohol use, 19% (literature-derived data); HCV RNA positivity, 0.75 (PTCC cohort data); and genotype-1, 45% (literature-derived data)
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[217]	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[45]	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[218]	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[51]	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[219]	RCT	20	F1-F4		PEG-IFN alfa-2a 180 µg plus ribavirin (n=20)	24 wks	At 48 wks: 50%
Jeffers, 2004[220]	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[221]	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[222]	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[223]	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[224]	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[225]	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[226]	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[54]	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[56]	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[227]	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[228]	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[46]	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[229]	RCT	32	F1-F4		PEG-IFN alfa-2a 180 µg plus ribavirin (n=14)	48 wks	At 72 wks: 50%
Alfaleh, 2004[230]	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[231]	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 [52]	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[232]	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[233]	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[234]	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[235]	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[236]	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[237]	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[238]	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[239]	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[240]	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[241]	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[242]	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[243]	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[244]	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[245]	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[246]	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[247]	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[248]	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[249]	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[250]	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[251]	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[252]	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%

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[33]	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[253]	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[55]	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[254]	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[255]	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[256]	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[257]	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[258]	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[46]	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[51]	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[229]	RCT	32	F1-F4		Peginterferon alfa-2a 180 µg plus ribavirin	14	48 wks	At 72 wks: 50%
Alfaleh, 2004[230]	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 [52]	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[236]	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[243]	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%

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
Krawitt, 2006[221]	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%
Mimidis, 2006[245]	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[222]	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[53]	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[54]	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[55]	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[56]	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%

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
Crespo, 2007[253]	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
[46,51,52,221,222,229,230,236,245]	9	HCV monoinfection	F1-F4	0.57 (0.54-0.59)	0.56 (0.50-0.61)
[46,51-54,56,221,222,229,230,236,245,253]	14	HCV monoinfection + HIV/HCV coinfection	F1-F4	0.51 (0.49-0.54)	0.49 (0.42-0.56)
[46,52,221]	3	HCV monoinfection	F0-F1	0.61 (0.57-0.65)	0.60 (0.52-0.68
[46,51,52,55,221,243]	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)[259]. 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	[19]
	>30/≤30	2313		2.3-27.1[†]	[84]
Sex	Male/Female		All paths	1.39	[19]
		2313		1.0-2.0	[84]
				1.08	[61]
Alcohol	<50g/none			1.14	[19]
	≥50g/none			1.34	[19]
	>50g/≤50 g/d			1.3-4.5	[84]
	>50g/≤50 g/d	2313		1.61	[61]
HIV co-infection	Yes/No	157	F4 to ESLD	3.74	[19]
	Yes/No	244	F0 to F4	1.44	[59]
	Yes/No	310	F0 to liver-related death	7.0	[260]
	Yes/No	1816	HIV seroconversion to ESLD/death	7.9 (4.2-15.2)	[261]
		183	HIV seroconversion to liver failure	21.4 (2.6-174.5)	[75]
		157	F0 to ESLD	3.7 (1.3-11.1)	[67]
ALT	≥45/<45	204	All paths	2.10	[39]
				1.23	[61]
HAI	>6			1.22	[61]

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[75]		0.0054 (20 yr: 10.8%)*				
Darby, 1997[90§]	0.0009 (25 yr: 2.2%)			0.0068 (25 yr: 17.1%)		
Benhamou,1999[59†]			0.106			0.153
Yee, 2000[77]	0.0023 (13.3 yr: 3.0%)			0.0158 (13.3 yr: 21.0%)		
Ragni, 2001[262]		0.0041 (24 yr: 9.7%)			0.0054 (24year: 12.9%)	
Goedert, 2002[263]		0.0088 (16 yr: 14.0%)				
Arnold, 2007[91]	0.0005 (21 yr: 1.1%)			0.0042 (21 yr: 8.8%)		
Krahn, 1999[264]	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[90‡]	3647	25529.0	All cause	200 (5.5)	7.0	1218	8526.0	401 (32.9)	6.0 (5.1-7.1)	
Darby, 1997[90‡]	3647	25529.0	Non-liver	170 (4.7)	7.0	1218	8526.0	351 (28.8)	6.2 (5.1-7.4)	
Soucie, 2000[88]	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[77]	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[77]	185	2460.5	Non-liver	10 (5.4)	13.3	125	1662.5	51 (40.8)	7.5 (3.8-14.9)	
Ragni, 2001[262]	72	1728.0	All cause	21 (29.2)	24.0	85	2040.0	62 (72.9)		3.8 (1.2-12.2)[†]
Arnold, 2007[91]	712	14952.0	All cause	58 (8.1)	21.0	444	9324.0	207 (46.6)	5.7 (4.3-7.7)	
Arnold, 2007[91]	712	14952.0	Non-liver	50 (7.0)	21.0	444	9324.0	168 (37.8)	5.4 (3.9-7.4)	
Darby, 2004[265]	6004	126084.0	All cause	848 (14.1)	21.0	1246	26166	802 (64.4)	4.6 (4.1-5.0)	
Goedert, 2002[263]	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[266]	349	5.8	95	2024.2	27.3	0.047
Imberti, 1993[267§]	228	3.7	43	843.6	18.9	0.051
Mandelli, 1994[268§]	396	4.2	57	1663.2	14.3	0.034
Nishiguchi, 1995[269]	45	5.5	17	247.5	38.0	0.069
Takano, 1995[270]	124	6.1	5	756.4	4.0	0.007
Bruno, 1997[271‡]	163	5.3	22	863.9	13.3	0.025
Fattovich, 1997[106‡]	384	5.1	29	1958.4	7.6	0.015
Gentilini, 1997[272§]	405	8.0	32	3240.0	7.9	0.010
Tsai, 1997[273§]	400	3.0	80	1185.0	20.0	0.068
del Olmo, 1998[108]	967	5.0	64	3048.0	6.6	0.021
Niederau, 1998[274]	141	4.0	13	588.0	9.2	0.022
Serfaty, 1998[103]	103	3.0	11	343.0	10.7	0.032
Chairamonte, 1999[275]	166	5.5	42	913.0	25.3	0.046
Hu, 1999[82‡]	112	4.5	11	504.0	9.5	0.021
Degos, 2000 [105‡]	416	5.0	60	2080.0	14.7	0.029
Fattovich, 2002[276]	136	6.8	23	924.8	16.9	0.025
Planas, 2004[277†]	200	2.8	33	560.0	16.5	0.059
Bruno, 2007[278±]	69	6.0	9	414.0	13.0	0.022
Pooled annual rate*						
Fixed effects model						0.020 (0.018-0.022)
Random effects model						0.031 (0.024-0.038)

[§]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.
* 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.* [15,16]

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[279]

Table 5.3.1. Baseline clinical and serological features of post-transfusion claimant cohort, 2007

Characteristics	Male		Female		Total	
	N=3112	62.2%	N=1892	37.8%	N=5004	
	N	%*	N	%*	N	%*
Survival status at 2007						
Alive	2181	70.1	1592	84.1	3773	75.4
Dead	931	29.9	300	15.9	1231	24.6
Biopsy evidence						
Yes	638	20.5	444	23.5	1082	21.6
No	2474	79.5	1448	76.5	3922	78.4
Level of compensation‡						
Level 1	429	15.8	378	20.6	807	17.7
Level 2	869	32.0	657	35.7	1526	33.5
Level 3	736	27.1	462	25.1	1198	26.3
Level 4	156	5.7	105	5.7	261	5.7
Level 5	217	8.0	102	5.5	319	7.0
Level 6	312	11.5	134	7.3	446	9.8
Missing	393	---	54	---	447	---
HCV antibody†						
Positive	2049	93.9	1346	93.3	3395	93.7
Negative	134	6.1	96	6.7	230	6.3
Unknown	929	---	450	---	1379	---
HCV RNA§						
Positive	1507	92.9	984	93.4	2491	93.1
Negative	116	7.1	69	6.6	185	6.9
Unknown	1489	---	839	---	2328	---
HCV therapy						
Yes	659	21.2	421	22.3	1080	21.6
No	2453	78.8	1471	77.7	3924	78.4
HIV Positive						
Yes	523	17.8	13	0.7	536	11.4
No	2395	81.5	1720	98.2	4115	87.8
Indeterminate	19	0.6	18	1	37	0.8
Missing	175	---	141	---	316	---
Hemophilics						
Yes	1157	37.2	148	7.8	1305	26.1
No	1955	62.8	1744	92.2	3699	73.9
Blood transfusion						
Yes	1933	62.1	1716	90.7	3649	72.9
No	1179	37.9	176	9.3	1355	27.1

Table 5.3.1. Baseline clinical and serological features of post-transfusion claimant cohort, 2007 (continued)

Characteristics	Male		Female		Total	
	N=3112	62.2%	N=1892	37.8%	N=5004	
	N	%*	N	%*	N	%*
Age at first blood transfusion (yr)						
0-9	142	7.4	100	5.9	242	6.7
10-19	106	5.5	122	7.2	228	6.3
20-29	250	13.1	356	20.9	606	16.8
30-39	313	16.4	363	21.3	676	18.7
40-49	296	15.5	263	15.5	559	15.5
50-59	348	18.2	208	12.2	556	15.4
60-69	359	18.8	194	11.4	553	15.3
70+	98	5.1	96	5.6	194	5.4
Missing	1200	---	190	---	1390	---
Year at first blood transfusion						
<1986	263	13.8	293	17.2	556	15.4
1986	371	19.4	330	19.4	701	19.4
1987	394	20.6	339	19.9	733	20.3
1988	366	19.1	309	18.1	675	18.7
1989	371	19.4	312	18.3	683	18.9
1990	147	7.7	120	7	267	7.4
Missing	1200	---	189	---	1389	---
Number of blood transfusions, 1986-1990						
1	654	34.2	592	34.8	1246	34.5
2	474	24.8	490	28.8	964	26.7
3	310	16.2	239	14	549	15.2
4	188	9.8	144	8.5	332	9.2
5	112	5.9	85	5	197	5.4
>5	174	9.1	153	9	327	9
Missing	1200	---	189	---	1389	---
Risk factor						
Underlying condition						
Duration of HCV infection, mean (SD) years						
Current age, mean (SD) years (among alive: n=3773)	52.5 (18.7)		56.1 (17.4)		54.0 (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: comparison between hemophilics and non-hemophilics

Characteristics	Total	Hemophilics		non-Hemophilics		Statistical test	
	N=5004	N=1305		N=3699			
	N	N	%*	N	%*	Chi	P
Sex							
Male	3112	1157	88.7	1955	52.9	526	<.0001
Female	1892	148	11.3	1744	47.1	---	---
Survival status at 2007							
Alive	3773	904	69.3	2869	77.6	35.7	<.0001
Dead	1231	401	30.7	830	22.4	---	---
Biopsy evidence							
Yes	1082	225	17.2	857	23.2	20.0	<.0001
No	3922	1080	82.8	2842	76.8	---	---
Level of compensation							
Level 1	807	145	14.1	662	18.7	99.5	<.0001
Level 2	1526	251	24.5	1275	36.1	---	---
Level 3	1198	358	34.9	840	23.8	---	---
Level 4	261	68	6.6	193	5.5	---	---
Level 5	319	104	10.1	215	6.1	---	---
Level 6	446	100	9.7	346	9.8	---	---
Missing	447	279	---	168	---	---	---
HCV-antibody[†]							
Positive	3395	773	93.9	2622	93.6	0.1	0.7183
Negative	230	50	6.1	180	6.4	---	---
Unknown	1379	482	---	897	---	---	---
HCV RNA[§]							
Positive	2491	609	92.8	1882	93.2	0.1	0.7702
Negative	185	47	7.2	138	6.8	---	---
Unknown	2328	649	---	1679	---	---	---
HCV therapy							
Yes	1080	315	24.1	765	20.7	6.8	0.0091
No	3924	990	75.9	2934	79.3	---	---
HIV Positive							
Yes	536	523	41.0	13	0.4	1495.4	<.0001
No	4115	754	59.0	3361	99.6	---	---
Missing	353	28	---	325	---	---	---

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

Characteristics	Total N=5004	Hemophilics N=1305		non-Hemophilics N=3699		Statistical test	
	N	N	%*	N	%*	Chi	P
Age at first blood transfusion (yr)							
0-9	242	---	---	242	6.7	---	---
10-19	228	---	---	228	6.3	---	---
20-29	606	---	---	606	16.8	---	---
30-39	676	---	---	676	18.7	---	---
40-49	559	---	---	559	15.5	---	---
50-59	556	---	---	556	15.4	---	---
60-69	553	---	---	553	15.3	---	---
70+	194	---	---	194	5.4	---	---
Missing	1390	1305	---	85	---	---	---
Year at first blood transfusion							
<1986	556	---	---	556	15.4	---	---
1986	701	---	---	701	19.4	---	---
1987	733	---	---	733	20.3	---	---
1988	675	---	---	675	18.7	---	---
1989	683	---	---	683	18.9	---	---
1990	267	---	---	267	7.4	---	---
Missing	1389	1305	---	84	---	---	---
Number of transfusions, 1986-1990							
1	1246	---	---	1246	34.5	---	---
2	964	---	---	964	26.7	---	---
3	549	---	---	549	15.2	---	---
4	332	---	---	332	9.2	---	---
5	197	---	---	197	5.4	---	---
>5	327	---	---	327	9	---	---
Missing	1389	1305	---	84	---	---	---
Among alive cohort (N=3773)							
HIV Positive							
Yes	218	210	23.8	8	0.3	623.7	<.0001
No	3289	674	76.2	2615	99.7	---	---
Missing	266	20	---	246	---	---	---
Sex							
Male	2181	770	85.2	1411	49.2	365.2	<.0001
Female	1592	134	14.8	1458	50.8	---	---
Current age, mean (SD) years	54.0 (18.2)	44.3 (13.8)		57.1 (18.4)		T=-22.3	<.0001

*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	-2.656	0.194	188.27	<.0001
Age	1	-0.006	0.003	4.86	0.0275
Gender – female	1	0.120	0.047	6.56	0.0105
Current compensation level§					
Level 1	1	-1.660	0.204	66.47	<.0001
Level 2	1	-2.867	0.249	132.34	<.0001
Level 3	1	1.613	0.116	192.03	<.0001
Level 4-6 (ref)		1.000			
HCV treatment – yes	1	0.166	0.097	2.95	0.0858
Deceased at 2007 – yes	1	0.621	0.064	95.24	<.0001
Hemophilic, transfused – yes	1	-0.427	0.055	60.14	<.0001

*Probability of having received a liver biopsy (see text section 5.4 for details of propensity score method).
†Based on 4,900 post-transfusion claimants.
§Level 1, HCV antibody positive (fibrosis 0); Level 2, HCV RNA positivity (fibrosis 0); Level 3, non-bridging fibrosis (fibrosis 1/2); Level 4, bridging fibrosis (fibrosis 3); Level 5, cirrhosis, unresponsive porphyria cutanea tarda, unresponsive thrombocytopenia (fibrosis 4); Level 6, liver transplant, decompensation of the liver, hepatocellular carcinoma, B-cell lymphoma, symptomatic mixed cryoglobulinemia, glomerulonephritis, renal failure.
df, degrees of freedom; SE, standard error; HCV, hepatitis C virus.

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

Stage	Propensity score<0.4		Propensity score 0.4-0.6		Propensity score≥0.6		Adjusted*	
	No LB	With LB	No LB	With LB	No LB	With LB	N	%
RNA- F0	704	1	---	---	---	---	705	24.57
RNA+ F0	811	4	---	---	---	---	815	28.41
F1/F2	83	3	380	314	53	33	700	24.38
F3	---	1	.---	7	---	169	343	11.97
Cirrhosis	15	---	1	5	28	129	178	6.20
Decompensated cirrhosis	2	2	---	1	30	13	48	1.67
Liver transplant	2	---	---	---	18	1	21	0.73
HCC	1	---	---	1	6	7	15	0.52
Other liver disease	17	---	1	1	24	1	44	1.53
Total	1635	11	382	329	159	353	2869	100

*Adjusted stage distribution using propensity score.
LB, liver biopsy; RNA, ribonucleic acid; HCC, hepatocellular carcinoma.

Table 5.3.5. Estimated stage distribution by propensity score: hemophilic patients

HCV stage	Propensity score<0.4		Propensity score 0.4-0.6		Propensity score≥0.6		Adjusted*	
	No LB	With LB	No LB	With LB	No LB	With LB	N	%
RNA- F0	146	---	---	---	---	---	146	16.15
RNA+ F0	207	---	---	---	---	---	207	22.90
F1/F2	29	1	271	55	---	---	206	22.81
F3	---	---	---	8	---	60	218	24.10
Cirrhosis	2	---	7	5	25	52	91	10.07
Decompensated cirrhosis	1	---	6	---	18	---	25	2.77
Liver transplant	---	---	1	---	2	---	3	0.33
HCC	---	---	1	---	3	---	4	0.44
Other liver disease	---	---	1	---	3	---	4	0.44
Total	385	1	287	68	51	112	904	100

*Adjusted stage distribution using propensity score.
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 2007

HCV stage	Observed						Adjusted*	
	Total	%	No liver biopsy	%	Liver biopsy	%	N	%
Survival status								
Alive	3773		2899		874			
Deceased	1231		1023		208			
Total alive	3773		2899		874		3773	
RNA- F0	851	22.55	850	29.32	1	0.11	851	22.55
RNA+ F0	1022	27.09	1018	35.12	4	0.46	1022	27.09
F1/F2	1222	32.39	816	28.15	406	46.45	906	24.01
F3	245	6.49	0	0.00	245	28.03	561	14.87
Cirrhosis	269	7.13	78	2.69	191	21.85	269	7.13
Decompensated cirrhosis	73	1.93	57	1.97	16	1.83	73	1.93
Liver transplant	24	0.64	23	0.79	1	0.11	24	0.64
HCC	19	0.50	11	0.38	8	0.92	19	0.50
Other liver disease	48	1.27	46	1.59	2	0.23	48	1.27

*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 2007

HCV stage	Observed						Adjusted	
	Total	%	No liver biopsy	%	Liver biopsy	%	N	%
Survival status								
Alive	2869		2176		693			
Deceased	830		666		164			
Total alive	2869		2176		693		2869	
RNA- F0	705	24.57	704	32.35	1	0.14	705	24.57
RNA+ F0	815	28.41	811	37.27	4	0.58	815	28.41
F1/F2	866	30.18	516	23.71	350	50.51	700	24.38
F3	177	6.17	---	---	177	25.54	343	11.97
Cirrhosis	178	6.20	44	2.02	134	19.34	178	6.20
Decompensated cirrhosis	48	1.67	32	1.47	16	2.31	48	1.67
Liver transplant	21	0.73	20	0.92	1	0.14	21	0.73
HCC	15	0.52	7	0.32	8	1.15	15	0.52
Other liver disease	44	1.53	42	1.93	2	0.29	44	1.53

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

Table 5.4.3. Observed and estimated stage distribution of living hemophilics, August 2007

HCV stage	Observed						Adjusted	
	Total	%	No liver biopsy	%	Liver biopsy	%	N	%
Survival status								
Alive	904		723		181			
Deceased	401		357		44			
Total alive	904		723		181		904	
RNA- F0	146	16.15	146	20.19	---	---	146	16.15
RNA+ F0	207	22.9	207	28.63	---	---	207	22.90
F1/F2	356	39.38	300	41.49	56	30.94	206	22.81
F3	68	7.52	---	---	68	37.57	218	24.10
Cirrhosis	91	10.07	34	4.7	57	31.49	91	10.07
Decompensated cirrhosis	25	2.77	25	3.46	---	---	25	2.77
Liver transplant	3	0.33	3	0.41	---	---	3	0.33
HCC	4	0.44	4	0.55	---	---	4	0.44
Other liver disease	4	0.44	4	0.55	---	---	4	0.44

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 2007

	<20	20+	30+	40+	50+	60+	70+	80+	90+	Total
HCV stage	N=60	N=165	N=218	N=579	N=591	N=445	N=441	N=293	N=77	N=2869
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N
RNA- F0	9.0 (15.0)	39.0 (23.6)	62.0 (28.4)	142.0 (24.5)	125.0 (21.2)	97.0 (21.8)	110.0 (24.9)	90.0 (30.7)	31.0 (40.3)	705
RNA+ F0	26.0 (43.3)	61.0 (37.0)	41.0 (18.8)	131.0 (22.6)	144.0 (24.4)	116.0 (26.1)	138.0 (31.3)	119.0 (40.6)	39.0 (50.6)	815
F1/F2	15.4 (25.7)	40.3 (24.4)	69.8 (32.0)	181.9 (31.4)	163.1 (27.6)	108.1 (24.3)	79.9 (18.1)	38.3 (13.1)	3.4 (4.4)	700
F3	7.6 (12.6)	19.7 (12.0)	34.2 (15.7)	89.1 (15.4)	79.9 (13.5)	52.9 (11.9)	39.1 (8.9)	18.7 (6.4)	1.6 (2.1)	343
F4 (Cirrhosis)	0.0 (0.0)	1.0 (0.6)	6.0 (2.8)	16.0 (2.8)	52.0 (8.8)	43.0 (9.7)	46.0 (10.4)	12.0 (4.1)	2.0 (2.6)	178
Decompensated cirrhosis	0.0 (0.0)	2.0 (1.2)	2.0 (0.9)	3.0 (0.5)	9.0 (1.5)	10.0 (2.2)	17.0 (3.9)	5.0 (1.7)	0.0 (0.0)	48
Liver transplant	1.0 (1.7)	0.0 (0.0)	1.0 (0.5)	3.0 (0.5)	6.0 (1.0)	4.0 (0.9)	4.0 (0.9)	2.0 (0.7)	0.0 (0.0)	21
HCC	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.2)	2.0 (0.3)	5.0 (1.1)	4.0 (0.9)	3.0 (1.0)	0.0 (0.0)	15
Other liver disease	1.0 (1.7)	2.0 (1.2)	2.0 (0.9)	12.0 (2.1)	10.0 (1.7)	9.0 (2.0)	3.0 (0.7)	5.0 (1.7)	0.0 (0.0)	44

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 2007

	<20 yr	20+	30+	40+	50+	60+	70+	80+	90+	Total
HCV stage	N=1	N=126	N=240	N=254	N=159	N=72	N=38	N=11	N=3	N=904
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N
RNA- F0	0.0 (0.0)	39.0 (31.0)	37.0 (15.4)	32.0 (12.6)	17.0 (10.7)	7.0 (9.7)	11.0 (28.9)	2.0 (18.2)	1.0 (33.3)	146
RNA+ F0	1.0 (100.0)	31.0 (24.6)	53.0 (22.1)	57.0 (22.4)	33.0 (20.8)	14.0 (19.4)	11.0 (28.9)	5.0 (45.5)	2.0 (66.7)	207
F1/F2	0.0 (0.0)	24.3 (19.3)	58.8 (24.5)	61.7 (24.3)	38.4 (24.1)	16.0 (22.3)	5.3 (14.1)	1.5 (13.3)	0.0 (0.0)	206
F3	0.0 (0.0)	25.7 (20.4)	62.2 (25.9)	65.3 (25.7)	40.6 (25.5)	17.0 (23.6)	5.7 (14.9)	1.5 (14.0)	0.0 (0.0)	218
F4 (Cirrhosis)	0.0 (0.0)	5.0 (4.0)	24.0 (10.0)	29.0 (11.4)	17.0 (10.7)	12.0 (16.7)	3.0 (7.9)	1.0 (9.1)	0.0 (0.0)	91
Decompensated cirrhosis	0.0 (0.0)	1.0 (0.8)	3.0 (1.3)	7.0 (2.8)	7.0 (4.4)	5.0 (6.9)	2.0 (5.3)	0.0 (0.0)	0.0 (0.0)	25
Liver transplant	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	3.0 (1.9)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	3
HCC	0.0 (0.0)	0.0 (0.0)	1.0 (0.4)	1.0 (0.4)	1.0 (0.6)	1.0 (1.4)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	4
Other liver disease	0.0 (0.0)	0.0 (0.0)	1.0 (0.4)	1.0 (0.4)	2.0 (1.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	4

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 2007

	<20 yr	20+	30+	40+	50+	60+	70+	80+	90+	Total
HCV stage	N=31	N=223	N=323	N=459	N=391	N=265	N=288	N=167	N=34	N=2181
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
RNA- F0	6.0 (19.4)	57.0 (25.6)	59.0 (18.3)	88.0 (19.2)	69.0 (17.6)	44.0 (16.6)	65.0 (22.6)	47.0 (28.1)	10.0 (29.4)	445 (20.4)
RNA+ F0	16.0 (51.6)	71.0 (31.8)	71.0 (22.0)	96.0 (20.9)	82.0 (21.0)	60.0 (22.6)	98.0 (34.0)	68.0 (40.7)	19.0 (55.9)	581 (26.6)
F1/F2	5.6 (18.1)	53.7 (24.1)	99.4 (30.8)	140.8 (30.7)	106.2 (27.2)	63.6 (24.0)	49.4 (17.2)	20.4 (12.2)	1.9 (5.6)	541 (24.8)
F3	3.4 (11.0)	33.3 (14.9)	61.6 (19.1)	87.2 (19.0)	65.8 (16.8)	39.4 (14.9)	30.6 (10.6)	12.6 (7.5)	1.1 (3.2)	335 (15.4)
F4 (Cirrhosis)	0.0 (0.0)	4.0 (1.8)	25.0 (7.7)	32.0 (7.0)	43.0 (11.0)	37.0 (14.0)	28.0 (9.7)	10.0 (6.0)	2.0 (5.9)	181 (8.3)
Decompensated cirrhosis	0.0 (0.0)	2.0 (0.9)	4.0 (1.2)	8.0 (1.7)	10.0 (2.6)	9.0 (3.4)	11.0 (3.8)	4.0 (2.4)	0.0 (0.0)	48 (2.2)
Liver transplant	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	6.0 (1.5)	4.0 (1.5)	1.0 (0.3)	1.0 (0.6)	0.0 (0.0)	12 (0.6)
HCC	0.0 (0.0)	0.0 (0.0)	1.0 (0.3)	1.0 (0.2)	1.0 (0.3)	3.0 (1.1)	3.0 (1.0)	1.0 (0.6)	0.0 (0.0)	10 (0.5)
Other liver disease	0.0 (0.0)	2.0 (0.9)	2.0 (0.6)	6.0 (1.3)	8.0 (2.0)	5.0 (1.9)	2.0 (0.7)	3.0 (1.8)	0.0 (0.0)	44 (2.0)

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 2007

	<20 yr	20+	30+	40+	50+	60+	70+	80+	90+	Total
HCV stage	N=30	N=68	N=135	N=374	N=359	N=252	N=191	N=137	N=46	N=1592
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
RNA- F0	3.0 (10.0)	21.0 (30.9)	40.0 (29.6)	86.0 (23.0)	73.0 (20.3)	60.0 (23.8)	56.0 (29.3)	45.0 (32.8)	22.0 (47.8)	406 (25.5)
RNA+ F0	11.0 (36.7)	21.0 (30.9)	23.0 (17.0)	92.0 (24.6)	95.0 (26.5)	70.0 (27.8)	51.0 (26.7)	56.0 (40.9)	22.0 (47.8)	441 (27.7)
F1/F2	8.6 (28.7)	14.2 (20.9)	39.5 (29.3)	105 (28.1)	92.6 (25.8)	56.2 (22.3)	30.9 (16.2)	16.7 (12.2)	1.2 (2.6)	365 (22.9)
F3	5.4 (18.0)	8.8 (12.9)	24.5 (18.1)	65 (17.4)	57.4 (16.0)	34.8 (13.8)	19.1 (10.0)	10.3 (7.5)	0.8 (1.7)	226 (14.2)
F4 (Cirrhosis)	0.0 (0.0)	2.0 (2.9)	5.0 (3.7)	13.0 (3.5)	26.0 (7.2)	18.0 (7.1)	21.0 (11.0)	3.0 (2.2)	0.0 (0.0)	88 (5.5)
Decompensated cirrhosis	0.0 (0.0)	1.0 (1.5)	1.0 (0.7)	2.0 (0.5)	6.0 (1.7)	6.0 (2.4)	8.0 (4.2)	1.0 (0.7)	0.0 (0.0)	25 (1.6)
Liver transplant	1.0 (3.3)	0.0 (0.0)	1.0 (0.7)	3.0 (0.8)	3.0 (0.8)	0.0 (0.0)	3.0 (1.6)	1.0 (0.7)	0.0 (0.0)	12 (0.8)
HCC	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (0.3)	2.0 (0.6)	3.0 (1.2)	1.0 (0.5)	2.0 (1.5)	0.0 (0.0)	9 (0.6)
Other liver disease	1.0 (3.3)	0.0 (0.0)	1.0 (0.7)	7.0 (1.9)	4.0 (1.1)	4.0 (1.6)	1.0 (0.5)	2.0 (1.5)	0.0 (0.0)	20 (1.3)

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 2007 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			[29]
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 2007	RNA-	pRNAnegative	0.226			Table 5.4.1
Transition from RNA+ to RNA- (without treatment)	RNA+→RNA-	PRNApostoRNAneg	0.020	0.013	0.027	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	0.066	0.051	0.084	Table 4.2.1-4.2.4
Transition from Fibrosis stage 1 to stage 2	F1→F2	pFibrosis1toFibrosis2	0.104	0.082	0.133	Table 4.2.1-4.2.4
Transition from Fibrosis stage 2 to stage 3	F2→F3	pFibrosis2toFibrosis3	0.162	0.130	0.202	Table 4.2.1-4.2.4
Transition from Fibrosis stage 3 to stage 4	F3→Cirr.	pFibrosis3toFibrosis4	0.184	0.133	0.253	Table 4.2.1-4.2.4
Transition from Fibrosis stage 4 (Cirrhosis) to liver decompensation	Cirr.→Dec.	PFibrosis4toDecom.	0.055	0.040	0.092	[13,14]
Transition from Decomp. cirrhosis to Liver transplantation	Dec.→Transp	pDecomCtoTransp	0.033	0.017	0.049	1998 Report Table 1
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	0.031	0.024	0.038	[13,14]; Table 4.4.1
HCC to death	HCC →Death	pHCCtoDeath	0.605	0.545	0.676	[13,14]
Liver transplantation to Death (first year)	Tran.→Death	pTransptoFail	0.169	0.127	0.210	1998 Report Table 1
Liver transplantation to Death (after first year)			0.034	0.024	0.043	1998 Report Table 1
Decompensation to liver death	Dec.→Death	PDecomCtoDeath	0.138	0.074	0.202	1998 Report Table 1
HCV treatment:						
Proportion eligible for treatment <65: 0.14*0.60 (0.52-0.68)[#]	RNA+ to F1	Treateffect1	0.084	0.073	0.095	Tables 4.3.1.1-4.3.1.2
0.80*0.49 (0.42-0.56)[#]	F1 to F2 F2 to F3 F3 to F4	Treateffect2	0.392	0.336	0.448	
0.75*0.25[#]	F4 to Decomp.	Treateffect3	0.188	0.038	0.334	
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	Table 4.3.3; Figure 4.3.3
Excess mortality associated with HIV infection			6.24	5.43	7.18	Table 4.3.4.2

#Product of the proportion of patients eligible for treatment and the response rate. Treatment rates were updated based on the Hepatologists survey in 2002. Response rate was updated based on the literature.

Table 7.1. Model validation: observed and predicted liver disease among living post-transfusion claimant cohort at August 2007

HCV stage	Observed-Adjusted†		Predicted*
	Total (%)	Non-hemophilics (%)	Non-hemophilics (%)
F0	49.64	52.98	51.78
F1/F2	24.01	24.38	30.85
F3	14.87	11.97	7.82
Cirrhosis	7.13	6.20	7.84
Decompensated cirrhosis	1.93	1.67	1.21
Liver transplant	0.64	0.73	0.11
HCC	0.50	0.52	0.38
Other liver disease	1.27	1.53	---

†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 age and sex of post-transfusion claimant cohort and literature-derived fibrosis stage transition rates with updated parameters: acute HCV RNA- 0.20; RNA+→RNA- 0.017; F0→F1 0.066; F1→F2 0.104; F2→F3 0.166; F3→F4 0.184; F4→HCC 0.035; and HCC→liver-related death 0.605.

HCC, hepatocellular carcinoma.

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

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

*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 and 2007 models

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

*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, and 2007. Numbers in the brackets are for entire transfused population.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	9.8	13.6	25.5	32.4	36.6	38.4	39.3
HCC	0.5	3.3	6.4	8.8	10.1	10.8	10.9
Liver transplant	0.6	0.7	1.3	2.0	2.4	2.7	2.9
Non-liver-related death	---	4.3	23.1	39.0	52.7	63.7	70.8
Liver-related death	---	1.2	7.8	14.5	19.4	22.2	23.5
All cause death	---	5.5	30.9	53.5	72.1	85.9	94.3
Sex distribution (%)							
Female	---	42.7	44.1	45.2	46.5	48.5	49.2
Age distribution (%)							
25 yr	9.3	9.6	2.2	---	---	---	---
35 yr	12.2	12.4	9.6	3.1	---	---	---
45 yr	22.1	22.8	14.8	12.4	4.6	---	---
55 yr	19.9	20.4	27.4	18.2	17.2	8.0	---
65 yr	13.7	13.9	23.1	32.2	23.2	26.7	16.1
75 yr	12.7	12.5	13.7	23.6	36.1	29.8	43.2
85 yr	8.0	7.0	7.8	9.0	16.9	31.2	30.3
95 yr	2.1	1.3	1.3	1.5	1.9	4.3	10.4
Stage distribution (%)†							
RNA- F0	22.9	24.0	29.4	34.5	39.8	45.9	52.6
RNA+ F0	27.4	23.3	11.2	5.5	3.0	1.8	1.0
Fibrosis 1	14.4	16.0	17.2	15.3	13.1	10.7	8.7
Fibrosis 2	10.0	10.0	9.9	9.7	8.7	8.1	6.8
Fibrosis 3	15.1	13.8	11.4	10.5	9.6	8.4	7.6
Cirrhosis	7.2	10.1	15.6	17.3	17.8	16.7	14.5
Decompensated cirrhosis	2.0	2.2	3.8	4.6	4.9	4.9	4.8
Liver transplant	0.6	0.1	0.8	1.5	2.3	2.8	3.1
HCC	0.5	0.4	0.8	0.9	1.0	0.8	1.1

Best estimates for all parameters. Starting distribution: observed stage distribution, August 2007.
*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.
HCC, hepatocellular carcinoma; RNA, ribonucleic acid.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)							
Cirrhosis	8.7	11.6	21.9	28.5	32.4	34.1	34.8
HCC	0.5	2.9	5.5	7.7	8.9	9.5	9.6
Liver transplant	0.7	0.7	1.2	1.8	2.1	2.4	2.5
Non-liver-related death	---	4.9	25.9	42.8	56.9	67.8	74.5
Liver-related death	---	1.1	6.5	12.1	16.4	18.9	20.0
All cause death	---	6.0	32.4	54.9	73.3	86.7	94.5
Sex distribution (%)							
Female	---	51.5	53.1	54.4	55.9	57.8	58.2
Age distribution (%)							
25 yr	7.8	8.1	2.9	---	---	---	---
35 yr	7.6	7.8	7.6	4.0	---	---	---
45 yr	20.2	21.0	10.0	10.3	6.0	---	---
55 yr	20.6	21.4	26.5	13.2	15.0	10.5	---
65 yr	15.5	15.8	25.3	32.8	18.2	24.4	21.1
75 yr	15.4	15.2	16.2	26.9	38.5	25.3	40.3
85 yr	10.2	9.0	9.8	10.9	19.8	34.6	26.6
95 yr	2.7	1.7	1.7	1.9	2.4	5.2	12.0
Stage distribution (%)							
RNA- F0	25.0	26.2	31.5	36.6	41.8	48.2	55.0
RNA+ F0	28.8	24.7	11.9	5.7	3.0	1.8	1.1
Fibrosis 1	14.8	16.5	17.8	15.7	13.2	10.6	8.6
Fibrosis 2	10.0	10.0	10.1	9.9	8.7	8.2	6.8
Fibrosis 3	12.2	11.7	10.4	9.7	9.0	7.7	7.3
Cirrhosis	6.3	8.5	13.9	16.2	17.0	15.7	13.1
Decompensated cirrhosis	1.7	1.8	3.1	4.1	4.5	4.7	4.5
Liver transplant	0.7	0.1	0.6	1.2	1.9	2.4	2.6
HCC	0.5	0.4	0.7	0.9	1.0	0.7	1.1

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)							
Cirrhosis	13.2	19.9	36.7	44.9	49.7	52.2	53.4
HCC	0.4	4.7	9.3	12.4	14.1	15.0	15.2
Liver transplant	0.3	0.5	1.7	2.8	3.5	3.8	4.0
Non-liver-related death	---	2.6	14.4	26.8	39.2	50.6	58.9
Liver-related death	---	1.4	11.9	22.2	29.0	32.8	34.6
All cause death	---	4.1	26.3	49.0	68.2	83.3	93.5
Sex distribution (%)							
Female	---	14.8	15.6	16.2	16.9	18.9	20.6
Age distribution (%)							
25 yr	14.0	14.4	0.1	---	---	---	---
35 yr	26.5	27.1	16.0	0.1	---	---	---
45 yr	28.1	28.7	30.1	19.1	0.1	---	---
55 yr	17.6	17.4	30.3	33.9	24.2	0.1	---
65 yr	8.0	7.7	16.3	30.5	38.9	33.9	0.1
75 yr	4.2	3.8	5.6	13.2	28.7	44.2	52.3
85 yr	1.2	0.8	1.6	3.0	7.6	20.4	42.0
95 yr	0.3	0.1	0.1	0.2	0.5	1.4	5.5
Stage distribution (%)							
RNA- F0	16.2	17.2	22.6	28.0	33.5	38.6	44.8
RNA+ F0	23.0	19.0	8.8	5.0	2.9	1.6	0.8
Fibrosis 1	13.1	14.3	15.3	14.1	12.7	10.9	9.0
Fibrosis 2	9.8	9.8	9.3	9.2	8.5	7.9	6.9
Fibrosis 3	24.2	20.6	14.6	12.9	11.3	10.6	8.5
Cirrhosis	10.1	15.0	21.1	20.9	20.5	19.8	18.8
Decompensated cirrhosis	2.8	3.3	6.0	6.3	6.0	5.6	5.6
Liver transplant	0.3	0.2	1.3	2.5	3.5	3.9	4.5
HCC	0.4	0.6	1.1	1.1	1.0	1.1	1.2

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

Table 8.1.4. Hepatitis C prognosis by calendar year: Non-hemophilics, Age 10-19

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	0.2	4.7	17.3	28.4	37.0	42.5	46.8
Decompensated cirrhosis	0.0	0.1	3.1	8.0	13.0	17.2	20.4
HCC	0.0	1.4	4.9	8.9	12.7	15.8	17.1
Liver transplant	0.2	1.7	1.9	2.6	3.4	4.2	4.8
Non-liver-related death	---	0.1	0.7	1.3	2.5	5.2	10.5
Liver-related death	---	0.4	3.7	11.1	19.8	27.9	34.3
All cause death	---	0.4	4.3	12.4	22.3	33.0	44.8
Alive	---	99.6	95.7	87.6	77.7	67.0	55.2
Stage distribution (%)†							
RNA- F0	15.3	17.0	23.2	27.9	32.3	36.9	41.6
RNA+ F0	44.1	38.4	17.5	8.9	5.0	3.1	2.0
Fibrosis 1	14.9	18.0	22.6	21.7	20.5	19.2	16.4
Fibrosis 2	11.2	11.2	11.8	11.2	10.7	10.9	11.2
Fibrosis 3	12.9	12.3	11.3	10.9	9.9	9.2	9.2
Cirrhosis	0.0	2.9	11.0	14.8	15.8	14.6	13.5
Decompensated cirrhosis	0.0	0.1	1.9	3.2	3.7	3.6	3.5
Liver transplant	0.2	.	0.2	0.7	1.2	1.8	2.1
HCC	0.0	0.1	0.5	0.7	0.9	0.8	0.7

Best estimates for all parameters. Starting distribution: observed stage distribution, August 2007.
*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.
HCC, hepatocellular carcinoma; RNA, ribonucleic acid.

Note: Table 8.1.5. Hepatitis C prognosis by calendar year: hemophilics, Age 10-19 is not created because there is only a single hemophilic patient in this group

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	1.8	4.7	16.5	26.7	34.1	39.3	45.1
Decompensated cirrhosis	1.2	1.4	4.4	8.9	13.5	17.2	20.6
HCC	0.0	1.6	4.8	8.6	11.7	14.2	14.8
Liver transplant	0.0	0.1	0.4	1.1	1.9	2.6	3.1
Non-liver-related death	---	0.1	0.8	2.3	5.1	12.1	25.4
Liver-related death	---	0.3	4.3	10.8	18.9	25.4	31.0
All cause death	---	0.5	5.1	13.1	24.0	37.5	56.3
Alive	---	99.5	94.9	86.9	76.0	62.5	43.7
Stage distribution (%)†							
RNA- F0	23.9	25.5	31.4	35.9	40.9	45.6	51.0
RNA+ F0	37.4	31.9	14.7	7.3	4.2	2.3	1.1
Fibrosis 1	14.1	16.5	19.9	18.7	17.3	14.7	9.5
Fibrosis 2	10.6	10.2	10.6	10.0	9.4	9.6	7.7
Fibrosis 3	12.1	11.4	10.5	9.7	8.7	8.2	8.0
Cirrhosis	0.6	3.2	10.3	13.7	14.2	13.6	15.4
Decompensated cirrhosis	1.2	1.0	1.9	3.0	3.2	3.5	4.1
Liver transplant	0.0	0.1	0.3	0.8	1.4	1.8	2.4
HCC	0.0	0.1	0.5	0.7	0.7	0.6	0.7

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	4.8	10.2	25.4	33.9	39.2	42.9	46.9
Decompensated cirrhosis	0.8	1.3	7.8	13.9	18.2	21.3	23.7
HCC	0.0	3.0	7.0	10.5	13.0	14.8	15.2
Liver transplant	0.0	0.0	0.7	1.7	2.6	3.2	3.6
Non-liver-related death	---	0.3	2.2	5.2	10.9	21.4	35.9
Liver-related death	---	0.3	7.1	16.5	24.5	30.3	34.2
All cause death	---	0.7	9.3	21.7	35.4	51.7	70.1
Alive	---	99.3	90.7	78.3	64.6	48.3	29.9
Stage distribution (%)†							
RNA- F0	31.0	32.1	37.6	43.3	49.0	54.1	59.6
RNA+ F0	24.6	20.1	8.6	4.4	2.5	1.5	0.7
Fibrosis 1	11.0	12.6	13.9	12.8	11.9	10.1	6.9
Fibrosis 2	8.3	8.3	8.1	7.6	7.3	7.1	5.5
Fibrosis 3	20.4	17.0	12.0	10.7	9.5	8.6	6.7
Cirrhosis	4.0	8.6	14.6	14.5	13.1	12.2	13.5
Decompensated cirrhosis	0.8	1.0	4.0	4.5	3.9	3.4	3.8
Liver transplant	0.0	0.0	0.6	1.4	2.1	2.3	2.5
HCC	0.0	0.3	0.8	0.8	0.8	0.6	0.8

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	4.2	7.8	22.7	32.8	39.6	46.1	48.7
Decompensated cirrhosis	0.9	1.2	5.4	10.9	15.7	19.9	22.1
HCC	0.0	2.3	6.9	11.0	14.1	16.2	16.5
Liver transplant	0.5	0.5	0.9	1.7	2.5	3.2	3.6
Non-liver-related death	---	0.2	1.6	4.6	11.3	24.5	45.3
Liver-related death	---	0.4	5.7	14.7	23.2	30.2	34.5
All cause death	---	0.6	7.4	19.4	34.5	54.7	79.7
Alive	---	99.4	92.6	80.6	65.5	45.3	20.3
Stage distribution (%)†							
RNA- F0	28.7	29.4	33.5	38.4	43.7	49.8	56.5
RNA+ F0	19.0	16.5	7.8	4.1	2.2	1.1	0.6
Fibrosis 1	18.5	18.1	16.1	14.6	12.4	8.3	6.8
Fibrosis 2	13.9	13.7	11.5	10.0	9.7	7.5	5.8
Fibrosis 3	15.8	15.2	12.9	11.1	9.6	8.5	6.7
Cirrhosis	2.8	6.0	14.4	16.1	15.8	17.0	15.3
Decompensated cirrhosis	0.9	0.9	2.7	3.8	4.2	4.6	4.4
Liver transplant	0.5	0.1	0.4	0.9	1.6	2.4	3.0
HCC	0.0	0.2	0.7	1.0	0.8	0.9	0.9

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	11.3	18.0	36.7	46.3	52.3	57.7	59.6
Decompensated cirrhosis	1.3	2.5	11.8	19.2	24.2	27.9	29.5
HCC	0.4	5.1	10.6	14.7	17.3	19.0	19.2
Liver transplant	0.0	0.1	1.1	2.5	3.5	4.1	4.4
Non-liver-related death	---	0.5	3.8	9.8	20.1	33.1	47.5
Liver-related death	---	1.0	11.6	24.1	33.1	39.2	42.5
All cause death	---	1.4	15.4	33.9	53.2	72.3	90.0
Alive	---	98.6	84.7	66.1	46.8	27.8	10.0
Stage distribution (%)†							
RNA- F0	15.5	16.5	21.4	26.6	31.9	37.8	45.6
RNA+ F0	22.2	18.5	8.3	4.7	2.7	1.3	0.7
Fibrosis 1	14.1	15.0	15.5	14.8	13.1	9.3	7.7
Fibrosis 2	10.5	10.3	9.9	9.4	9.6	7.8	5.8
Fibrosis 3	26.0	22.0	15.5	14.2	12.7	10.6	8.5
Cirrhosis	10.0	15.0	21.5	21.0	20.2	21.9	20.0
Decompensated cirrhosis	1.3	2.1	5.8	6.0	5.7	6.3	6.0
Liver transplant	0.0	0.1	1.0	2.2	3.1	4.0	4.5
HCC	0.4	0.6	1.1	1.1	1.1	1.1	1.2

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	3.8	7.6	22.2	32.8	41.6	45.4	46.1
Decompensated cirrhosis	0.5	0.9	5.3	10.8	16.0	19.1	19.9
HCC	0.2	2.4	6.3	10.4	13.1	14.0	14.1
Liver transplant	0.5	0.6	1.0	1.8	2.6	3.1	3.3
Non-liver-related death	---	0.5	3.6	11.1	25.8	48.9	67.1
Liver-related death	---	0.5	5.5	13.9	22.2	27.8	29.5
All cause death	---	0.9	9.1	25.0	48.0	76.7	96.7
Alive	---	99.1	90.9	75.0	52.0	23.3	3.3
Stage distribution (%)†							
RNA- F0	25.0	26.2	30.6	35.1	40.5	47.6	55.3
RNA+ F0	23.1	19.8	9.2	4.7	2.5	1.2	0.6
Fibrosis 1	18.3	18.7	17.8	14.9	10.7	9.2	8.0
Fibrosis 2	13.8	13.3	11.6	10.9	8.8	7.1	6.3
Fibrosis 3	15.7	15.0	12.7	11.3	10.0	7.6	6.7
Cirrhosis	2.8	6.1	14.2	17.1	19.3	18.3	15.1
Decompensated cirrhosis	0.5	0.7	2.8	4.0	5.3	5.5	4.3
Liver transplant	0.5	0.0	0.4	1.0	1.8	2.6	2.4
HCC	0.2	0.2	0.7	0.9	1.2	0.8	1.2

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	14.3	21.1	39.3	48.9	55.6	57.9	58.2
Decompensated cirrhosis	2.8	4.1	13.7	20.7	25.6	27.7	28.1
HCC	0.4	5.2	10.4	14.0	16.1	16.7	16.7
Liver transplant	0.0	0.2	1.4	2.7	3.5	4.0	4.1
Non-liver-related death	---	0.9	8.5	20.9	36.4	52.3	61.3
Liver-related death	---	1.3	13.1	24.6	32.6	36.7	37.7
All cause death	---	2.2	21.7	45.5	69.0	89.0	99.0
Alive	---	97.8	78.3	54.5	31.0	11.0	1.1
Stage distribution (%)†							
RNA- F0	12.7	13.6	18.4	23.4	28.8	35.4	43.6
RNA+ F0	22.5	18.7	8.9	4.8	2.7	1.4	0.8
Fibrosis 1	13.9	14.8	15.8	14.1	10.9	9.8	9.7
Fibrosis 2	10.4	10.2	9.7	10.5	9.5	8.0	5.5
Fibrosis 3	25.8	22.3	16.2	13.6	11.2	9.9	9.1
Cirrhosis	11.5	16.4	22.3	23.2	24.6	23.1	19.0
Decompensated cirrhosis	2.8	3.3	6.3	6.7	7.5	6.4	4.6
Liver transplant	0.0	0.1	1.3	2.5	3.5	4.6	5.9
HCC	0.4	0.7	1.1	1.2	1.4	1.5	1.7

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	11.6	14.6	27.6	37.6	42.2	43.3	43.3
Decompensated cirrhosis	1.6	2.4	7.6	13.0	16.2	17.2	17.2
HCC	0.3	3.6	7.6	10.7	11.9	12.0	12.0
Liver transplant	1.0	1.1	1.8	2.6	3.2	3.4	3.4
Non-liver-related death	---	0.9	9.4	25.3	51.6	71.8	75.0
Liver-related death	---	1.2	8.4	16.8	22.8	24.9	25.0
All cause death	---	2.1	17.7	42.1	74.4	96.7	100.0
Alive	---	97.9	82.3	57.9	25.6	3.3	---
Stage distribution (%)†							
RNA- F0	21.5	23.2	28.4	33.7	39.3	46.4	---
RNA+ F0	24.8	21.3	10.2	5.0	2.5	1.4	---
Fibrosis 1	16.1	17.1	16.8	13.7	11.7	10.6	---
Fibrosis 2	12.0	12.0	11.6	10.2	8.2	8.1	---
Fibrosis 3	13.8	13.2	11.5	10.4	9.6	7.5	---
Cirrhosis	9.0	10.8	16.3	19.6	19.4	17.1	---
Decompensated cirrhosis	1.6	1.9	3.6	4.9	5.5	4.6	---
Liver transplant	1.0	0.1	0.7	1.6	2.5	3.1	---
HCC	0.3	0.5	0.8	1.0	1.3	1.3	---

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	17.2	23.8	41.7	50.5	53.6	54.1	54.1
Decompensated cirrhosis	4.5	5.8	14.2	20.4	23.0	23.6	23.6
HCC	0.6	5.2	9.7	12.2	13.0	13.0	13.0
Liver transplant	1.9	2.1	3.3	4.4	4.9	5.1	5.1
Non-liver-related death	---	2.6	19.2	38.6	57.4	68.3	69.6
Liver-related death	---	2.3	14.0	23.9	29.0	30.3	30.4
All cause death	---	4.9	33.2	62.5	86.4	98.7	100.0
Alive	---	95.1	66.8	37.5	13.6	1.3	---
Stage distribution (%)†							
RNA- F0	10.8	12.1	16.9	22.0	26.8	35.1	---
RNA+ F0	21.0	18.1	9.0	4.9	2.6	1.4	---
Fibrosis 1	14.0	15.2	15.2	13.0	11.8	9.8	---
Fibrosis 2	10.5	10.7	10.4	9.6	8.5	8.7	---
Fibrosis 3	25.9	22.3	15.0	12.9	11.6	8.9	---
Cirrhosis	10.8	16.2	24.1	25.9	25.7	21.5	---
Decompensated cirrhosis	4.5	4.5	6.6	7.5	6.9	6.8	---
Liver transplant	1.9	0.2	1.5	2.9	4.7	6.6	---
HCC	0.6	0.7	1.3	1.3	1.3	1.4	---

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	13.1	16.0	27.3	33.2	34.5	34.6	34.6
Decompensated cirrhosis	2.3	3.3	8.3	11.8	12.8	12.9	12.9
HCC	1.2	4.4	7.4	8.7	8.8	8.8	8.8
Liver transplant	0.9	1.0	1.8	2.3	2.5	2.5	2.5
Non-liver-related death	---	2.6	22.2	53.9	78.3	82.3	82.3
Liver-related death	---	2.0	9.4	15.4	17.5	17.7	17.7
All cause death	---	4.6	31.6	69.3	95.8	100.0	100.0
Alive	---	95.4	68.4	30.7	4.2	---	---
Stage distribution (%)†							
RNA- F0	22.3	24.2	29.6	35.2	41.0	---	---
RNA+ F0	26.6	23.1	11.1	5.8	3.0	---	---
Fibrosis 1	14.2	15.4	16.5	15.2	14.2	---	---
Fibrosis 2	10.6	10.5	10.3	9.7	9.0	---	---
Fibrosis 3	12.1	11.9	10.5	9.3	8.1	---	---
Cirrhosis	9.9	11.7	16.2	17.5	16.3	---	---
Decompensated cirrhosis	2.3	2.5	4.0	4.8	4.9	---	---
Liver transplant	0.9	0.1	0.8	1.6	2.3	---	---
HCC	1.2	0.6	0.9	1.1	1.1	---	---

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	23.6	30.6	44.6	48.8	49.7	49.7	49.7
Decompensated cirrhosis	6.9	9.1	17.5	20.9	21.8	21.8	21.8
HCC	1.4	6.5	9.6	10.6	10.7	10.7	10.7
Liver transplant	0.0	0.4	1.8	2.4	2.6	2.6	2.6
Non-liver-related death	---	6.2	35.5	59.8	73.8	75.5	75.5
Liver-related death	---	3.3	16.2	22.7	24.4	24.5	24.5
All cause death	---	9.5	51.7	82.5	98.2	100.0	100.0
Alive	---	90.5	48.3	17.5	1.8	---	---
Stage distribution (%)†							
RNA- F0	9.7	10.8	15.8	21.1	24.4	---	---
RNA+ F0	19.4	16.4	8.4	4.8	2.7	---	---
Fibrosis 1	12.7	13.7	14.3	14.0	11.9	---	---
Fibrosis 2	9.5	9.6	9.6	9.0	8.7	---	---
Fibrosis 3	23.6	19.7	14.7	13.8	14.3	---	---
Cirrhosis	16.7	21.2	25.6	25.0	24.5	---	---
Decompensated cirrhosis	6.9	7.2	8.0	7.4	5.9	---	---
Liver transplant	0.0	0.4	2.1	3.4	5.5	---	---
HCC	1.4	1.1	1.5	1.5	2.2	---	---

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	15.3	17.7	24.4	26.1	26.2	26.2	26.2
Decompensated cirrhosis	3.9	5.0	8.6	9.6	9.7	9.7	9.7
HCC	0.9	3.6	4.8	5.0	5.0	5.0	5.0
Liver transplant	0.9	1.2	1.8	2.0	2.0	2.0	2.0
Non-liver-related death	---	7.1	51.7	84.3	89.0	89.0	89.0
Liver-related death	---	2.2	8.7	10.8	11.0	11.0	11.0
All cause death	---	9.3	60.4	95.1	100.0	100.0	100.0
Alive	---	90.7	39.6	4.9	---	---	---
Stage distribution (%)†							
RNA- F0	25.1	27.0	34.0	39.0	---	---	---
RNA+ F0	31.5	27.3	13.2	7.3	---	---	---
Fibrosis 1	10.4	12.9	16.3	15.2	---	---	---
Fibrosis 2	7.8	7.8	8.6	9.1	---	---	---
Fibrosis 3	8.9	8.7	8.4	7.9	---	---	---
Cirrhosis	10.5	11.6	14.0	15.5	---	---	---
Decompensated cirrhosis	3.9	3.8	3.8	3.4	---	---	---
Liver transplant	0.9	0.2	0.9	1.5	---	---	---
HCC	0.9	0.7	0.9	1.1	---	---	---

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	13.2	16.9	23.7	24.9	25.0	25.0	25.0
Decompensated cirrhosis	5.3	6.0	9.1	9.9	9.9	9.9	9.9
HCC	0.0	2.0	3.0	3.1	3.1	3.1	3.1
Liver transplant	0.0	0.3	0.9	1.0	1.0	1.0	1.0
Non-liver-related death	---	14.9	64.1	88.6	91.8	91.8	91.8
Liver-related death	---	1.4	6.6	8.1	8.2	8.2	8.2
All cause death	---	16.3	70.7	96.7	100.0	100.0	100.0
Alive	---	83.7	29.3	3.4	---	---	---
Stage distribution (%)†							
RNA- F0	29.0	30.8	37.7	42.3	---	---	---
RNA+ F0	29.0	24.3	11.9	6.3	---	---	---
Fibrosis 1	8.0	10.4	13.8	13.7	---	---	---
Fibrosis 2	6.0	6.1	7.5	6.9	---	---	---
Fibrosis 3	15.0	12.3	9.1	9.3	---	---	---
Cirrhosis	7.9	10.9	14.3	14.3	---	---	---
Decompensated cirrhosis	5.3	4.5	3.7	4.2	---	---	---
Liver transplant	0.0	0.3	1.2	2.3	---	---	---
HCC	0.0	0.4	0.8	0.7	---	---	---

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	6.6	7.9	10.8	11.0	11.0	11.0	11.0
Decompensated cirrhosis	1.7	2.0	3.1	3.2	3.2	3.2	3.2
HCC	1.0	1.9	2.1	2.1	2.1	2.1	2.1
Liver transplant	0.7	0.8	0.9	1.0	1.0	1.0	1.0
Non-liver-related death	---	18.9	85.9	96.2	96.3	96.3	96.3
Liver-related death	---	1.5	3.4	3.7	3.7	3.7	3.7
All cause death	---	20.5	89.4	99.9	100.0	100.0	100.0
Alive	---	79.5	10.6	0.1	---	---	---
Stage distribution (%)†							
RNA- F0	31.3	33.3	39.7	55.3	---	---	---
RNA+ F0	41.3	36.1	16.6	2.1	---	---	---
Fibrosis 1	7.6	11.5	17.3	17.0	---	---	---
Fibrosis 2	5.7	5.7	8.0	10.6	---	---	---
Fibrosis 3	6.5	6.1	6.6	6.4	---	---	---
Cirrhosis	4.2	5.2	8.5	4.3	---	---	---
Decompensated cirrhosis	1.7	1.6	2.0	---	---	---	---
Liver transplant	0.7	0.1	0.5	---	---	---	---
HCC	1.0	0.4	0.7	4.3	---	---	---

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	9.1	11.9	15.1	15.3	15.3	15.3	15.3
Decompensated cirrhosis	0.0	0.7	2.3	2.3	2.3	2.3	2.3
HCC	0.0	1.3	1.5	1.5	1.5	1.5	1.5
Liver transplant	0.0	0.0	0.1	0.2	0.2	0.2	0.2
Non-liver-related death	---	33.6	90.9	97.6	97.7	97.7	97.7
Liver-related death	---	0.2	2.1	2.3	2.3	2.3	2.3
All cause death	---	33.8	93.0	100.0	100.0	100.0	100.0
Alive	---	66.2	7.0	---	---	---	---
Stage distribution (%)†							
RNA- F0	18.2	20.4	27.3	---	---	---	---
RNA+ F0	45.5	37.7	18.1	---	---	---	---
Fibrosis 1	7.8	12.1	18.9	---	---	---	---
Fibrosis 2	5.8	5.8	8.6	---	---	---	---
Fibrosis 3	13.6	11.3	8.8	---	---	---	---
Cirrhosis	9.1	11.3	12.9	---	---	---	---
Decompensated cirrhosis	0.0	0.9	3.6	---	---	---	---
Liver transplant	0.0	0.0	0.7	---	---	---	---
HCC	0.0	0.4	1.0	---	---	---	---

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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

	2007	2010	2020	2030	2040	2050	2060
Cumulative proportion (%)*							
Cirrhosis	2.6	2.9	3.3	3.3	3.3	3.3	3.3
Decompensated cirrhosis	0.0	0.2	0.3	0.3	0.3	0.3	0.3
HCC	0.0	0.2	0.2	0.2	0.2	0.2	0.2
Liver transplant	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Non-liver-related death	---	41.4	99.1	99.7	99.7	99.7	99.7
Liver-related death	---	0.0	0.3	0.3	0.3	0.3	0.3
All cause death	---	41.5	99.3	100.0	100.0	100.0	100.0
Alive	---	58.5	0.7	---	---	---	---
Stage distribution (%)†							
RNA- F0	40.3	41.9	47.0	---	---	---	---
RNA+ F0	50.7	43.2	16.9	---	---	---	---
Fibrosis 1	2.5	7.7	16.9	---	---	---	---
Fibrosis 2	1.9	2.2	8.7	---	---	---	---
Fibrosis 3	2.1	2.0	3.0	---	---	---	---
Cirrhosis	2.6	2.7	5.4	---	---	---	---
Decompensated cirrhosis	0.0	0.2	1.2	---	---	---	---
Liver transplant	0.0	0.1	0.9	---	---	---	---
HCC	0.0	0.1	0.5	---	---	---	---

*Proportion computed with reference to the number of patients who were alive in year 2007.
†Proportion computed with reference to the number of patients who were alive in predicted year (e.g. 2007, 2010).
Stage distribution of the living patients in year 2007 is taken from the post-transfusion claimant cohort data.

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 2007

Event	2010	2020	2030	2040	2050	2060
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Cirrhosis (%)	13.6 (9.0-18.2)	25.5 (16.1-34.9)	32.4 (20.7-44.1)	36.6 (23.4-49.8)	38.4 (25.3-51.5)	39.3 (27.2-51.4)
Hepatocellular carcinoma (%)	3.3 (2.4-4.2)	6.4 (3.6-9.2)	8.8 (4.5-13.1)	10.1 (5.5-14.7)	10.8 (5.7-15.9)	10.9 (5.2-16.6)
Liver-related death (%)	1.2 (0.6-1.8)	7.8 (5.0-10.6)	14.5 (9.0-20.0)	19.4 (13.0-25.8)	22.2 (14.7-29.7)	23.5 (15.9-31.1)

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 2007

	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+/-	51.78	1520	4785	3265	50.82	4196	2676	50.59	3625	2105	50.26	3108	1588	49.78	2589	1069	48.81	2071	551	45.13
F1	20.27	400	1873	1473	22.92	1643	1243	23.49	1419	1019	24.33	1216	816	25.59	1014	614	28.01	811	411	33.63
F2	10.58	300	977	677	10.54	857	557	10.54	741	441	10.52	635	335	10.50	529	229	10.46	423	123	10.09
F3	7.82	343	722	379	5.91	634	291	5.50	547	204	4.88	469	126	3.96	391	48	2.19	313	0	0.00
F4	7.84	178	724	546	8.50	635	457	8.65	549	371	8.85	470	292	9.17	392	214	9.77	314	136	11.10
Decomp	1.21	48	112	64	0.99	98	50	0.95	85	37	0.88	73	25	0.77	61	13	0.57	48	0	0.03
HCC	0.38	15	35	20	0.31	31	16	0.30	27	12	0.28	23	8	0.24	19	4	0.18	15	0	0.02
Transplant	0.11	21	10	0	0.00	9	0	0.00	8	0	0.00	7	0	0.00	6	0	0.00	4	0	0.00
Total	100	2825	9239	6425	100.00	8104	5290	100.00	6999	4188	100.00	6000	3190	100.00	5000	2190	100	4000	1221	100

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

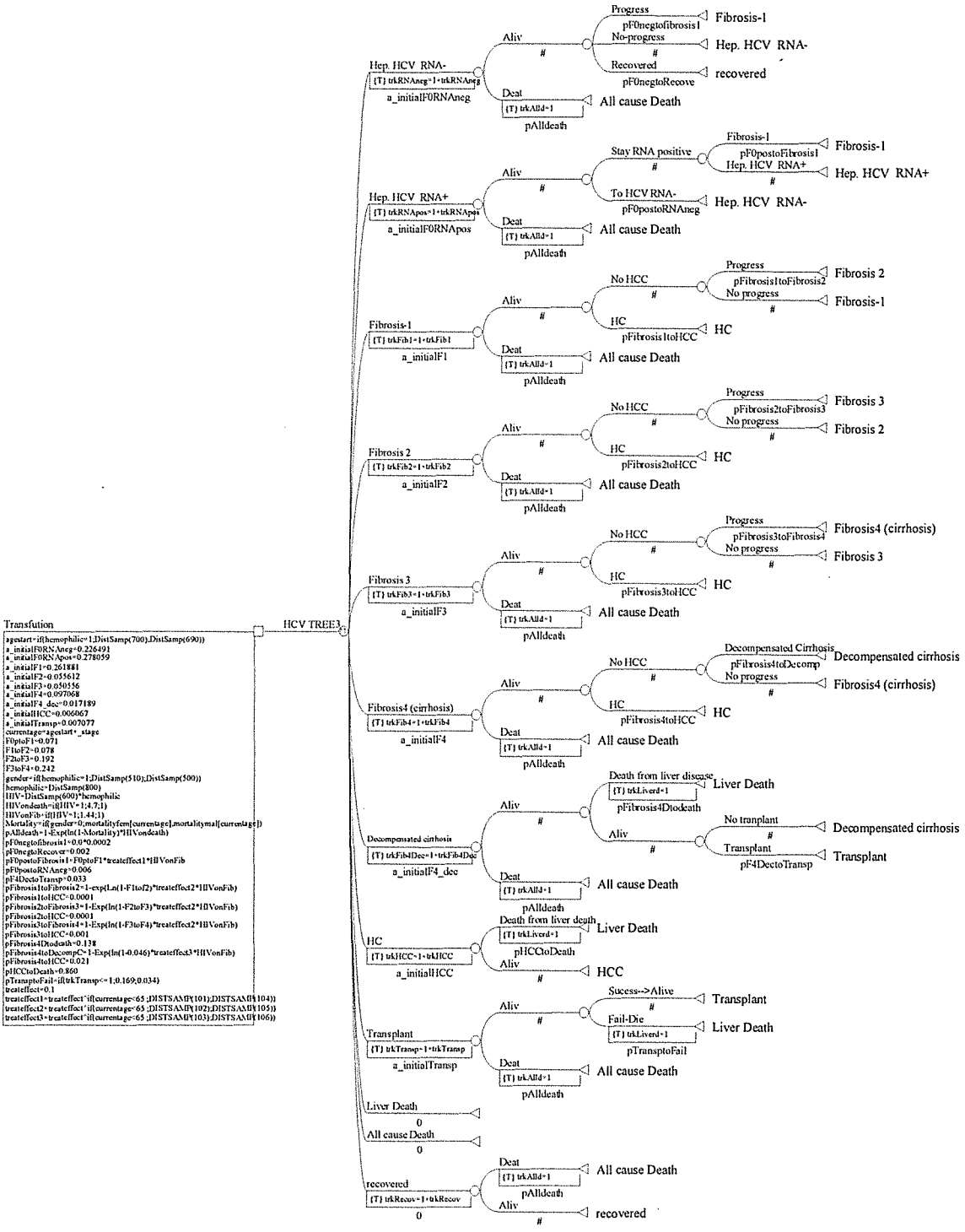
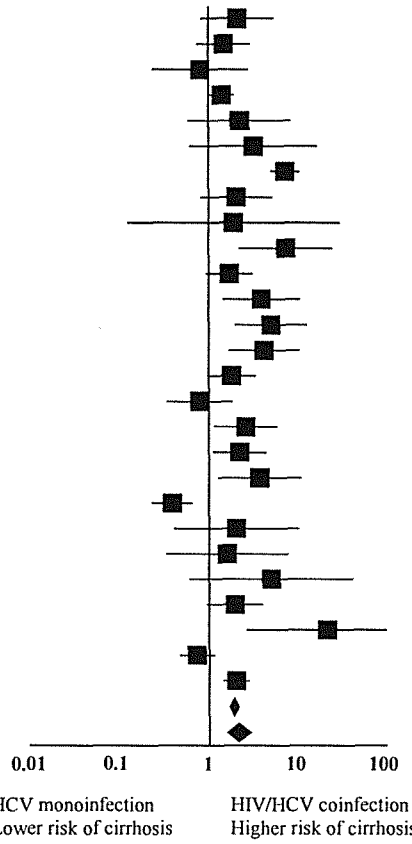


Figure 4.3.3. Risk of cirrhosis: Comparison between HCV monoinfection and HIV/HCV coinfection – meta-analysis

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		

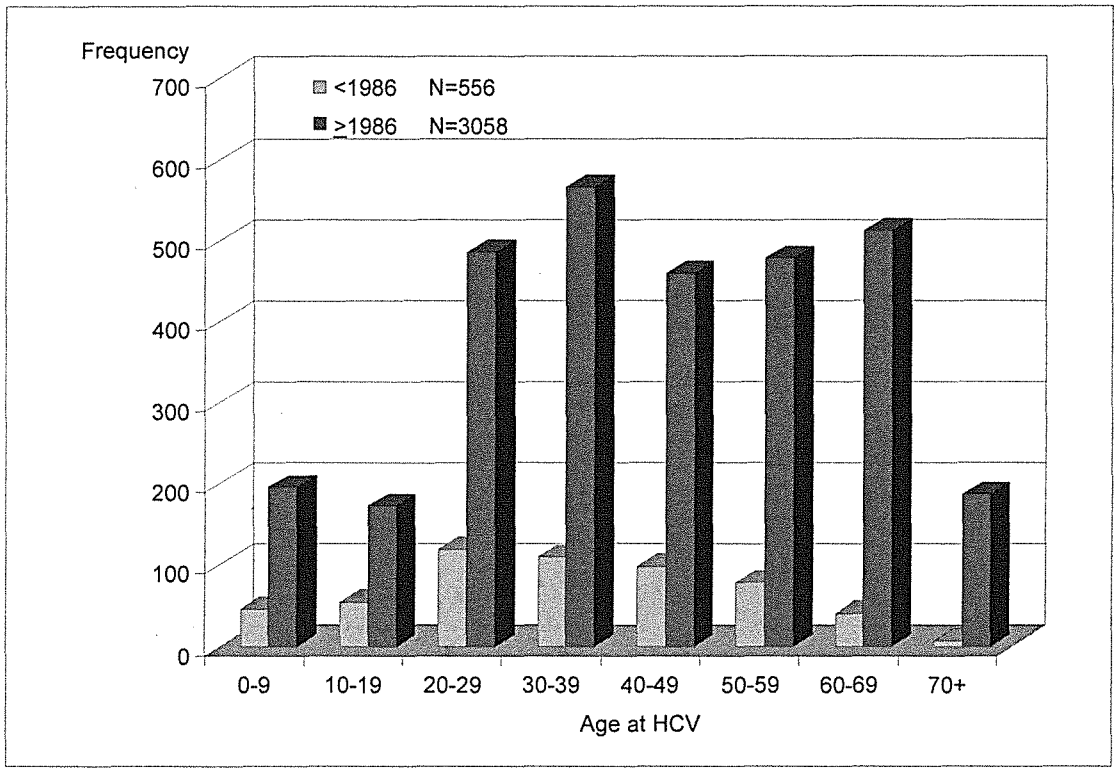


References: [59,67,68,70-76,133,148,161,163,174,176,178,181,280-288]

Risk ratios were calculated from available data. Adjusted relative risk were obtained directly from the following papers:[67,68,70-75]

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



HCV, hepatitis C virus

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

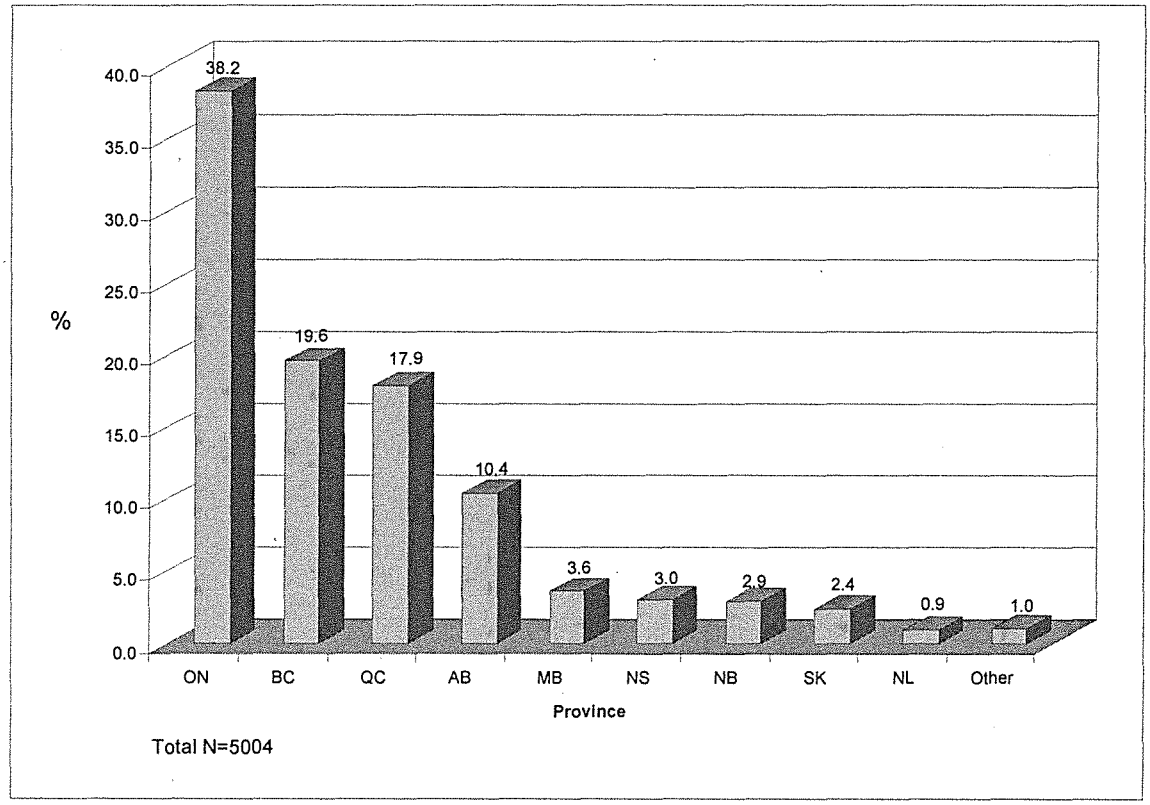
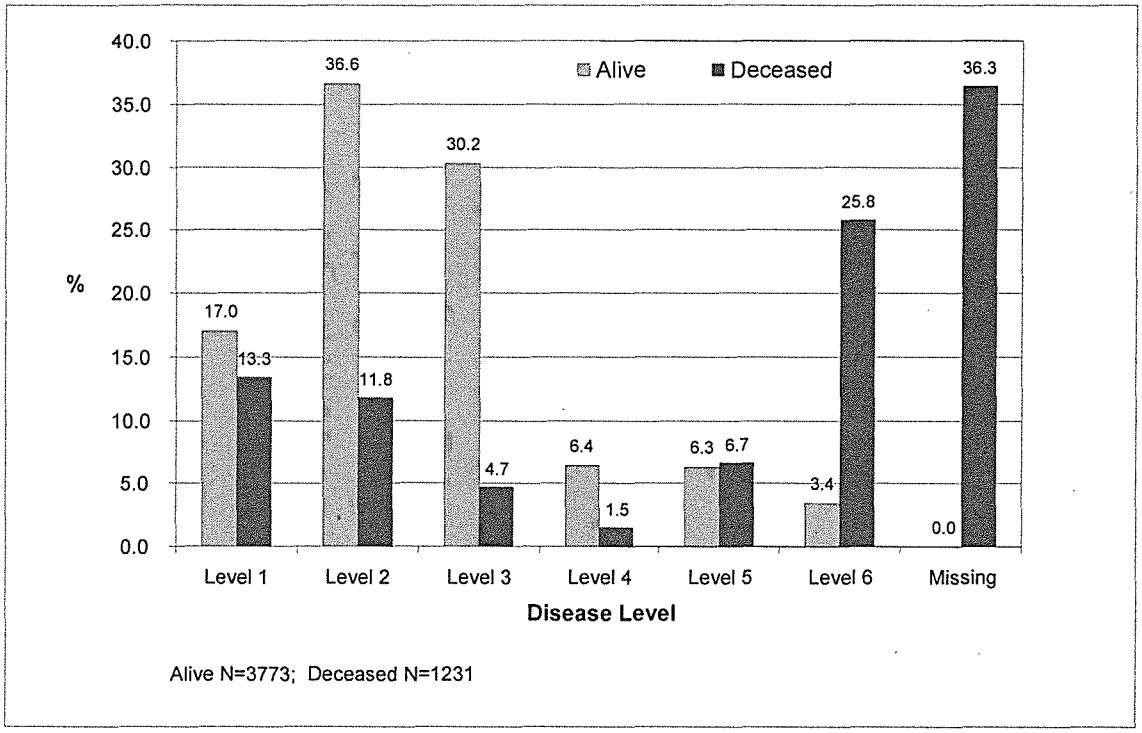
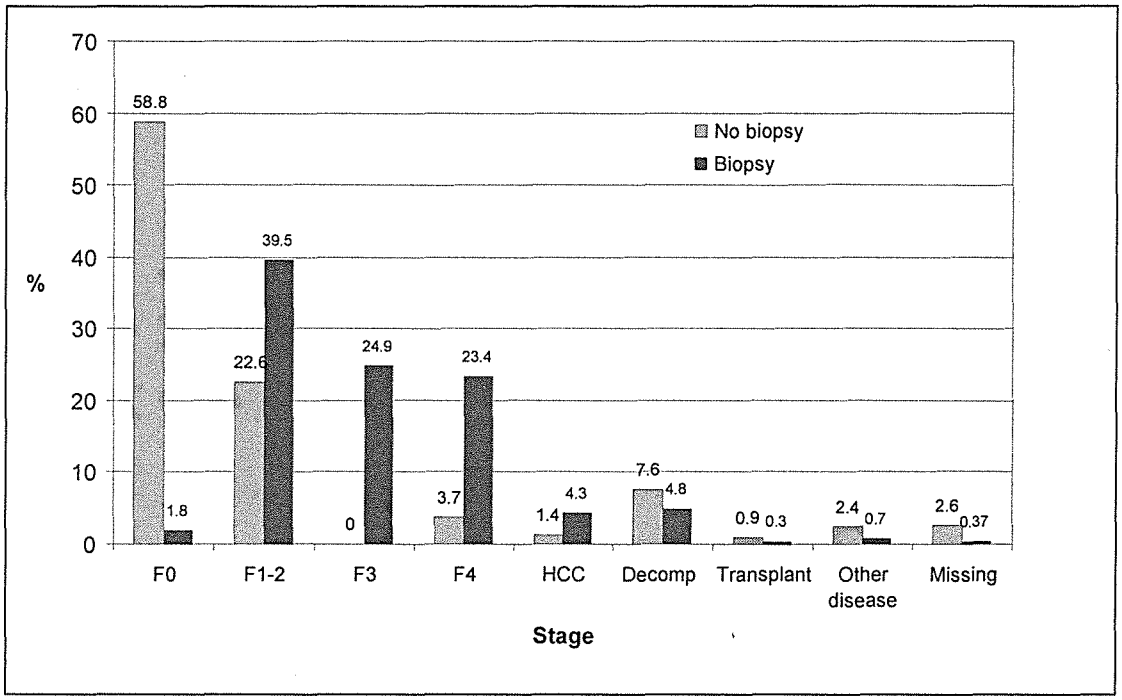


Figure 5.3. Compensation level of post-transfusion compensation claimants by survival status at August 2007



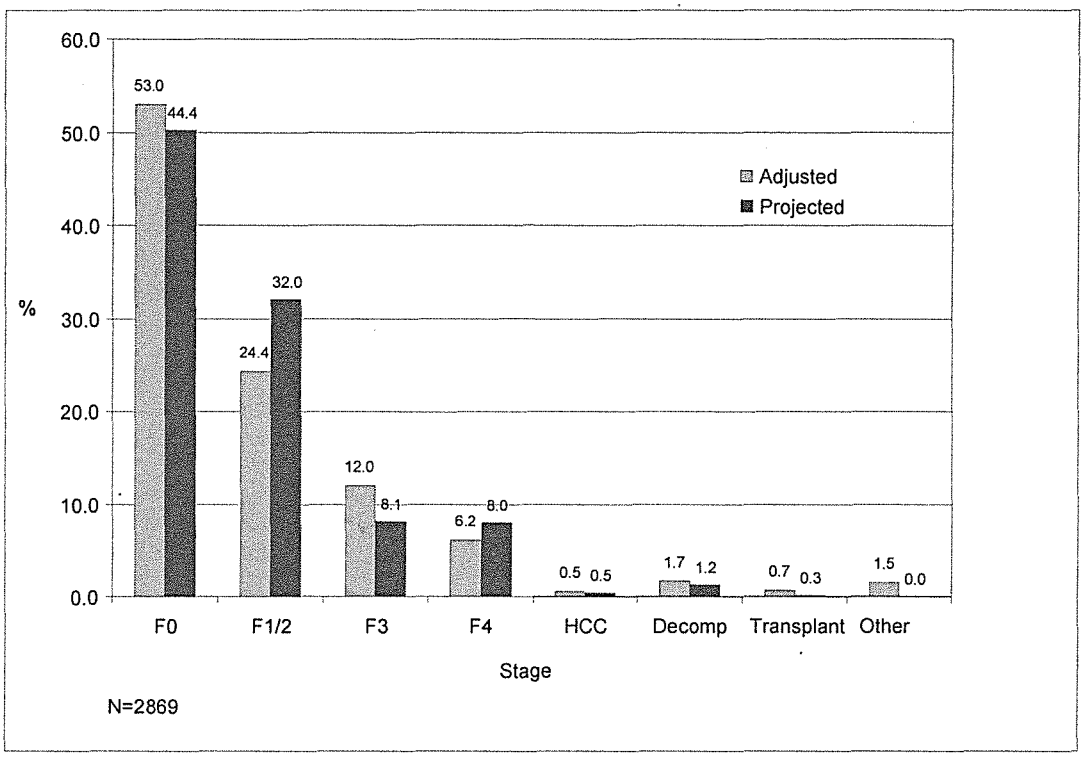
Level 1, HCV antibody positivity ; Level 2, HCV-RNA positivity; Level 3, Non-bridging fibrosis; Level 4, Bridging fibrosis; Level 5, Cirrhosis of liver, unresponsive porphyria cutanea tarda, unresponsive thrombocytopenia; Level 6, liver transplant, decompensation of the liver, hepatocellular cancer (HCC), 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



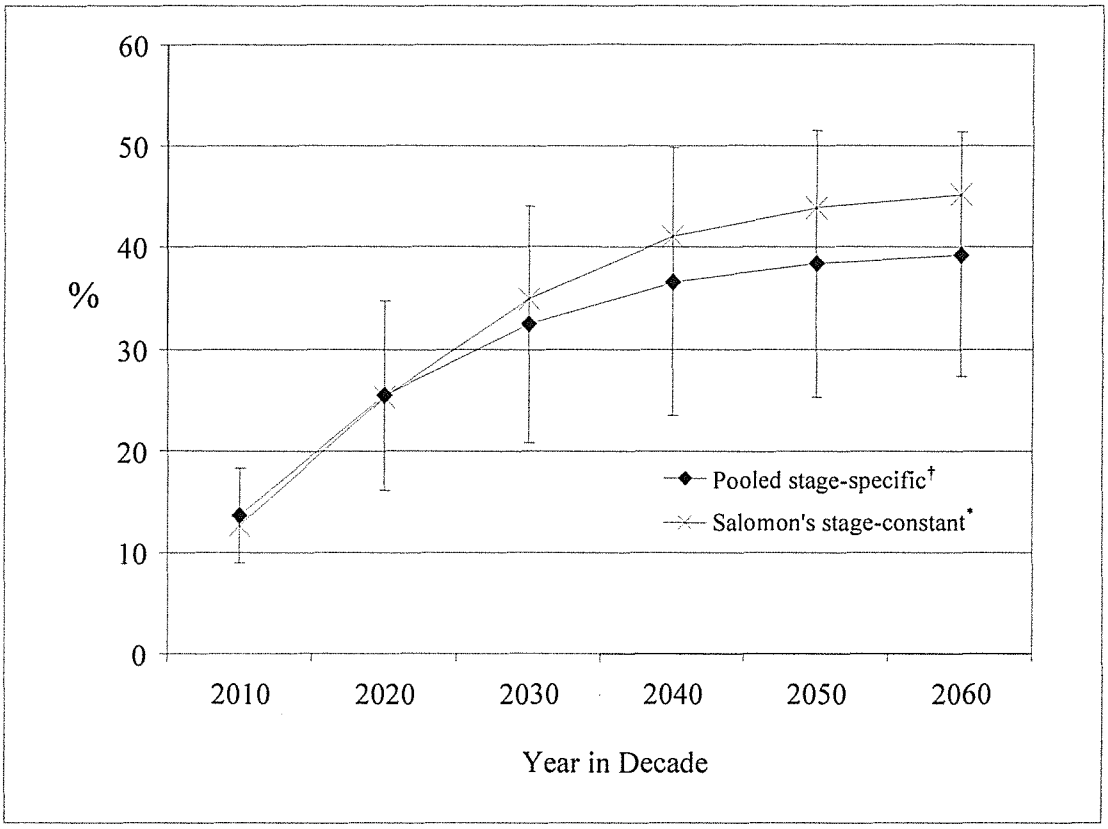
F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis; HCC, hepatocellular carcinoma; decomp, decompensated cirrhosis; transplant, liver transplant

Figure 5.5. Distribution of projected and adjusted HCV stage distribution among living non-hemophilic post-transfusion compensation claimants at August 2007



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

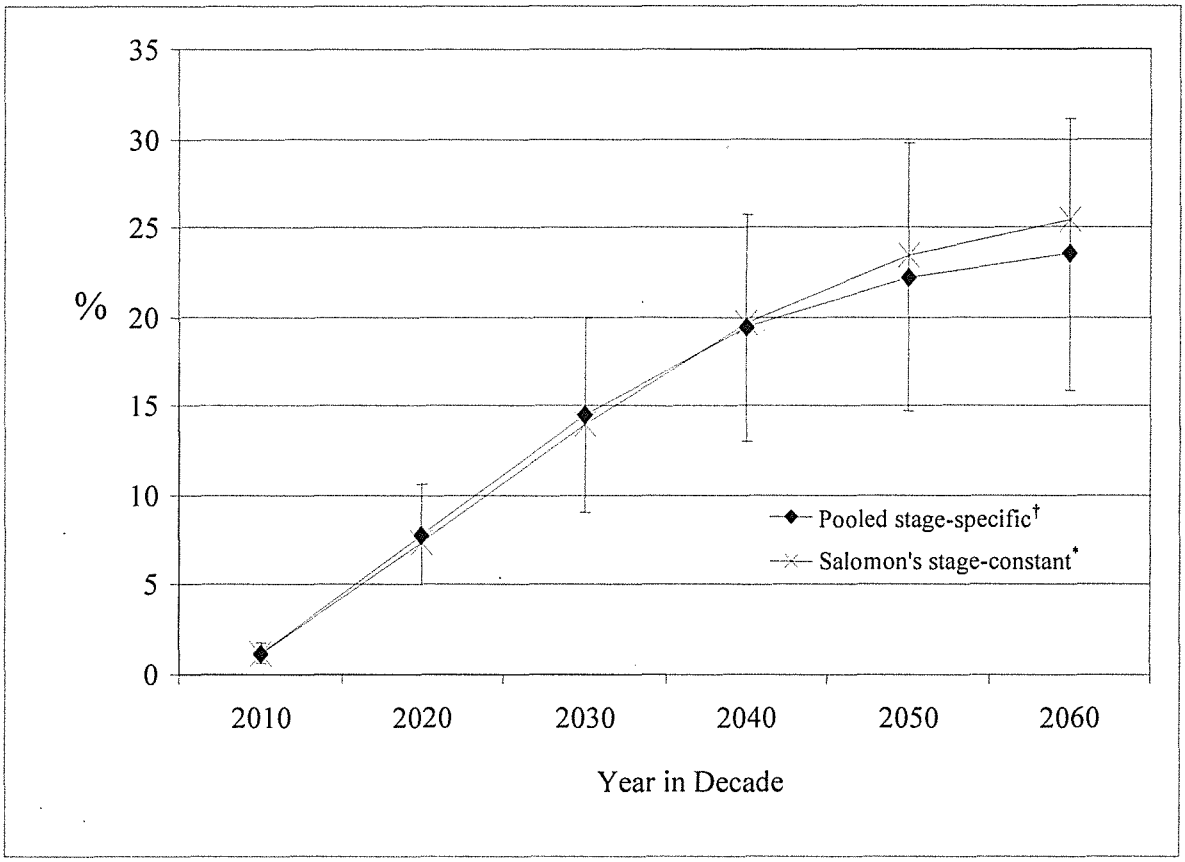
Figure 7.1. Model validation: Cumulative proportion of cirrhosis, 2007 model – comparing pooled stage-specific transition rates and Salomon *et al's*[1] age- and gender-specific rates



†Source of transition probabilities: from literature and post-transfusion claimant cohort. Best estimates for all other parameters.

*Based on Salomon *et al's* empirically calibrated annual fibrosis progression rates for chronic hepatitis C virus infection. Rates are fixed across fibrosis classes; that is, transitions from no fibrosis to portal fibrosis without septa occur at the same rate as transitions from portal fibrosis without septa to few septa, etc.[1]

Figure 7.2. Model validation: Cumulative proportion of liver-related death, 2007 model – comparing pooled stage-specific transition rates and Salomon *et al's*[1] age- and gender-specific rates



†Source of transition probabilities: from literature and post-transfusion claimant cohort. Best estimates for all other parameters.

*Based on Salomon *et al's* empirically calibrated annual fibrosis progression rates for chronic hepatitis C virus infection. Rates are fixed across fibrosis classes; that is, transitions from no fibrosis to portal fibrosis without septa occur at the same rate as transitions from portal fibrosis without septa to few septa, etc.[1]

Appendix A. Publications derived from this study:

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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

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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.

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