National Hepatitis C Database

for infection acquired through blood and blood products

2010 Report

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

hpsc

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Health Protection Surveillance Centre
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Foreword

On behalf of the National Hepatitis C Database Steering Committee, I am delighted to introduce the 2010 report of the National Hepatitis C Database. The Steering Committee oversees the management and development of the database and I would like to thank most sincerely Dr Lelia Thornton and her team in the HSE Health Protection Surveillance Centre for their continuing commitment and dedication in developing and managing the database.

The database will provide an invaluable resource to researchers, clinicians and to those involved in planning future service provision for people who are infected with hepatitis C through contaminated blood and blood products. We would like to thank everyone who has given their consent to be included in the database and to thank those who actively encourage participation through the hepatology units and the hepatitis C patient support groups. Without this participation and co-operation, the gathering of this valuable information would not be possible.

This report is based on information collected during 2008 and describes the main findings from these data. Over three quarters of those known to have been infected with hepatitis C through contaminated blood and blood products are now participating in the database. The continuing collection of their data provides very useful information on disease progression and the impact of treatment. There are ongoing efforts to improve participation rates and the quality of the data collected. This is especially important at this time given that the participants have been infected for an average of 30 years and most are now aged over 50, so following the progress of their disease now is crucial.

Some important information which is now being presented to us through the database includes data relating to numbers of people with signs of serious liver disease. The majority of participants in the database, including those chronically infected, do not show evidence of having serious liver disease. We have also learned that those participants with high alcohol intake have almost five times higher odds of having serious liver disease than those without. Another valuable piece of information coming from the database is the high success rates of treatment amongst the Irish population. We also know that the majority of those chronically infected do continue to attend their hepatology unit regularly and also to avail of other out-patient services, all of which are provided without charge under the terms of the Health (Amendment) Act 1996.

The National Hepatitis C Database Steering Committee looks forward to continuing to work with the project and to the ongoing learning which is emerging.

Michele Tait
Chair,
National Hepatitis C Database Steering Committee

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We would also like to thank:

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Members of the Database Steering Committee (Appendix A)

Members of the Scientific and Technical Group (Appendix B)

Dr Elizabeth Kenny, Chair of the Consultative Council on Hepatitis C

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Executive Summary

Hepatitis C infection is a major cause of liver disease and it is estimated that up to 20% of people with chronic infection will develop cirrhosis over a 20 to 25 year period. Very effective treatment is now available, which eradicates the virus in over 50% of cases.

Approximately 1,700 people in Ireland became infected with hepatitis C virus (HCV) through contaminated blood and blood products. The National Hepatitis C Database was established to gather information on people infected in this way. This report describes the results of the third round of data collection.

Main findings

Profile of participants

- Twenty eight people have been added to the database since the last round of data collection. The total number of participants is 1,303 (76% of those eligible).
- Older people were more likely to participate in the database.
- The majority of database participants were infected through contaminated anti-D immunoglobulin (62%), with 26% infected through receipt of blood transfusions or treatment for renal disease, and 12% through blood clotting factors.
- 73% of the database population are females, reflecting the large anti-D cohort.
- The average age of the database population is now 57 years and the average duration of infection is 30 years. These figures vary by source of infection:
    - The larger anti-D cohort (1977-79 outbreak) have an average age of 58 years and duration of infection of 31 years.
    - The smaller anti-D cohort (1991-94 outbreak) have an average age of 45 years and duration of infection of 15 years.
    - The blood transfusion/renal group have an average age of 60 years and duration of infection of 23 years.
    - The blood clotting factor group have an average age of 44.5 years and duration of infection of 31 years.

Hepatitis C status

- Overall, 62% of participants had tested HCV RNA positive (indicating active infection) at least once, and a further 15% had positive HCV confirmatory antibody tests but no positive RNA results. The remaining 23% tested either ELISA/EIA (screening test) positive/weak positive or had an indeterminate result on confirmatory testing.
- The true viral clearance rate for participants is likely to be between 19% and 36% (having taken account of those who died before RNA testing, and allowing for the possibility that some participants may have had false positive screening test results).
- Females were significantly more likely to have cleared the virus at the time of diagnosis.
- 76% were HCV genotype 1 and 19% genotype 3.

Alcohol consumption

- Information about alcohol consumption was infrequently recorded. However, alcohol intake in excess of the recommended limits (for the general population) was recorded in the medical

notes of 15% of chronically infected participants where data were available; this was more common in males (32%) than females (9%).

Outcomes

The overall impression from this latest round of data collection is that, although there is evidence of progression of disease in some people, the majority of the database population, even those chronically infected, do not have any evidence of serious liver disease.

In the absence of a population-based comparison group, we have compared chronically infected database participants (ever RNA positive) with those who never became chronically infected, in the reporting of most medical outcomes.

- Depression, hypertension, fibromyalgia/myalgia, dermatitis, diabetes, osteoporosis, and gastro-oesophageal reflux were all recorded significantly more often for those chronically infected than those who were never chronically infected.
- Elevated alanine aminotransferase (ALT) levels were associated with chronic infection, male gender, high alcohol consumption and being infected for more than 30 years.
- Cirrhosis had developed in fourteen percent of those with chronic infection and in none who did not have chronic infection.
- The average duration of being RNA positive at the estimated date of cirrhosis was 21 years and the average age at cirrhosis was 51 years.
- The number of participants with cirrhosis has increased by 19 since the last round of data collection.
- After RNA status, alcohol intake was the biggest determinant of risk of cirrhosis.
- Male gender and older age at latest follow-up were independent risk factors for cirrhosis. Those infected through transfusion/renal treatment or through blood clotting factors were significantly more likely to have developed cirrhosis.
- The number of participants with hepatocellular carcinoma (HCC) has increased by three, giving a total of 23 (3%).
- The average duration of infection at the estimated date of HCC was 25 years and the average age at HCC was 63 years.
- Twenty five percent of chronically infected participants had moderate or severe inflammation on last biopsy compared to 1% of participants who were never chronically infected.
- Nineteen percent of chronically infected participants had a high fibrosis score (including cirrhosis) on their most recent biopsy compared to 4% of those who did not have chronic infection.
- The average age at the first high fibrosis score was 51 years and the average duration of infection was 19 years.
- A high fibrosis score (including cirrhosis) was associated with high alcohol intake, older age at biopsy, longer duration of infection, male gender, infection through blood transfusion or renal treatment, and genotype 3 infection.
- One hundred and eighty eight participants had died, an additional 15 since the last round of data collection.
- Mortality rates were higher in chronically infected participants (16%) compared to those who were never chronically infected (4%), and were also higher in those infected through blood transfusions or clotting factors, those who had high alcohol intake and those who were older at the time of infection.
- Liver-related mortality occurred in 48 participants, and was higher in chronically infected participants, those with high alcohol intake, males, those infected through blood transfusion or clotting factors, and participants who were older when infected.

- For chronically infected participants there has been a small but clear progression in the prevalence of all liver-related outcome measures since baseline data collection about three years ago.
- A summary measure was developed to classify participants as having severe, moderate or mild/no liver disease (described on page 38). Of chronically infected participants, 27%, 20% and 53% were classified as having severe, moderate and mild/no liver disease respectively, compared to 2%, 1% and 97% of those who never became chronically infected.
- The determinants of having severe liver disease were high alcohol intake, older age at follow-up, male gender, longer duration of being RNA positive, and HCV genotype 3.
- Participants who had high alcohol intake had almost five times higher odds of having severe disease than those without.
- Eighteen database participants had received liver transplants, at an average age of 52.5 years and an average duration of HCV infection of 28.5 years. Where post-transplant information was available, most showed accelerated disease progression.

Anti-viral treatment

- Almost 41% of chronically infected participants had received at least one course of anti-viral treatment. Those with HCV genotype 2 or 3 were more likely to have been treated (68% and 70% respectively) than those with genotype 1 (33%).
- Twenty four percent of all treatment courses were stopped early due to side effects.
- Treatment naïve participants on combination therapy for 48 weeks or more achieved a sustained virological response (SVR) in 77% of genotype 2 or 3 cases and in 47% of genotype 1.
- Other factors associated with SVR included younger age at treatment, female gender, and lower fibrosis score.
- Participants infected through clotting factors were less likely to achieve SVR.

Focus on the different patient groups

Participants infected through anti-D immunoglobulin

- This group had the lowest prevalence of serious liver-related outcomes.
- Nineteen percent were classified as having severe liver disease.
- Nine percent had developed cirrhosis.
- The relatively low level of disease progression in this group is probably attributable to the fact that they are female, were infected at a young age and have lower prevalence of high alcohol intake (4%).
- The 1977-79 outbreak group (genotype 1) have a low uptake of anti-viral treatment (27%) and a low overall SVR on last treatment, compared with treatment uptake of 89% for the 1991-1994 outbreak group (genotype 3), who had an overall SVR on last treatment of 90%.

Participants infected through blood transfusion/renal treatment

- This group had the highest rate of chronic infection, 82%, at time of diagnosis.
- They also had the highest prevalence of severe liver disease at 38%.
- Twenty two percent had developed cirrhosis.
- These findings may be explained by the fact that many of this group had co-morbidities and many became infected with HCV as a result of treatment for serious conditions. They were also slightly older at the time of infection and had a higher prevalence of high alcohol intake (13%).

Participants infected through blood clotting factors

- Thirty one percent were classified as having severe liver disease.
- Fourteen percent were diagnosed as having cirrhosis.
- These findings may be partly explained by the fact that most of this group are male, 17% were reported as having a high alcohol intake, and 42% were co-infected with HIV.
- Forty one percent had received combination treatment for HCV and the SVR rates were not statistically worse in the HIV co-infected participants than in those who were mono-infected, and were comparable to those achieved by participants infected through other means. However, numbers were low.

Clinical management

- The proportion of chronically infected participants taking long-term medications to treat depression, anxiety or diabetes was significantly higher than for those not chronically infected.
- Seventy seven percent of all living database participants had attended their hepatology unit in 2007 or 2008, this figure being higher for those chronically infected (88%).
- Twenty two percent of chronically infected participants and 11% of those never chronically infected had visited the hospital on an in-patient basis since last follow-up.
- The specialist hospital services, other than hepatology, most commonly attended by chronically infected participants were haematology, psychiatry/psychology/counselling, endocrinology and rheumatology.
- Information on the use of complementary and alternative therapies is recorded in the database, whenever it is available in the medical charts. However, this is not likely to be a reliable source of this information. Information on the use of these therapies has been gathered by a separate health and lifestyle survey which will be published shortly.

Conclusion

The National Hepatitis C Database project has progressed in both participation rate and quality of data since its establishment six years ago. The ongoing support of participants, support groups and health professionals is essential to its success. Eligible people who have not yet participated may join at any time through their hepatology unit.

We would encourage hepatology unit staff to record body weight/BMI and alcohol consumption information as a routine at clinic visits. In the next round of data collection, additional information, where available, will be collected on: insulin resistance, steatosis, fibroscans, details of adverse effects of treatment, both starting and finishing treatment doses, and clinic follow-up/discharge status of patients. We also look forward to carrying out more detailed analysis of viral load data.

The data in the database are available for use by researchers and by the participating hepatology units. We welcome any comments and suggestions that participants, health professionals or other interested people may have on ways in which we could improve the database and the use of the information contained in it.

Summary tables

Table 1. Summary of main outcomes by hepatitis C RNA status for all participants

Outcomes	All		Ever chronically infected *		Never chronically infected †		No RNA results in chart	
	Number	%	Number	%	Number	%	Number	%
Signs of liver disease	167	12.8	155	19.2	5	1.1	7	14.0
Cirrhosis	116	8.9	111	13.8	0	0.0	5	10.0
Liver tumours or HCC	25	1.9	23	2.9	0	0.0	2	4.0
High fibrosis score on biopsy ‡	161	12.4	154	19.1	4	0.9	3	6.0
Deceased	188	14.4	129	16.0	18	4.0	41	82.0
Liver related disease directly caused death §	48	3.7	38	4.8	2	0.5	8	17.4
All	**1303**		**806**		**447**		**50**	

* At least one positive hepatitis C RNA result – testing carried out some time after infection so this is a good indicator of chronic infection

† Positive or indeterminate line-immunoassay results (RIBA/INNO-LIA) or positive/weak positive EIA/ELISA results, RNA tests done but never tested RNA positive. These participants cleared the hepatitis C virus spontaneously and are likely to have done so within a year of infection

‡ Ever had a fibrosis score of 3 or 4 on biopsy scored from 0 to 4 or a fibrosis score of 4, 5 or 6 on biopsy scored from 0 to 6. The proportion of chronically infected participants who had biopsies was significantly higher than that for participants who did not become chronically infected

§ Denominator for this is all participants minus those whose cause of death was not available (n=1289)

Table 2. Current RNA status (this includes the last known status of deceased participants) for all participants

Final status	All		Ever chronically infected*	
	Number	%	Number	%
Currently chronically infected †	612	48.8	612	75.9
Treated and cleared virus	161	12.9	161	20.0
Cleared virus without treatment ‡	480	38.3	33	4.1
Had positive confirmatory antibody results §	223	17.8	33	4.1
Not confirmed positive‖	257	20.5		
All	**1253**	**100**	**806**	**100**

* At least one positive hepatitis C RNA result

† Hepatitis C RNA positive at most recent test (includes participants who have died)

‡ Hepatitis C antibody positive, never treated

§ Positive line-immunoassay results (RIBA/INNO-LIA) results

‖ positive/weak positive EIA/ELISA results or indeterminate line-immunoassay results, RNA tests done but never tested RNA positive.

Note: Participants with no RNA results in their charts were omitted from this table as there is no way of determining their RNA status (n=50)

Table 3. Summary of main outcomes by hepatitis C RNA status for all anti-D participants

Outcomes	All*		Ever chronically infected		Never chronically infected	
	Number	%	Number	%	Number	%
Signs of liver disease	53	6.6	49	11.4	3	0.8
Cirrhosis	39	4.9	38	8.8	0	0.0
Liver tumours or HCC	3	0.4	3	0.7	0	0.0
High fibrosis score on biopsy	72	9.0	69	16.1	2	0.6
Deceased	43	5.4	31	7.2	11	3.0
Liver related disease directly caused death †	8	1.0	6	1.4	1	0.3
All	**803**		**430**		**363**	

* There were no RNA results in the charts of 10 participants. These are included under all, but not under ever or never chronically infected

† Denominator for this is all participants minus those whose cause of death was not available (n=797)

Table 4. Current RNA status (this includes the last known status of deceased participants) for all anti-D participants

Final status	All		Ever chronically infected	
	Number	%	Number	%
Currently chronically infected	342	43.1	342	79.5
Treated and cleared virus	67	8.5	67	15.6
Cleared virus without treatment	384	48.4	21	4.9
Had positive confirmatory antibody results	167	21.1	21	4.9
Not confirmed positive	217	27.4		
All	**793**	**100**	**430**	**100**

Note: Participants with no RNA results in their charts were omitted from this table as there is no way of determining their RNA status (n=10)

Table 5. Summary of main outcomes by hepatitis C RNA status for anti-D participants infected between 1977 and 1979

Outcomes	All*		Ever chronically infected		Never chronically infected	
	Number	%	Number	%	Number	%
Signs of liver disease	49	7.3	45	12.0	3	1.0
Cirrhosis	36	5.3	35	9.3	0	0.0
Liver tumours or HCC	3	0.4	3	0.8	0	0.0
High fibrosis score on biopsy	69	10.2	66	17.6	2	0.7
Deceased	42	6.2	30	8.0	11	3.8
Liver related disease directly caused death †	8	1.2	6	1.6	1	0.3
All	**675**		**376**		**293**	

* There were no RNA results in the charts of 6 participants. These are included under all, but not under ever or never chronically infected

† Denominator for this is all participants minus those whose cause of death was not available (n=670)

Note: One participant who was infected during this anti-D outbreak period had a non-outbreak genotype and was excluded from this table

Table 6. Current RNA status (this includes the last known status of deceased participants) for anti-D participants infected between 1977 and 1979

Final status	All		Ever chronically infected	
	Number	%	Number	%
Currently chronically infected	325	48.6	325	86.4
Treated and cleared virus	33	4.9	33	8.8
Cleared virus without treatment	311	46.5	18	4.8
Had positive confirmatory antibody results	154	23.0	18	4.8
Not confirmed positive	157	23.5		
All	**669**	**100**	**376**	**100**

Note: Participants with no RNA results in their charts were omitted from this table as there is no way of determining their RNA status (n=6). One participant who was infected during this anti-D outbreak period had a non-outbreak genotype and was also excluded from this table

Table 7. Summary of main outcomes by hepatitis C RNA status for anti-D participants infected between 1991 and 1994

Outcomes	All*		Ever chronically infected		Never chronically infected	
	Number	%	Number	%	Number	%
Signs of liver disease	3	4.2	3	8.1	0	0.0
Cirrhosis	2	2.8	2	5.4	0	0.0
Liver tumours or HCC	0	0.0	0	0.0	0	0.0
High fibrosis score on biopsy	2	2.8	2	5.4	0	0.0
Deceased	0	0.0	0	0.0	0	0.0
Liver related disease directly caused death	0	0.0	0	0.0	0	0.0
All	**72**		**37**		**31**	

* There were no RNA results in the charts of 4 participants. These are included under all, but not under ever or never chronically infected

Note: 5 participants who were infected during this anti-D outbreak period had non-outbreak genotypes and were excluded from this table

Table 8. Current RNA status (this includes the last known status of deceased participants) for anti-D participants infected between 1991 and 1994

Final status	All		Ever chronically infected	
	Number	%	Number	%
Currently chronically infected	6	8.8	6	16.2
Treated and cleared virus	29	42.7	29	78.4
Cleared virus without treatment	33	48.5	2	5.4
Had positive confirmatory antibody results	6	8.8	2	5.4
Not confirmed positive	27	39.7		
All	**68**	**100**	**37**	**100**

*Participants with no RNA results in their charts were omitted from this table as there is no way of determining their RNA status (n=4). Five participants who were infected during this anti-D outbreak period had non-outbreak genotypes and were also excluded from this table

Table 9. Summary of main outcomes by hepatitis C RNA status for blood transfusion/renal participants

Outcomes	All*		Ever chronically infected		Never chronically infected	
	Number	%	Number	%	Number	%
Signs of liver disease	79	23.7	76	28.3	2	3.3
Cirrhosis	59	17.7	58	21.6	0	0.0
Liver tumours or HCC	15	4.5	15	5.6	0	0.0
High fibrosis score on biopsy	80	24.0	76	28.3	2	3.3
Deceased	77	23.1	68	25.3	6	9.8
Liver related disease directly caused death †	21	6.4	20	7.5	1	1.6
All	**333**		**269**		**61**	

* There were no RNA results in the charts of 3 participants (all deceased). These are included under all, but not under ever or never chronically infected

† Denominator for this is all participants minus those whose cause of death was not available (n=329)

Table 10. Current RNA status (this includes the last known status of deceased participants) for blood transfusion/renal participants

Final status	All		Ever chronically infected	
	Number	%	Number	%
Currently chronically infected	195	59.1	195	72.5
Treated and cleared virus	67	20.3	67	24.9
Cleared virus without treatment	68	20.6	7	2.6
Had positive confirmatory antibody results	33	10.0	7	2.6
Not confirmed positive	35	10.6		
All	**330**	**100**	**269**	**100**

Note: Participants with no RNA results in their charts were omitted from this table as there is no way of determining their RNA status (n=3)

Table 11. Summary of main outcomes by hepatitis C RNA status for blood clotting factor participants

Outcomes	All		Ever chronically infected		Never chronically infected		No RNA results in chart	
	Number	%	Number	%	Number	%	Number	%
Signs of liver disease	34	21.1	29	27.9	0	0.0	5	13.5
Cirrhosis	17	10.6	14	13.5	0	0.0	3	8.1
Liver tumours or HCC	7	4.4	5	4.8	0	0.0	2	5.4
High fibrosis score on biopsy	9	5.6	9	8.7	0	0.0	0	0.0
Deceased	67	41.6	29	27.9	1	5.0	37	100.0
Liver related disease directly caused death *	18	11.5	11	10.7	0	0.0	7	20.6
All	**161**		**104**		**20**		**37**	

* Denominator for this is all participants minus those whose cause of death was not available (n=157)

Table 12. Current RNA status (this includes the last known status of deceased participants) for blood clotting factor participants

Final status	All		Ever chronically infected	
	Number	%	Number	%
Currently chronically infected	72	58.1	72	69.2
Treated and cleared virus	27	21.8	27	26.0
Cleared virus without treatment	25	20.2	5	4.8
Had positive confirmatory antibody results	21	16.9	5	4.8
Not confirmed positive	4	3.2		
All	**124**	**100**	**104**	**100**

Note: Participants with no RNA results in their charts were omitted from this table as there is no way of determining their RNA status (n=37)

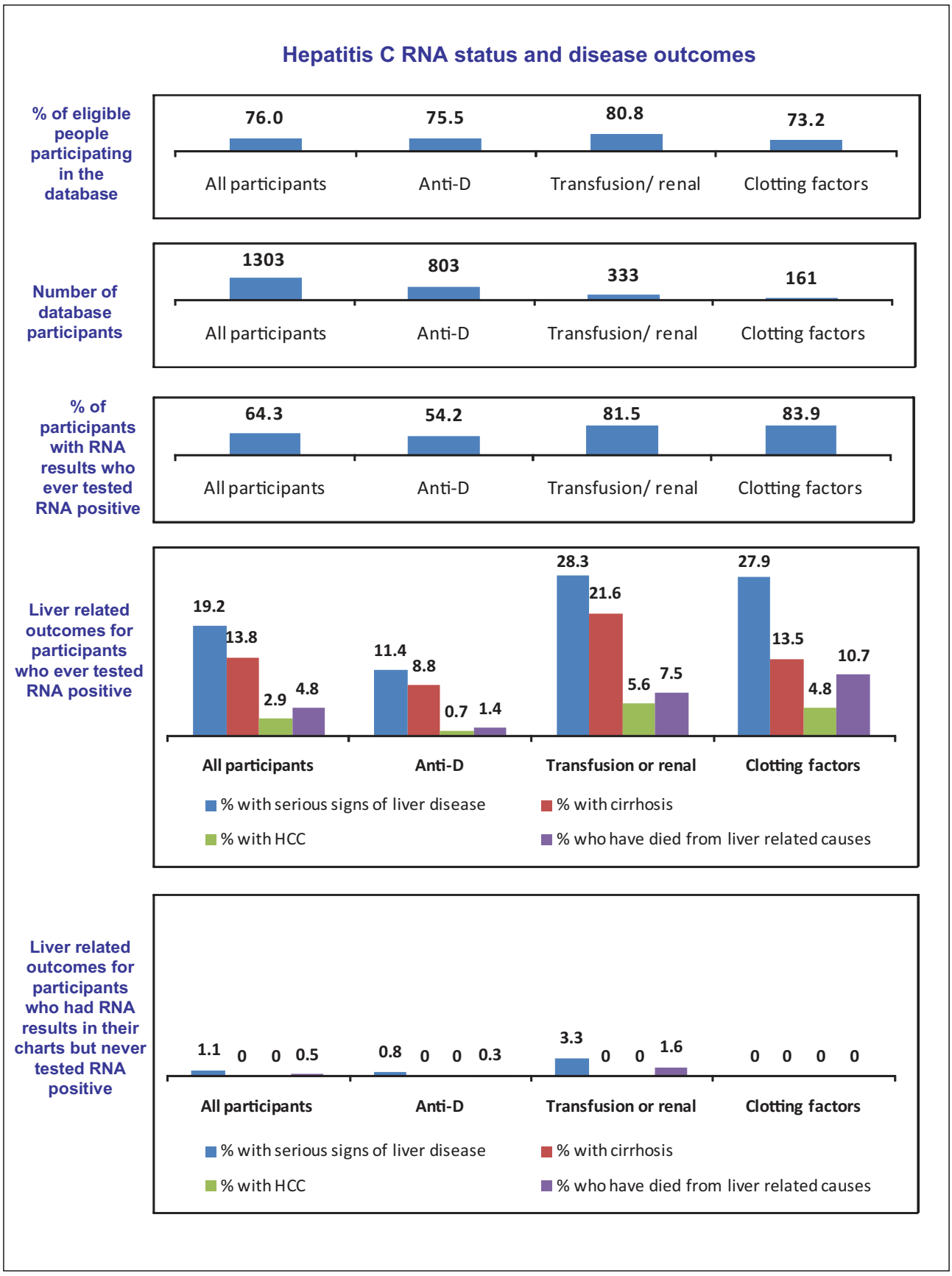

Figure 1. Summary of RNA status, and disease progression by RNA status, for all participants and by source of infection

Note: 50 participants had no RNA results in their charts. Of these, 37 were infected through contaminated blood clotting factors. These participants were similar to the participants who became chronically infected in terms of outcomes. Six participants had a source of infection other than those shown.

Chapter 1 Hepatitis C Virus Infection

Chronic hepatitis C infection is a major cause of chronic liver disease and death throughout the world.[1] Approximately 3% of the world's population is infected with hepatitis C virus (HCV).[2] Hepatitis C infection is caused by an RNA virus that was first identified in 1989.[3] Six distinct but related genotypes and multiple subtypes have been identified. In Western Europe genotypes 1a and 1b are most common, followed by genotypes 2 and 3.[4]

HCV is transmitted by blood and now occurs primarily through injecting drug use, and less frequently through sex with an infected partner, occupational exposure, and maternal-fetal transmission. In some cases no risk factors can be identified.[4,5] Transfusion-related HCV infection is rare now since the introduction of routine screening of blood for HCV antibodies in the early 1990s.

Acute HCV infection, in general, is relatively mild with only 20-30% of infected persons developing symptoms or clinically evident acute infection.[2] In most persons who become infected with HCV, viraemia persists. Chronic HCV infection is marked by persistence of HCV RNA for at least 6 months after onset of infection. Spontaneous resolution after 6 or 12 months of infection is unusual.[3] Between 55 and 85% of those infected develop chronic infection[6], the lower end of the range being accounted for mainly by women, particularly young women.[7,8]

Chronically infected people are at risk for progressive liver disease characterised by hepatocellular inflammation, hepatic fibrosis, cirrhosis and hepatocellular carcinoma (HCC).[6] These complications develop only in a proportion of patients and only after many years or decades of infection.[3] It has been estimated that up to 20% of chronically infected individuals will develop cirrhosis of the liver over a 20 to 25 year period, and that, of patients with cirrhosis, approximately 3% to 4% will develop HCC per year.[9] Factors that have been shown to be associated with progression of liver fibrosis include older age at infection, male gender, genetic factors, metabolic factors (steatosis, diabetes and obesity), co-infection with human immunodeficiency virus (HIV) or hepatitis B, duration of infection, and alcohol intake.[1,4,6,9]

Chronic HCV infection has been associated with several extrahepatic manifestations including essential mixed cryoglobulinemia, B-cell non-Hodgkin lymphoma, glomerulonephritis, seronegative arthritis, keratoconjunctivitis sicca and sialadenitis, lichen planus, neuropathies and neurological conditions including cognitive disorders and porphyria cutanea tarda.[3]

Very effective treatment is now available, which eradicates the virus in over 50% of cases.[1,10,11] Genotype and serum viral load are useful predictors of response to treatment. Response rates to treatment by pegylated interferon and ribavirin combination are more than 75% for genotypes 2 and 3, and 40-50% for genotype 1.

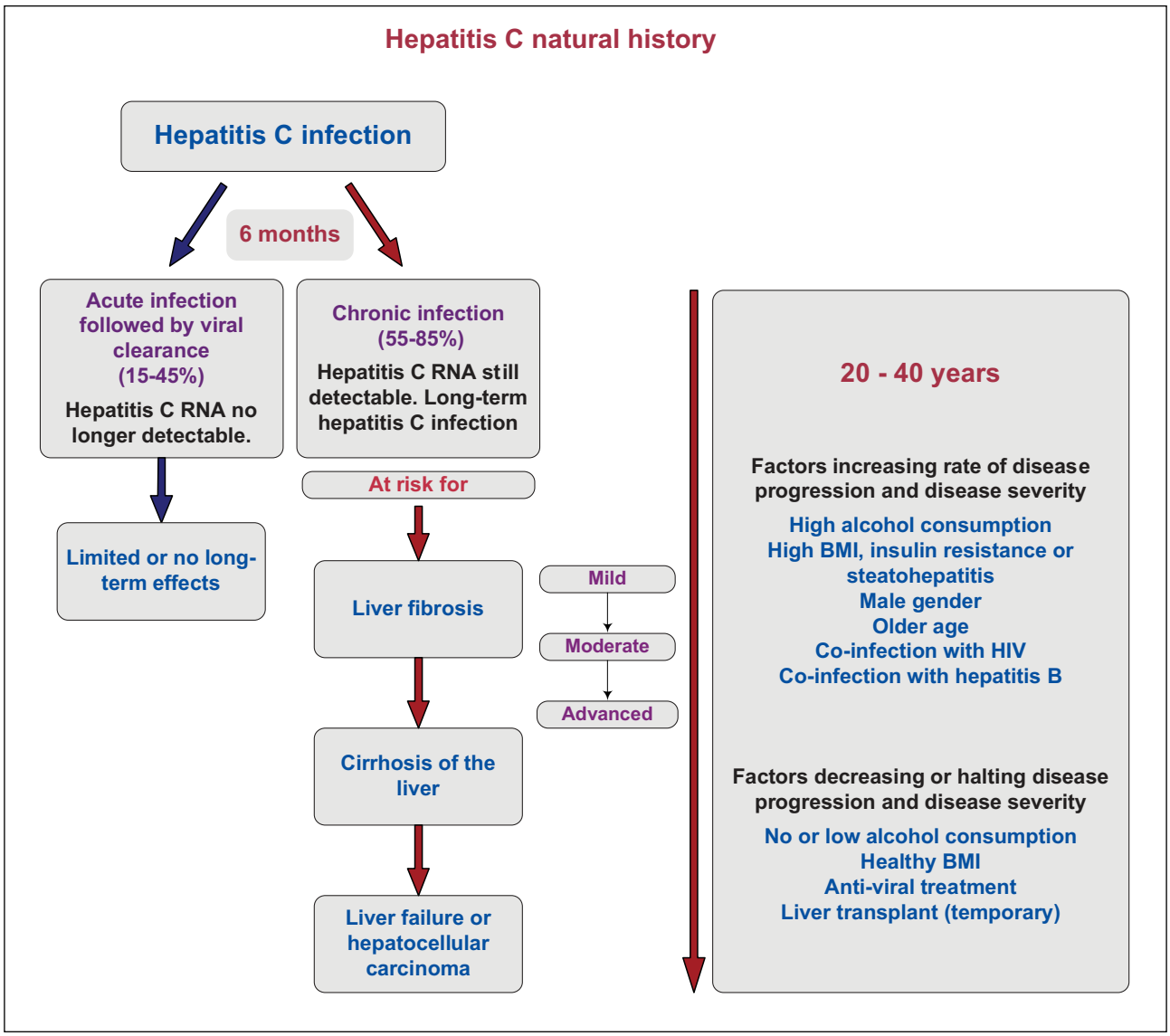

Figure 2. Summary of natural history of hepatitis C infection

Chapter 2 National Hepatitis C Database

Background to the database

Approximately 1,700 people have been identified as being infected with HCV through the receipt of contaminated blood and blood products in Ireland. These include women infected through anti-D immunoglobulin, recipients of blood transfusion, people with haemophilia and other blood clotting disorders and people who received treatment for renal disease.[12] Specialist hepatology services were set up in eight designated hospitals to provide services for this group. Those infected are also entitled to a range of additional hospital and primary care services under the Health (Amendment) Act, 1996 (HAA). Many of these people have a known year of infection and a large proportion has now been infected for over 25 years.

The National Hepatitis C Database for infection acquired through blood and blood products was set up by the Health Protection Surveillance Centre (HPSC) in association with the eight specialist hepatology units and is supported financially by the Health Service Executive (HSE) and formerly by the Department of Health and Children (DoHC). Approval for this project was obtained from the ethics committees of all eight hospitals and from the Office of the Data Protection Commissioner. The development and management of the database project is overseen by a steering committee (appendix A). A scientific and technical group supports and advises HPSC on the scientific and technical development of the database (appendix B).

The objectives of the database are:

1. To follow the natural history of infection in people infected through blood and blood products
2. To evaluate the impact of various host factors on the progression of the disease
3. To evaluate the outcomes of treatment
4. To monitor the uptake of services
5. To provide information for the planning and evaluation of health services
6. To serve as a resource for future research into hepatitis C

Baseline data were collected in 2005 and 2006 and included all relevant data from the date of diagnosis on all consented participants. A report describing these data was published in October 2007.[13] A report on the first round of follow-up data was published in February 2009.[14] This is currently the second round of follow-up data collection and includes information on all participants up to the end of 2008. All reports and patient newsletters are available through the hepatology units, patient support groups, hepatitis C liaison officers and on the database website (www.hcvdatabase.ie).

Database population

Any person (alive or dead) who contracted HCV infection through the administration of blood or blood products within the state is eligible to be included in the database. These include women infected through anti-D immunoglobulin, recipients of blood transfusion, people with haemophilia and other blood clotting disorders and people who received treatment for renal disease. Eligible patients were identified by the eight specialist hepatology units.[13]

For the purpose of this database, hepatitis C infection is defined as the detection of hepatitis C specific antibodies or the detection of hepatitis C nucleic acid. This includes all those who are ELISA (enzyme linked immunosorbent assay)/EIA (enzyme immunoassay) positive or weak positive, recombinant immunoblot assay (RIBA)/INNO-LIA positive or indeterminate, or hepatitis C polymerase chain reaction (PCR)/RNA positive.

Information is collected only on eligible people who consent to participate in the database and on eligible participants who have died. Relatives of deceased people are entitled to refuse participation and no data are collected on those who refused to participate in the database when they were alive.

Source of data

Information is gathered from the participants' medical records (hospital charts) in the eight hepatology units and is updated on an annual basis. No direct contact is made with any participant. No names or addresses are recorded in the database.

Data security

The database was built using MS SQL server 2000. It is physically located in a secure computer room in HPSC with access strictly limited to key technical support staff. Access to the database is secured by a combination of network, SQL server and MS Access security permissions. All paper forms are stored in a locked cabinet in HPSC.

Chapter 3 Follow-up Data Collection to end 2008

Data Collection

Data collection is carried out annually on participants in the database. This second round of follow-up data collection began in January 2008. The data collection form used is shown in appendix C. Data are extracted from the participants' medical notes by a HPSC research nurse. The follow-up data collected include all new clinical, demographic and lifestyle data added to the participants' medical records between the date of last data collection and the date of follow-up data collection (up to 31st December 2008). Data were entered into the database by a surveillance assistant. Double entry was used to maximise accuracy.

In order to improve the information held on participants, some additional data have been requested on the latest follow-up data collection form. Information regarding glucose tolerance testing, current hepatitis B status and fibroscan results have now been added to the follow-up form.

Recruitment of new participants

Recruitment of new participants to the database is ongoing and new participants are welcome to join at any time. These would include those people who did not consent to database participation when first invited to do so in 2004, and those newly identified as eligible since 2004. Patients are given the opportunity to consent at their hospital appointments where they are given further information about the database by staff. This has proven to be a successful method of encouraging patients who have not yet consented to consider participating in the database. Those who refused to consent at any time are not asked again. The patient support groups also encourage their members to participate through their newsletters and meetings.

There is a small number of people living abroad (approximately 25, personal communication, Michelle Tait HSE), who meet the eligibility criteria for the database but who do not attend a clinical service in Ireland. They are not currently included in the database due to the difficulties that would arise in terms of data collection, data quality, confidentiality and consent.

Assumptions

Various assumptions were made where data were missing. These related mainly to the year of infection. These assumptions were:

- Anti-D: If the person had received anti-D on multiple occasions, and one of these was the year of an outbreak period, i.e. 1977-1979 or 1991-1994, this year was taken as the year of infection. If none of the years fell into either of the outbreak periods, the earliest year that anti-D had been administered was used as the year of infection.
- Blood transfusion/treatment for renal disease: If the person had received multiple blood transfusions and none of them had been identified as being infectious, the earliest transfusion year was taken as the year of infection. Where the person had also been on dialysis for extended periods of time, the year of starting dialysis or of first blood transfusion, whichever was the earlier, was used as an estimate of the year of infection.
- Clotting factors: For people with haemophilia and other blood clotting disorders, if the year of infection was not available, the year that the patient first received clotting factors was used as a proxy for the year of infection. Where the year of infection and the year when first factor was administered were missing, then the year of diagnosis of haemophilia was used as the year of infection.
- Where precise day or month were missing from dates (e.g. date of infection), the year of infection was converted to 02/07/YYYY, where YYYY was the year of infection and 02/07 was the midpoint of the

year. All ages calculated were truncated and all durations were rounded based on the outcome of the calculation.

Estimating dates of cirrhosis and hepatocellular carcinoma (HCC)/liver cancer

Variables were created to indicate if participants had cirrhosis or liver cancer on biopsy or mentioned elsewhere in their medical charts or death certificates. Estimated dates of onset were generated for both conditions, but these were approximate. If multiple biopsies, ultrasounds or CT scans were done, the midpoint between the first positive and last negative date was used. Where cirrhosis or liver cancer was first mentioned on death certificates, the midpoint between the date of death and last negative diagnostic test or last visit to the hepatology unit was used. Otherwise the earliest date mentioned in relation to a diagnosis of cirrhosis or liver cancer was taken.

Estimating duration of hepatitis C ribonucleic acid (RNA) positivity

All RNA results were recorded for each participant. A variable was created to record the duration of RNA positivity in years for all participants who ever tested RNA positive. The following rules were used:

- If a participant remained RNA positive when last tested and was still alive, the duration of RNA positivity was calculated as their date of last visit minus their date of infection. If they were deceased, their date of death minus their date of infection was used.
- For participants who had tested RNA positive and cleared the virus, the duration of RNA positivity was calculated as the midpoint between the first negative and last positive result minus their date of infection.

Coding of death certificates

Death certificates were collected on deceased participants from the General Register Office (GRO). This was done by the research nurse, acting on behalf of the hepatology unit. No named data were brought to HPSC. The cause of death was coded using the World Health Organization (WHO) ICD-10 coding format. Analysis was done on the underlying cause of death as defined by the ICD system.

The cause of death was further classified using the following broad categories:

- Death directly caused by liver-related disease
- Death not directly caused by liver-related disease, but liver disease or hepatitis C listed as a contributing condition on the death certificate
- Death was not liver-related

Death was considered to be directly caused by liver-related disease in the following situations:
If hepatocellular carcinoma or end-stage liver disease (varices, ascites, liver failure or hepatic encephalopathy) were listed as any of the causes of death in section I of the death certificate
Or if liver disease was not specified as end-stage (e.g. cirrhosis) but the sequence of causes of death on the certificate suggested death was due to liver disease,
Or if liver disease was coded as the underlying and only cause of death.

The classification of all deaths was carried out by a consultant hepatologist and a medical epidemiologist, blinded to the hepatitis C immunoblot or RNA status.

Long-term medications

Long-term medications mentioned in the patient's chart are recorded in the database and were coded using the Anatomical Therapeutic Chemical (ATC) classification system. This is a standardised coding system, controlled by the World Health Organization, and is based on the organ or system on which the drug acts.

Liver biopsies

Different scoring systems were used to stage and grade the hepatitis C liver biopsies in the different hepatology units (appendix D):

- Knodell system:[15] fibrosis scored from 0-4
- Modified Knodell system,[16,17] also known as the Ishak or the modified HAI system: fibrosis scored from 0-6
- Scheuer system:[18] fibrosis scored from 0-4
- International Group of Hepatopathologists system: fibrosis scored from 0-4

For some of the analyses, the biopsies scored from 0 to 6 were converted to 0 to 4 scores so that all scored biopsies could be considered together. The following conversions were used: 0=0, 1=1, 2=1, 3=2, 4=3, 5=3 and 6=4.

Data analysis

Data analysis was done using Business Objects, Microsoft Access 2007, Microsoft Excel 2007 and Stata/SE version 10.0. Either Pearson's Chi-square or the Wald test, with corresponding probability value (P-value) and 95% confidence intervals, were used to test for differences between odds of a given outcome in logistic regression analysis. Poisson regression was used to examine survival since infection with HCV. All statistical tests were 2-tailed and a p-value of < 0.05 was taken as statistically significant.

Chapter 4 Main Findings

The main findings of the second round of follow-up data collection are presented as follows:

- Summary of participation rates and representativeness of the database cohort
- Description of database population
    - RNA results
    - End of latest follow-up
    - Age, gender, source of infection, duration of infection and genotype
- Alcohol consumption
- Outcomes
    - Medical conditions
    - Liver function tests – alanine amino transferase (ALT)
    - Signs of serious liver disease, cirrhosis and hepatocellular carcinoma
    - Biopsy results
    - Deceased participants
- Changes in the prevalence of the main outcomes since baseline data were collected
- Summary of disease progression and the factors associated with disease severity
- Anti-viral treatment for hepatitis C
- Liver transplants
- Focus on the different patient groups
- Clinical management and health service usage
    - Long term medications other than anti-viral treatment
    - Visits to the hepatology unit
    - Specialist health services and procedures
    - Complementary and alternative therapies

Summary of participation rates and representativeness of the database cohort

New participants

Twenty eight people have been added to the database since the first round of follow-up data collection, bringing the total number of participants to 1,303. The new database participants include twenty five new consents and three people who are newly deceased or newly identified as deceased. The overall participation rate is now 76%, including people who have died, and the consent rate is 74% (figure 3).

Sixty two percent (n=803) of database participants were infected with HCV through contaminated anti-D, 26% (n=333) were infected either through receipt of contaminated blood transfusions or through treatment for renal disease, 12% (n=161) of participants were infected through contaminated blood clotting factors and six participants were infected through sexual or vertical contact with people with state-acquired infection.

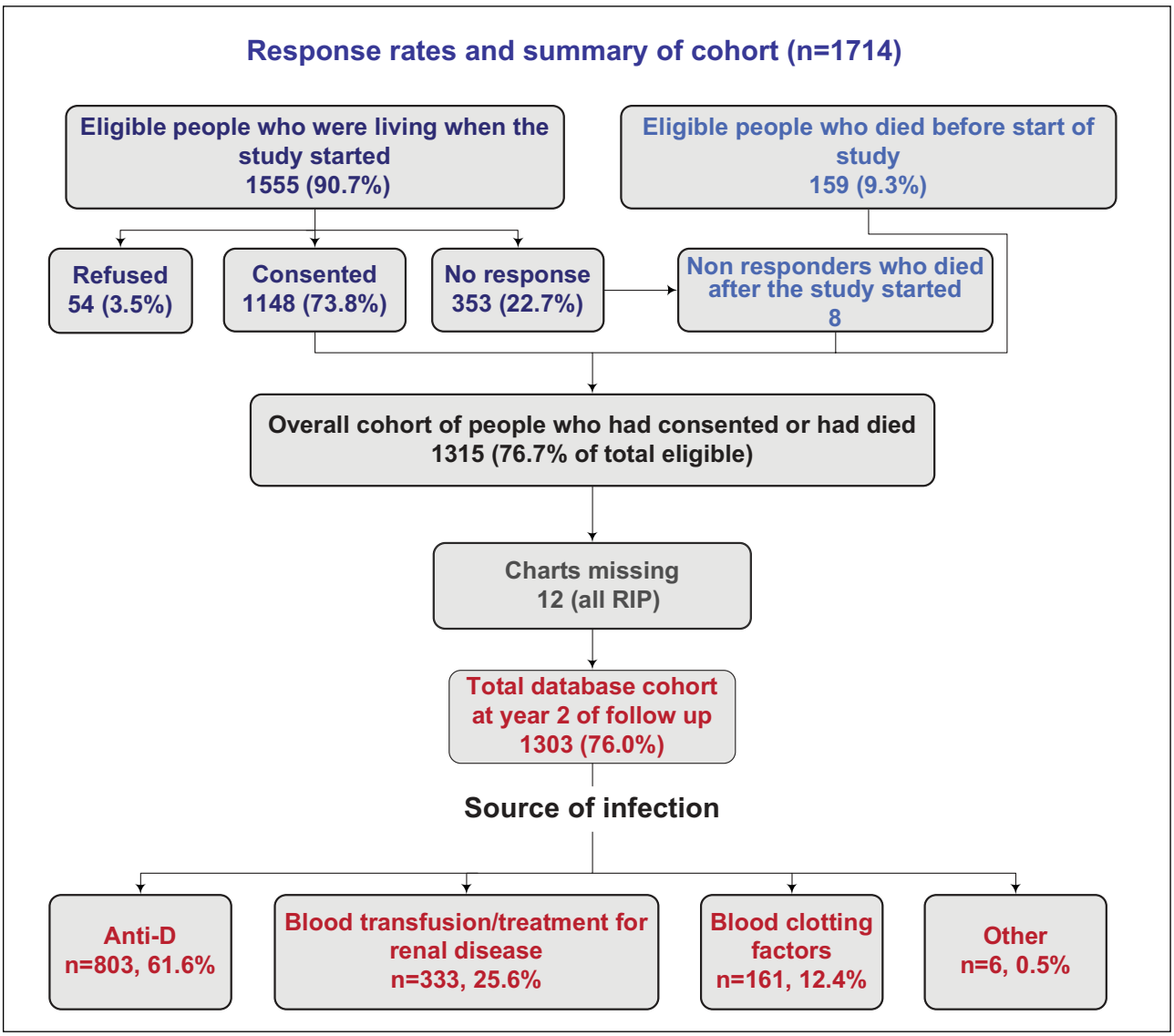

Figure 3. Summary of participation rates and database cohort

Note: Source of infection = "Other" includes participants infected through vertical or sexual contact with people with state-acquired infection

Although we do not have patient-based data on source of infection or gender for non-participants, the hepatology units provide us with summary data to enable us to assess how representative the database population is of the entire eligible population.

The proportion of patients infected through blood transfusions who were included in the database was higher than the proportions of the other two groups, but this difference was due to the higher proportion of deceased patients in the transfusion group. There was no statistically significant difference in participation by gender (figure 4). Database participation varied with age, with older people more likely to participate. This difference was statistically significant and held true even when deceased patients were excluded from the analysis (figure 4).

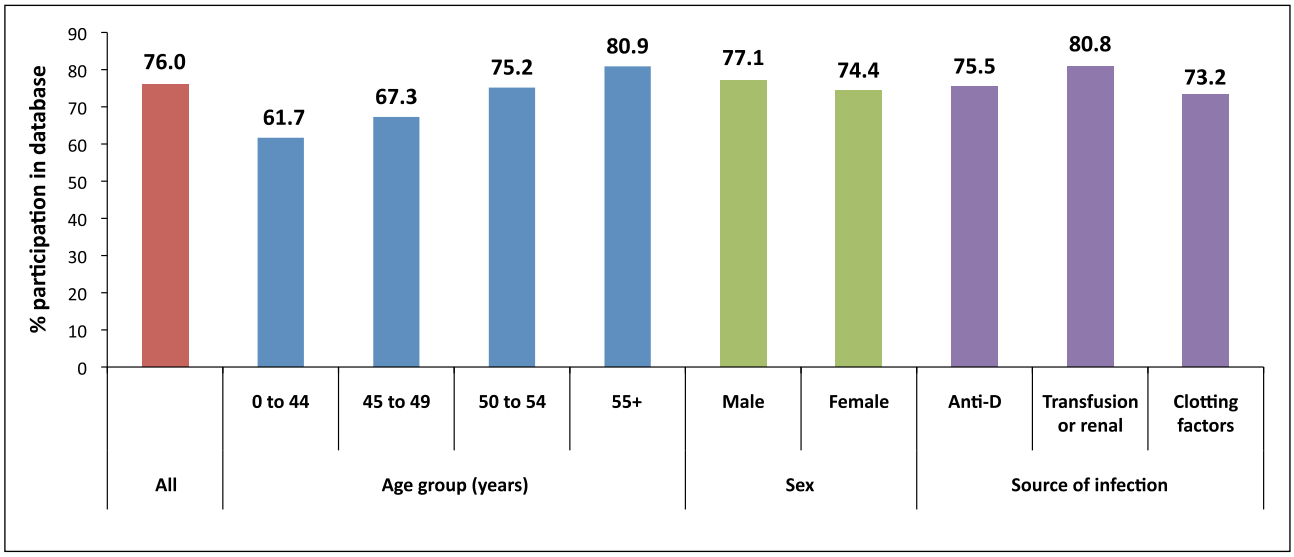

Figure 4. Percentage of eligible people participating in the database by age group at the end of 2008, gender and source of infection

Description of database population

RNA results

RNA tests are used to test for circulating virus. Positive results indicate current infection. In general, ELISA/EIA tests are used as screening tests for HCV antibodies, and line-immunoassay tests (e.g. RIBA/INNO-LIA) are used to confirm positive antibody results. The combination of a positive HCV antibody result and a negative RNA result indicates past infection.

As the vast majority of participants were diagnosed some years after infection, ever testing RNA positive was found to be an excellent indicator of chronic long-term infection. Most of those who ever tested RNA positive and subsequently cleared the virus have done so relatively recently (almost all as a result of anti-viral treatment) as the median duration of RNA positivity for those who ever tested positive (29 years) was found to be similar to the median time between infection and end of latest follow-up (30 years). Throughout this report, we treat participants who ever tested RNA positive as having been chronically infected with HCV and these participants are the primary focus when looking at clinical outcomes and disease progression to date.

We have no way of knowing the timing of viral clearance for participants who cleared the virus spontaneously prior to HCV testing (and thus had no positive RNA results). However, studies have found that spontaneous viral clearance usually occurs within a year of infection, so we assumed that these participants experienced acute infection only and were never chronically infected.[19,20]

In order to facilitate the comparison of participants who developed chronic infection and those who cleared the virus spontaneously after acute infection with HCV and never developed chronic infection, most data are presented separately for participants who ever tested RNA positive and those who had RNA tests done but had no positive RNA results. The participants who had no RNA results in their charts were omitted from most of the results presented by RNA status as they could not be classified as either "ever" or "never" testing RNA positive.

Overall, 62% (n=806) of database participants had at least one positive RNA result in their charts (figure 5) and a further 15% (n=193) had positive confirmatory tests for HCV antibodies but no positive RNA results. The remaining 23% (n=304) tested either ELISA/EIA positive or weak positive, or RIBA/INNO-LIA indeterminate, and had no other positive HCV results. People with positive or weak positive ELISA/EIA tests or indeterminate RIBA/INNO-LIA tests were included in the database as many patients were tested many years after suspected infection, had documented exposure to HCV and may have cleared the virus and since sero-reverted. HCV antibody levels have been demonstrated to drop below detection limits in some patients.[21,22,23]

Twenty three percent (n=37) of participants infected through clotting factors had no RNA test results in their charts (figure 5). All were deceased and most had died in the early to mid 1990s. RNA tests were only commonly used from 1994 onwards in Ireland. These participants were found to be similar to participants known to be chronically infected in terms of liver-related outcomes and it is likely that a large proportion would have been RNA positive if they had been tested prior to their death.

Once participants with no RNA results were excluded, the overall spontaneous viral clearance rate, as determined by testing RNA negative at the time of first diagnosis, was 36%. This varied by gender and source of infection. Females (n=411, 41%) were significantly more likely to have cleared the virus by the time of their diagnosis than males (n=36, 14%). This gender imbalance remained but was significantly lessened when anti-D participants were excluded (23% for females compared to 14% for males).

Some participants did not have positive confirmatory results for HCV. A small proportion of these may have had false positive ELISA/EIA results, making the viral clearance rate appear higher than it actually was. When only participants with positive confirmatory results for HCV were analysed, 19% had cleared the virus spontaneously by the time they were diagnosed. Therefore the true viral clearance rate is likely to be between 19 and 36%.

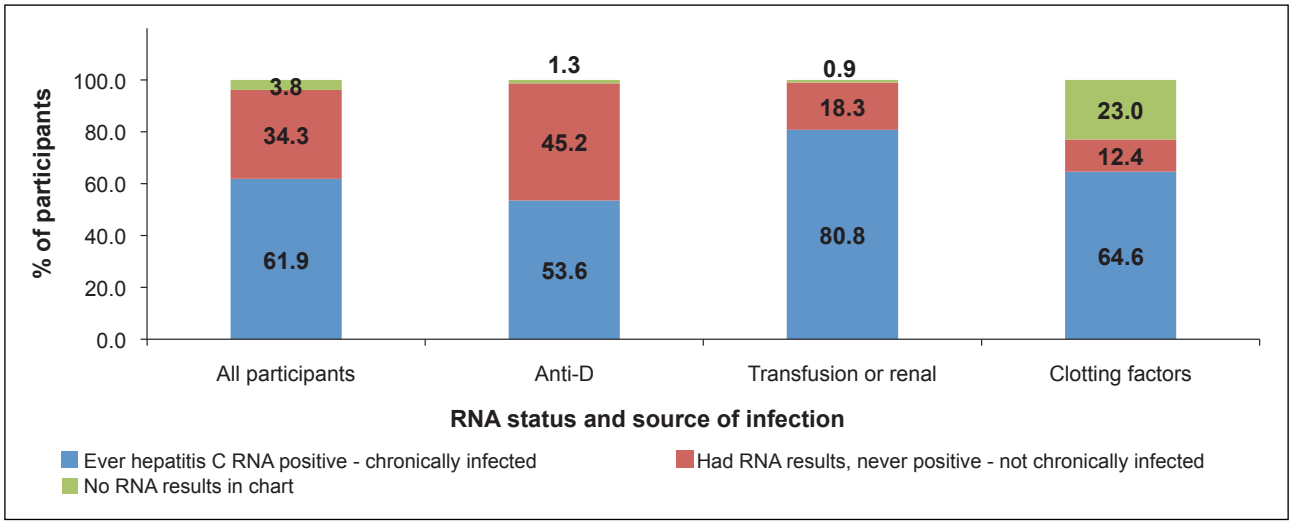

Figure 5. Hepatitis C RNA results for all participants and by source of infection (n=1303)

End of latest follow-up

Data up to the end of 2008, where available, were collected for this round of data collection. However, latest follow-up for each participant is effectively the last time they visited their hepatology unit or their date of death as this is the last date when information was recorded in their medical charts.

Of the living patients who became chronically infected, last hospital follow-up was in 2008 for 82%, 2007 for 8%, 2006 for 4% and 2005 or earlier for 6%. Participants who did not become chronically infected were less likely to have been followed up recently: 49% last attended in 2008, 15% in 2007, 7% in 2006 and 30% in 2005 or earlier. Some database participants are likely to have moved abroad and may be lost to follow-up and some of the participants who never became chronically infected may have been discharged to the care of their GPs.

Age, gender, source of infection, duration of infection and genotype

Participants infected through contaminated anti-D

The anti-D group is entirely composed of females who were infected during their child-bearing years (median age: 28 years) (figure 6, table 13). As a group, they would be expected to have been relatively healthy when infected.

Infection due to contaminated anti-D has been largely traced to batches of anti-D from two infected donors.[24] Batches from the first donor were contaminated with genotype 1 HCV and were distributed between 1977 and 1979. Eighty four percent (n=676) of anti-D participants were infected during this

period. Batches from the second donor were infected with genotype 3 HCV. These were administered between 1991 and 1994 and accounted for ten percent (n=78) of participating anti-D participants. The genotypes for one participant infected between 1977 and 1979 and for five participants infected between 1991 and 1994 did not match the outbreak genotypes. The estimated year of infection for the remaining fifty participants was outside of these outbreak periods and sixty six percent (n=33) did not have positive confirmatory results for HCV. The source of their infection is unclear.

By latest follow-up, the median age of anti-D participants who became chronically infected was 57 years and the median duration of RNA positivity was 31 years (table 13). Eighty three percent had been RNA positive for 25 years or longer.

Participants infected through contaminated blood transfusions or treatment for renal disease
This group was the most heterogeneous in terms of age and gender (figure 6, table 13). They had the highest median age at infection (33 years for the group as a whole and 32 years for chronically infected participants), but this ranged from 0 to 77 years. Fifty seven percent of chronically infected participants were female and forty three percent were male, making this the only group with sizeable proportions of each gender. Using the assumptions outlined in chapter 3, most of the blood transfusion/renal participants were infected in the late 1970s and 1980s. They had the shortest duration of RNA positivity at latest follow-up, with 34% positive for 25 years or longer. At latest follow-up, the median age of transfusion/renal participants who became chronically infected was 60 years and the median duration of RNA positivity was 21 years (table 13).

Participants infected through contaminated blood clotting factors
Participants infected through clotting factors were predominantly male (94%) and 42% were co-infected with HIV (figure 6). Using the assumptions outlined in chapter 3, most were infected as children in the mid-1970s to early 1980s. The median age at infection was 13 years for the group as a whole and 14 years for those who were chronically infected (table 13). By latest follow-up, the median age for clotting factor participants who became chronically infected was 45 years and the median duration of RNA positivity was 29 years (table 13). Seventy one percent were RNA positive for 25 years or longer.

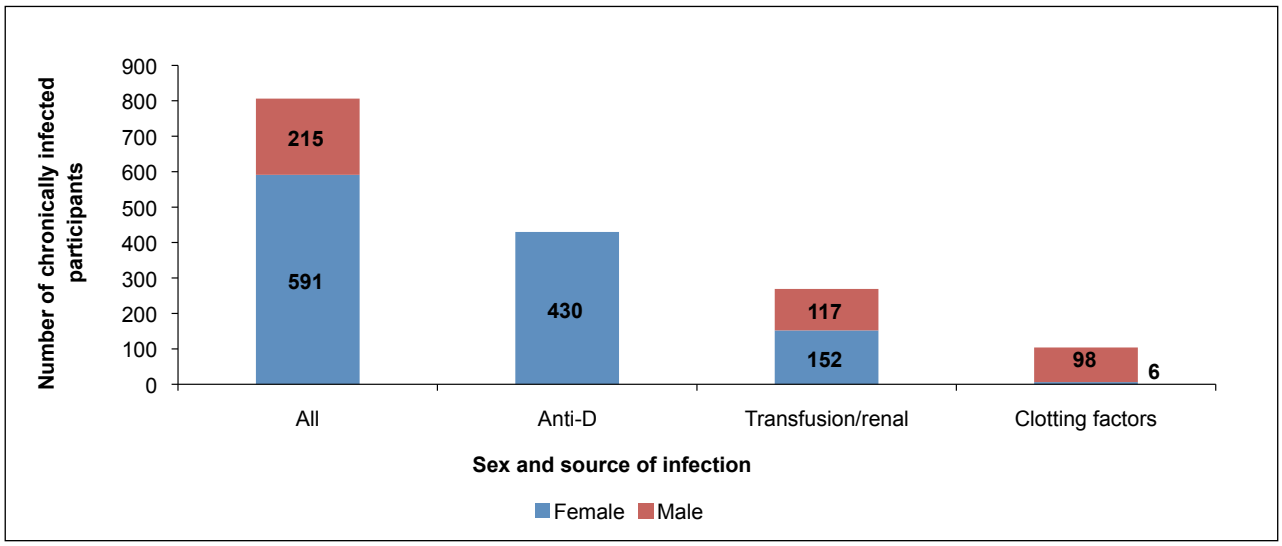

Figure 6. Number of chronically infected participants by gender and source of infection (n=806)
Note: The 'All' category includes 3 participants with "other" sources of infection.

Table 13. Summary of age at infection, age at end of latest follow-up, years since infection and duration of RNA positivity by source of infection for chronically infected participants

Source of infection		Age at infection	Age at end of follow up	Duration of infection (years since infection)	Duration RNA positivity
Anti-D	Median	28	57	31	31
	Minimum	17	31	9	2
	Maximum	44	75	42	42
Anti-D 1977-1979	Median	28	58	31	31
	Minimum	17	33	17	15
	Maximum	44	75	32	32
Anti-D 1991-1994	Median	30	45	15	6
	Minimum	19	31	10	2
	Maximum	39	55	17	16
Transfusion/renal	Median	32	60	23	21
	Minimum	0	16	1	1
	Maximum	77	91	47	46
Clotting factors	Median	14	44.5	31	28.5
	Minimum	0	18	14	12
	Maximum	53	81	48	48
All	Median	28	57	30	29
	Minimum	0	16	1	1
	Maximum	77	91	48	48

Genotype

The HCV genotype was available for nearly all of the database participants who became chronically infected (n=767, 95%). Genotype 1 predominated: 76% (n=584) were infected with genotype 1, 19% (n=142) were infected with genotype 3, 5% (n=37) were infected with genotype 2 and four participants were infected with genotypes 4 or 5 (figure 7).

Genotype 1 was significantly more common in anti-D participants compared to transfusion/renal or clotting factor participants. This is due to the large group of females infected with genotype 1 HCV through batches of anti-D administered between 1977 and 1979. Ninety percent of the anti-D participants who have been genotyped had genotype 1 HCV compared to 58% of blood transfusion/renal participants and 63% of blood clotting factor participants (figure 7).

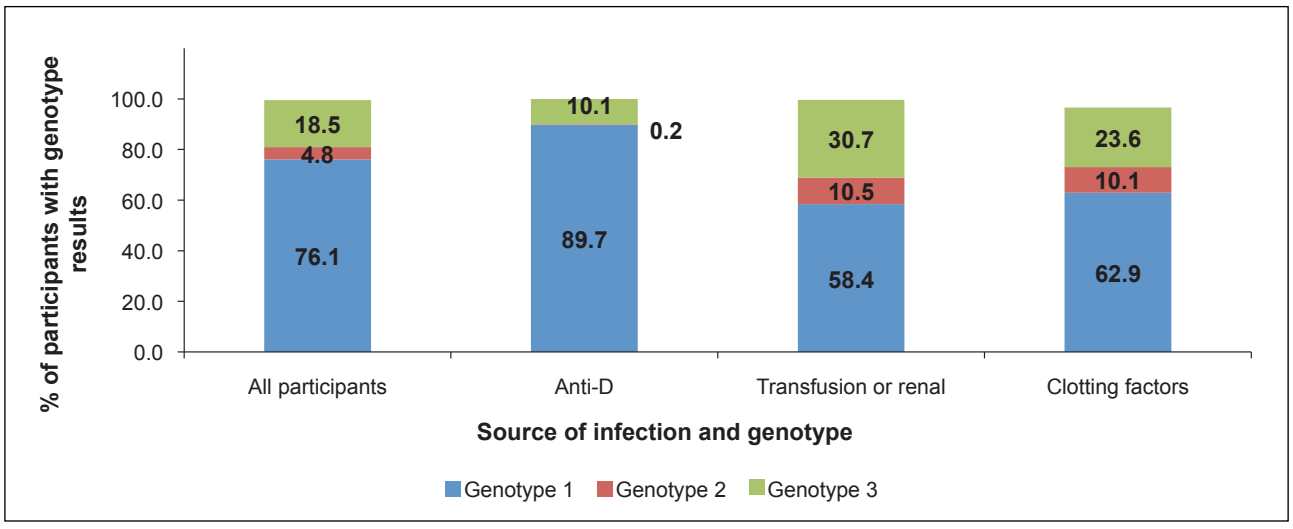

Figure 7. Distribution of hepatitis C genotypes by source of infection (n=763, genotypes 4 & 5 omitted, n=4)

Alcohol consumption

The recommended upper limits for alcohol consumption for the general population in Ireland are 21 units per week for males and 14 units per week for females.[25] Participants consuming between these limits and 40 units per week were classified as having moderately high alcohol intake and those consuming over 40 units were classified as having high alcohol intake. Some data on units of alcohol were available for 90% of all participants, and 92% of those who became chronically infected. However, it is unusual for alcohol consumption to have been recorded at every visit, and in many cases it was last recorded many years ago. Alcoholic liver disease or alcohol abuse was also mentioned in the charts of some participants. This additional information was combined with alcohol intake data when looking at the effects of alcohol on disease progression and these participants were considered to have had high alcohol intake at some stage. Alcohol intake in excess of the recommended limits was recorded in the medical charts of 15% of chronically infected participants for whom data were available (table 14).

Table 14. Highest recorded alcohol intake for all database participants and by RNA status (where data available, n=1168, 90%)*

Alcohol consumption	All		Chronically infected		Never chronically infected	
	Number	%	Number	%	Number	%
Non drinker	292	25.0	181	24.4	105	25.9
Within recommended limits	729	62.4	453	61.0	268	66.0
Moderately high	64	5.5	45	6.1	18	4.4
High	83	7.1	64	8.6	15	3.7
Total	**1168**	**100.0**	**743**	**100.0**	**406**	**100.0**

* no alcohol intake data for 135 database participants, RNA status not known for 19 participants with alcohol intake data. Data for these participants shown under the "All" category, but not under the "Chronically infected" and "Never chronically infected" categories.

Differences in alcohol consumption by gender and source of infection

Males and females differed in their reported exposure to alcohol with 32% (n=59) of chronically infected males exceeding the recommended limits for alcohol intake compared to 9% (n=50) of females (figure 8). Alcohol consumption also differed by source of infection with participants infected through anti-D significantly less likely to consume alcohol in excess of recommendations compared to those infected through other means (figure 9). However, this is likely to be largely attributable to the differences in gender distribution by source of infection.

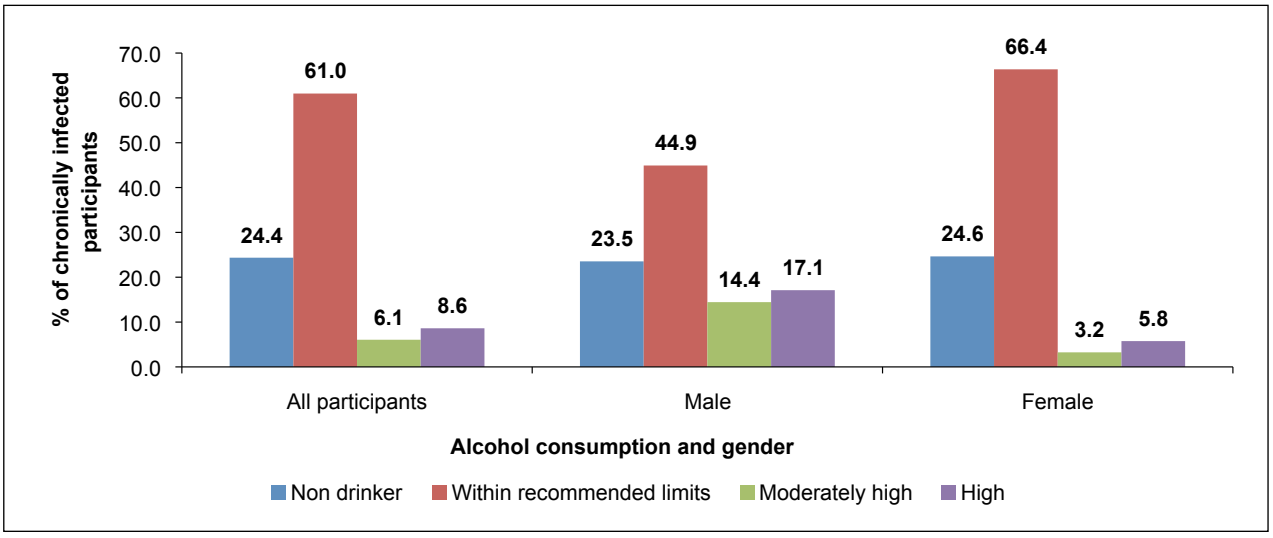

Figure 8. Distribution of highest reported alcohol consumption by gender for participants who became chronically infected (where data available, n=743, 92%)

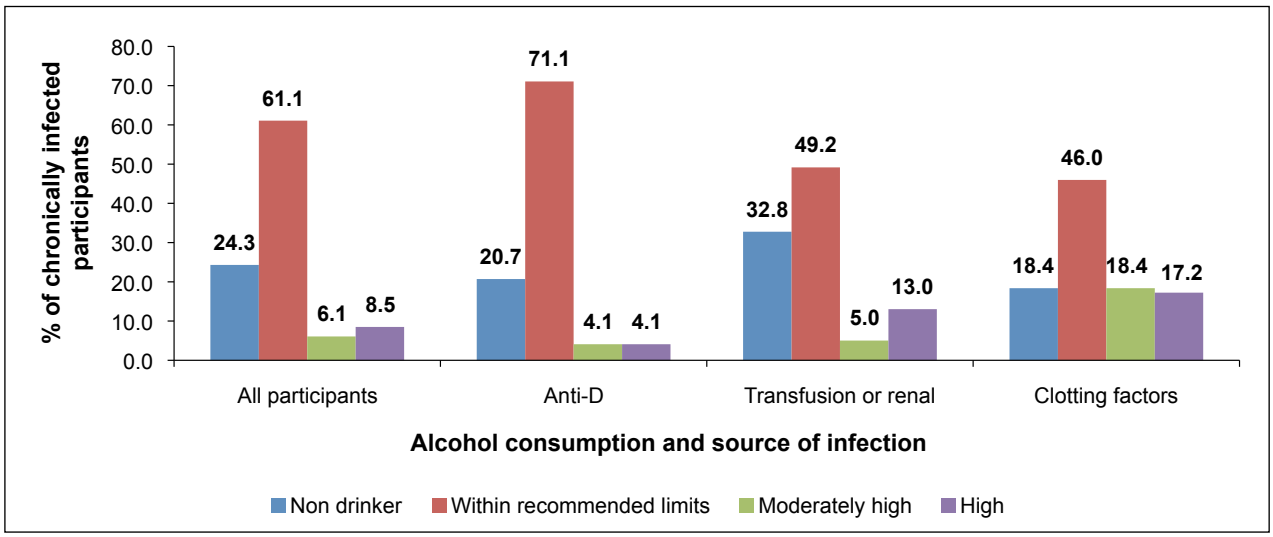

Figure 9. Distribution of highest reported alcohol consumption by source of infection for participants who became chronically infected (where data available, n=740, 92%)

Changes in alcohol consumption between first visit to the hepatogy unit and subsequent visits for chronically infected participants

Alcohol data were available at first and at least one subsequent visit to the hepatology units for 359 (45%) chronically infected participants. These data were more likely to be available for participants who had high (92%) or moderately high (71%) alcohol consumption than for those whose consumption was within recommended limits (47%) or who were non drinkers (32%). Where data were available, 22% (n=77) initially consumed alcohol in excess of recommended limits. Latest data for these participants show a significant reduction with 7% (n=26) having moderately high or high alcohol intake (table 15, figure 10).

Table 15. Changes in alcohol consumption for chronically infected participants (where data available at first and subsequent visits to the hepatology unit, n=359, 45%)

Changes in alcohol consumption	Number	%
No change: moderately high or high	15	4.2
Decrease: high or moderately high to within limits/non drinker	62	17.3
Increase: within limits/non drinker to moderately high or high	11	3.1
No change: within limits/non drinker	271	75.5
All	**359**	**100**

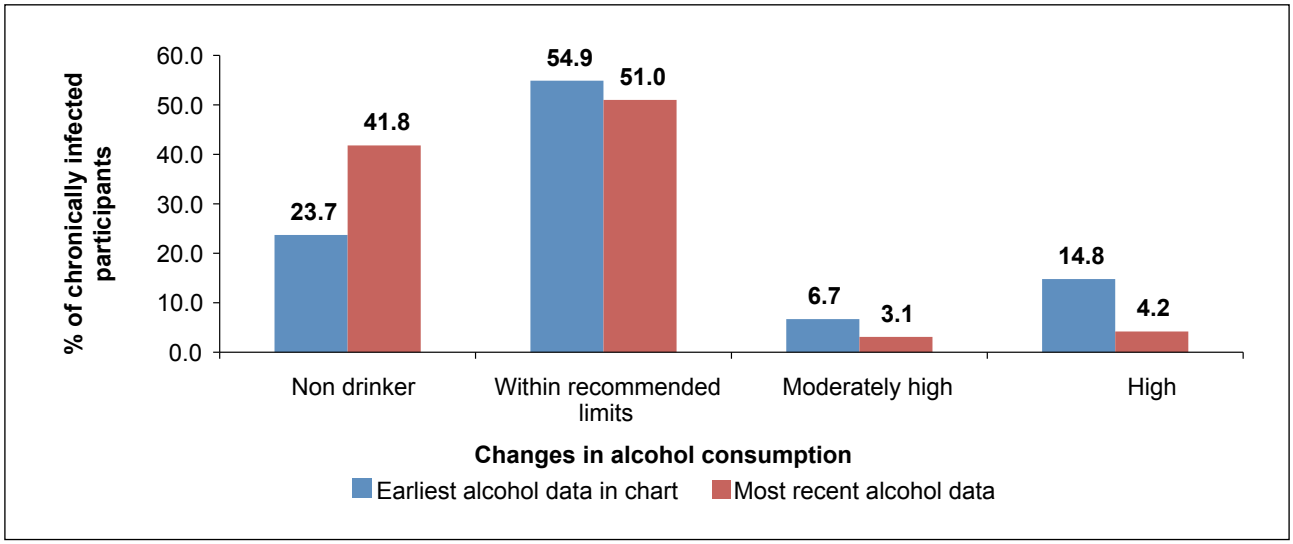

Figure 10. Changes in alcohol consumption for chronically infected participants (where data available at first and subsequent visits to the hepatology unit, n=359, 45%)

Outcomes

Medical conditions

Medical conditions recorded in participants' medical charts were entered into the database. However, these conditions may not have always been diagnosed according to standardised criteria and may not be related to HCV infection. Some medical conditions may also be underestimated if patients are treated privately and the condition is not discussed with the consultant hepatologist. However, if the condition was serious or known to be associated with HCV infection it is more likely to have been reported and recorded.

Without a comparison group, it is not possible to determine if the prevalence of these conditions and procedures differed from the general population. However, if the condition was strongly associated with HCV infection, we would expect to see a significant difference in the prevalence of the condition between participants who became chronically infected and those who cleared the virus after acute infection. We excluded medical conditions that were known to pre-date HCV infection, but the year the condition was diagnosed was not always known.

Table 16 shows the most common medical conditions recorded by RNA status and indicates conditions where there is statistically significant difference (Chi-square test $p < 0.05$) in the prevalence of the condition between participants who were ever chronically infected and those who were not. Differences should be interpreted with caution as follow-up was better for chronically infected participants and this may have led to a bias in the reporting and recording of medical conditions.

Depression was recorded in the medical charts of 359 participants. The prevalence was significantly higher for chronically infected participants (n=264, 33%) compared to those who did not become chronically infected (n=95, 21%). Females were more likely to report depression than males after accounting for the effects of RNA status. Participants who had received anti-viral treatment were also more likely to have depression recorded in their medical charts. Long-term medications for depression, sleep disorders or anxiety were noted in the charts of 60% (n=160) of chronically infected participants with depression.

Osteoporosis was significantly more likely to be recorded for females, participants who were older at most recent follow-up and those who became chronically infected

Participants who were male, who were older at infection or older at latest follow-up, and those who became chronically infected, were significantly more likely to have diabetes.

Twenty percent of chronically infected females had hysterectomies compared to 16% of those who never became chronically infected. The difference in hysterectomy prevalence by RNA status was not statistically significant. A study looking at hysterectomies in a population of 17,735 Irish women aged between 50 and 65 years who attended breast screening services was carried out in 2000. The prevalence of hysterectomies in this population was 22% and the peak age at the time of the operation in this population was 45-49 years.[26] The prevalence in female database participants in the same age group was 20% and did not differ according to HCV RNA status. The median age at operation was also similar (43 years for chronically infected participants and 44 years for those who did not become chronically infected).

Table 16. Medical conditions recorded in charts of participants – most common conditions and other conditions of interest* excluding conditions known to pre-date hepatitis infection

Disease or condition	Chronically infected		Never chronically infected		Statistically significant difference	Statistically significant difference in females	Statistically significant difference in males
	Number	%	Number	%			
Malaise, fatigue and lethargy	261	32.4	132	29.5	No	Yes	No
Depression	265	32.9	94	21.0	Yes	Yes	No
Arthralgia and joint pain	195	24.2	113	25.3	No	No	No
Hypertension	168	20.8	69	15.4	Yes	No	No
Hysterectomy †	119	20.1	67	16.3		No	
Fibromyalgia or myalgia	108	13.4	43	9.6	Yes	Yes	No
Disorders of the thyroid gland	90	11.2	36	8.1	No	Yes	No
Anaemia	64	7.9	28	6.3	No	No	No
Cholecystectomy	83	10.3	36	8.1	No	No	No
Osteoarthritis	84	10.4	34	7.6	No	Yes	No
Osteopaenia & other disorders of bone density/structure	73	9.1	36	8.1	No	No	No
Chronic lower respiratory diseases	75	9.3	28	6.3	No	Yes	No
Dermatitis or eczema	69	8.6	20	4.5	Yes	Yes	Yes
Disorders of lipoprotein metabolism and other lipidaemias	41	5.1	43	9.6	Yes ‡	Yes ‡	No
Diabetes	62	7.7	15	3.4	Yes	Yes	No
Dry/itchy/gritty eyes or conjunctivitis	57	7.1	23	5.1	No	No	No
Helicobacter pylori	51	6.3	23	5.1	No	No	No
Irritable bowel syndrome	39	4.8	27	6.0	No	No	No
Osteoporosis	55	6.8	10	2.2	Yes	Yes	No
Operations on appendix	45	5.6	18	4.0	No	No	No
Hiatus hernia	37	4.6	23	5.1	No	No	No
Excessive, frequent and irregular menstruation †	34	5.8	25	6.1		No	
Gastro-oesophageal reflux disease	46	5.7	11	2.5	Yes	Yes	No
Alcohol abuse or excess	45	5.6	7	1.6	Yes	Yes	No
Gastric, duodenal or other peptic ulcer	36	4.5	20	4.5	No	No	No
Anxiety disorders	42	5.2	13	2.9	No	Yes	No
Sicca/Sjorgen syndrome or polymyalgia rheumatica	20	2.5	6	1.3	No	No	No
Operations on thyroid, parathyroid, other endocrine glands	19	2.4	6	1.3	No	No	No
Diseases of the gallbladder	20	2.5	2	0.4	Yes	Yes	No
Thrombocytopenia and other Purpura	18	2.2	3	0.7	Yes	Yes	No
Sarcoidosis	7	0.9	3	0.7	No	No	No
Cryoglobulinaemia	6	0.7	1	0.2	No	No	No
Neuropathies	5	0.6	1	0.2	No	No	No
Non-Hodgkin's lymphoma	5	0.6	0	0.0	No	No	No
Parkinson's disease	3	0.4	2	0.4	No	No	No
Myeloid leukaemia	3	0.4	1	0.2	No	No	Yes
Lupus erythematosus	3	0.4	0	0.0	No	No	No

* All conditions where n≥45 are included. Data for some other conditions, mentioned in literature, or raised by patient groups, are also included (darker blue). **Conditions known to pre-date hepatitis C infection were excluded from this table**.
† Percentage calculated using female denominator figures.
‡ Participants who were never chronically infected were more likely to have this condition than those who were chronically infected. For all other conditions where statistically significant differences are indicated, prevalence was higher in chronically infected participants.

Liver function tests – alanine aminotransferase (ALT)

Ninety four percent of database participants had at least one ALT result in their charts and 69% had two or more tests done. Levels were elevated on at least one test for 60% of chronically infected participants and 12% of those with no positive RNA results. Two of more abnormally high ALT results were recorded for 35% of chronically infected participants and 2% of participants who did not develop chronic infection. Nineteen percent of chronically infected participants had ALT levels 2.5 or more times the upper normal limit on at least one test compared to 1% of those who were not chronically infected.

In addition to chronic infection, the independent risk factors for ever having elevated ALT levels and for having ALT levels 2.5 or more times the upper normal limit on any test were: male gender, moderately high or high alcohol consumption and being infected for over 30 years. Table 17 shows the highest ALT results by source of infection for chronically infected database participants.

Table 17. Highest alanine aminotransferase results by source of infection for ever chronically infected participants

Alanine aminotransferase results	All		Anti-D		Transfusion/ renal		Clotting factors	
	Number	%	Number	%	Number	%	Number	%
Normal	313	40.0	157	36.9	124	47.2	30	32.6
Elevated: <2.5 times upper normal limit	320	40.9	195	45.9	86	32.7	38	41.3
Elevated: ≥ 2.5 times upper normal limit	150	19.2	73	17.2	53	20.2	24	26.1
Total	**783**	**100**	**425**	**100**	**263**	**100**	**92**	**100**

Signs of serious liver disease

One hundred and sixty seven (12.8%) participants had one or more signs of serious liver disease recorded in their charts at latest follow-up (table 18). Ninety three percent of these (n=155) tested RNA positive at some stage, 4% (n=7) had no RNA results in their charts and 3% (n=5) never tested RNA positive. The most common conditions or signs recorded were cirrhosis, varices, ascites and portal hypertension.

Table 18. Number and percentage of participants with signs of serious liver disease by RNA status

	All		Chronically infected		Never chronically infected	
Serious signs of liver disease	Number	%	Number	%	Number	%
Cirrhosis	116	8.9	111	13.8	0	0.0
Hepatomegaly or splenomegaly or both	64	4.9	60	7.4	4	0.9
Varices	60	4.6	58	7.2	0	0.0
Portal hypertension	48	3.7	47	5.8	0	0.0
Ascites	47	3.6	43	5.3	3	0.7
HCC	25	1.9	23	2.9	0	0.0
Encephalopathy	22	1.7	20	2.5	1	0.2
Decompensated liver disease	11	0.8	10	1.2	0	0.0
Hepato Renal Syndrome	1	0.1	1	0.1	0	0.0
Hepatic Synthetic Dysfunction	1	0.1	1	0.1	0	0.0
Portal Gastropathy	1	0.1	1	0.1	0	0.0
Hepatopulmonary syndrome	1	0.1	1	0.1	0	0.0
One or more signs of liver disease	**167**	**12.8**	**155**	**19.2**	**5**	**1.1**

*7 participants with one or more signs of liver disease (including 5 with cirrhosis) had no RNA results in their charts.

Cirrhosis

By latest follow-up, 14% (n=111) of chronically infected participants had developed cirrhosis (table 18). Sixty nine were female (12% of RNA positive females) and forty two were male (20% of RNA positive males). Five deceased participants with no RNA results in their charts had also developed cirrhosis. For

RNA positive database participants, the median duration of RNA positivity at the estimated date of cirrhosis (see chapter 3) was 21 years and the median age at cirrhosis was 51 years.

The number of participants with cirrhosis has increased by 19 since the last round of data collection. Six were new database participants and two had previous comments relating to potential cirrhosis which were since clarified. The remaining eleven were newly diagnosed with cirrhosis since their previous visit to the hepatology unit. Four were estimated to have developed cirrhosis in 2008, six in 2007 and one in 2006.

Note: *A diagnosis of cirrhosis was assigned if cirrhosis was mentioned in the patient's medical chart (whether ever diagnosed by biopsy, ultrasound scan, CT scan etc) or on death certificate. Based on biopsy results alone, 78 of 644 chronically infected participants (12.1%) ever had a diagnosis of cirrhosis.*

After RNA status, alcohol consumption was the biggest determinant of risk of cirrhosis in the database cohort. Where alcohol data were recorded, 26% of chronically infected participants with cirrhosis had consumed over 40 units of alcohol per week or had alcohol abuse or alcoholic liver disease recorded in their charts at some stage (table 19). Male gender and older age at latest follow-up were additional independent risk factors for cirrhosis. The prevalence of cirrhosis also varied by source of infection, with participants infected through transfusions/treatment for renal disease and those infected through clotting factors significantly more likely to have developed cirrhosis. However, this may be due to differences in the demographic and lifestyle characteristics of the different source groups (table 19).

Table 19. Summary of cirrhosis by source of infection for chronically infected participants

Source of infection	Number with cirrhosis	% with cirrhosis	% of those with cirrhosis with high alcohol consumption	Median age at cirrhosis in years (range)	Median duration RNA positivity at cirrhosis in years (range)
Anti-D	38	8.8	23.7	49 (37 - 69)	21 (7 - 31)
Transfusion or renal	58	21.6	25.0	55 (23 - 80)	19.5 (2 - 45)
Clotting factors	14	13.5	30.8	43 (31 - 57)	26 (13 - 36)

Hepatocellular carcinoma (HCC)/liver cancer

By latest follow-up, 23 (3%) chronically infected participants and two participants with no RNA results had developed HCC or liver cancer. This is an additional three participants compared to the first round of follow-up data collection.

Eight were female (1.4% of RNA positive females) and fifteen were male (7% of RNA positive males). Twenty two (88%) of the participants with HCC were known to be deceased. The cause of death was directly liver-related for eighteen, not liver-related for two and the death certificate was missing for the remaining two participants. The median duration of infection at the estimated date of HCC was 25 years and the median age at HCC was 63 years. The prevalence of HCC was significantly higher in the transfusion/renal and clotting factor groups compared to the participants infected through contaminated anti-D (table 20). Where alcohol intake was available, eight (38.1%) had high alcohol use.

Table 20. Summary of HCC by source of infection for chronically infected participants

Source of infection	Number with HCC	% with HCC	Median age at HCC in years (range)	Median duration RNA positivity at HCC in years (range)
Anti-D	3	0.7	65 (45 - 67)	28 (25 - 29)
Transfusion or renal	15	5.6	70 (43 - 81)	21 (5 - 39)
Clotting factors	5	4.8	54 (49 - 61)	27 (19 - 36)

Biopsy results

Most of the biopsies were carried out in the mid to late 1990s, with much smaller numbers being done in more recent years (figure 11). Forty six participants had a biopsy in 2007 and thirty four had a biopsy in 2008. Overall, the likelihood of having a biopsy varied by RNA status with 83% of chronically infected

participants having a biopsy compared to 25% of those with no positive RNA results. Participants infected through contaminated clotting factors were least likely to have had biopsies, with only 37% of those ever testing RNA positive having biopsy results in their charts compared to 96% of chronically infected anti-D participants and 80% of those infected through blood transfusions or treatment for renal disease. Disease progression may be more likely to be monitored using ultrasounds, CT scans and other tests for participants infected through clotting factors and the available biopsy results in these participants are not likely to be a good indicator of disease status or progression.

Of the 1,634 biopsies carried out, inflammation grade was available for 99% and fibrosis score for 91%.

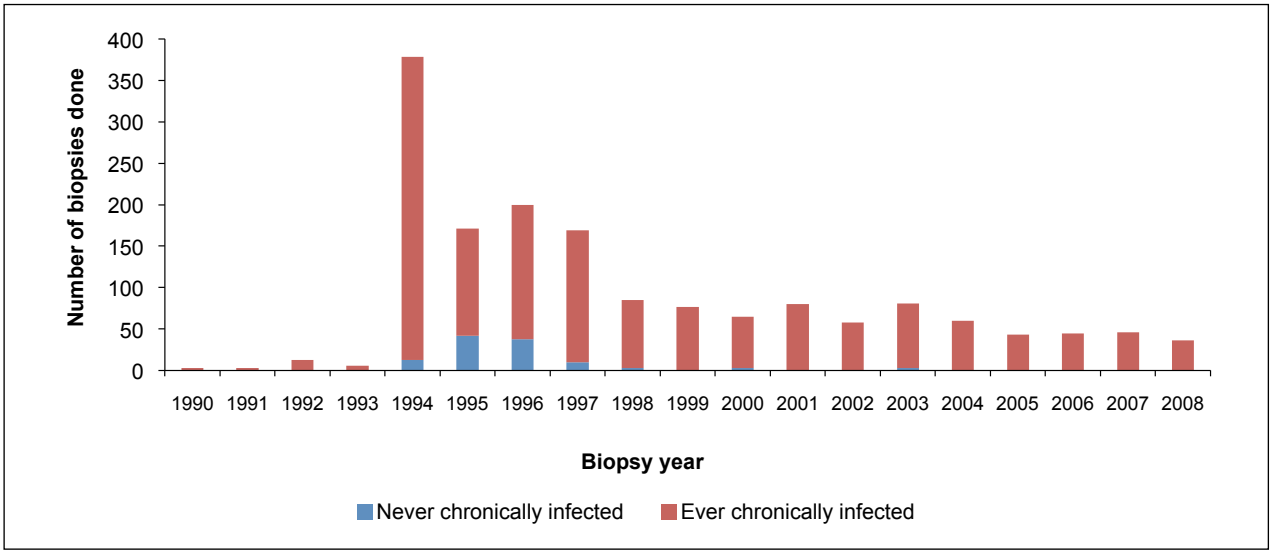

Figure 11. Number of biopsies done by year of biopsy and RNA status of participant

Inflammation

Twenty five percent (n=161) of chronically infected participants had moderate or severe inflammation on last biopsy compared to 1% of participants who did not become chronically infected. Inflammation grade on biopsy varied by source of infection with 46% of chronically infected transfusion/renal participants having moderate or severe inflammation on one or more biopsies compared to 35% of anti-D participants and 24% of participants infected through clotting factors.

Fibrosis

Fibrosis was scored using different scoring systems in different units. Overall 78% of biopsies were scored using a 0-6 scoring system, and a 0-4 system was used for the remaining 22%. Biopsy results scored from 0 to 6 were converted to the 0 to 4 scores (see chapter 3 for details) for some analyses to allow all biopsy results to be analysed together.

We considered high fibrosis scores to be scores of 4-6 on biopsies scored from 0-6 and scores of 3-4 on biopsies scored from 0-4. Nineteen percent (n=122) of chronically infected participants had a high fibrosis score on their most recent biopsy (where fibrosis score was recorded, n=644) compared to 4% (n=4) of those who never tested RNA positive (where fibrosis score was recorded, n=104). Fibrosis also varied by source of infection. Thirty three percent (n=65) of chronically infected blood transfusion/renal participants had a high fibrosis score on most recent biopsy compared to 24% (n=9) of clotting factor participants and 12% (n=48) of anti-D participants (figure 12).

For chronically infected participants who ever had a high fibrosis score on biopsy, the median age at first biopsy with a high score was 51 years (range: 22-76) and the median duration of infection was 19 years (range: 0 to 39 years).

In those who were chronically infected, a high fibrosis score was associated with high alcohol consumption, older age at last biopsy, longer duration of infection, male gender and genotype 3 infection.

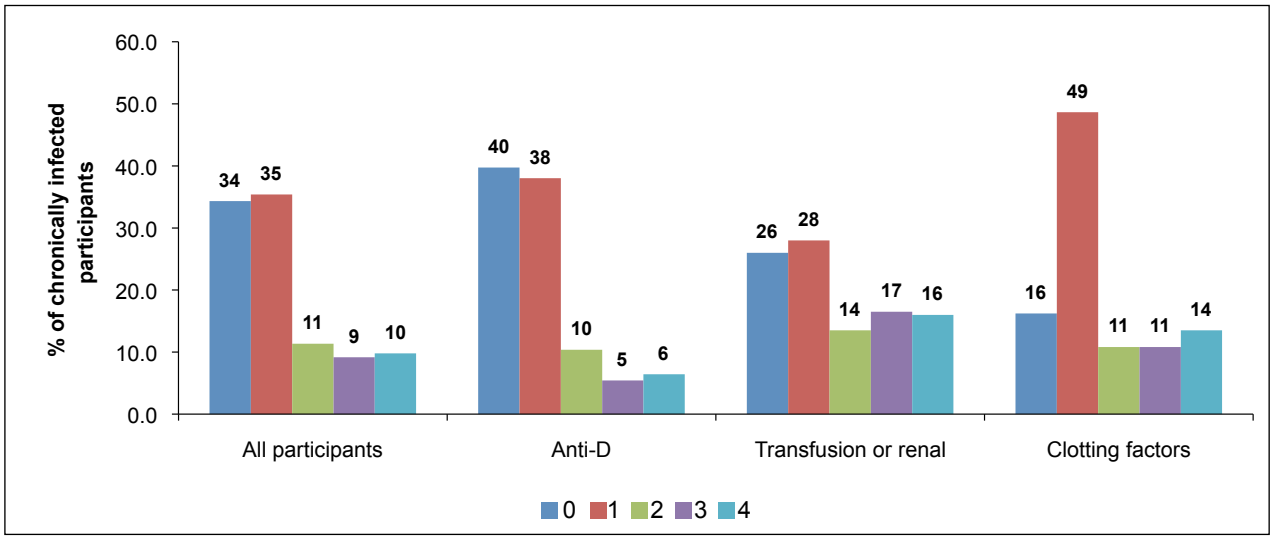

Figure 12. Fibrosis score* on last biopsy for chronically infected participants by source of infection (n=644)

*All 0-6 scores standardised to 0-4 (see chapter 3 for description) to allow all biopsies to be analysed together.
Note: results for clotting factor participants are not representative as data are only available for 37 and the last biopsy was several years ago for many patients.

Rate of fibrosis progression for untreated chronically infected participants

Six hundred and seven chronically infected participants (75%) had biopsy results with fibrosis scores before or without undergoing anti-viral treatment or transplants. The median duration of infection at last scored biopsy before treatment or transplant for these participants was 20 years. Nineteen percent had high fibrosis scores. In order to look at the rate of fibrosis progression for these patients, we assumed that all had fibrosis scores of 0 when infected. The overall estimated fibrosis rate was 0.064 units of fibrosis per year of infection (range: 0-1.022), meaning that the expected time from infection to cirrhosis would be 62.5 years in this cohort overall. Progression rates were lower in females who had never had high alcohol intake and who had been infected when aged less than 40 years (n=429, 0.05 units per year, 80 years from infection to cirrhosis) and higher in participants with high alcohol consumption (n=35, 0.15 units per year, 27 years from infection to cirrhosis).

Changes in biopsy results post-treatment

One hundred and eight chronically infected participants had pre- and post-treatment biopsy results. The changes in fibrosis scores (all standardised to 0 to 4 system) by anti-viral treatment response are shown in figure 13. Fibrosis scores improved for 56% (n=27) of those who achieved sustained virological response (SVR) on treatment compared to 30% (n=18) of those who did not.

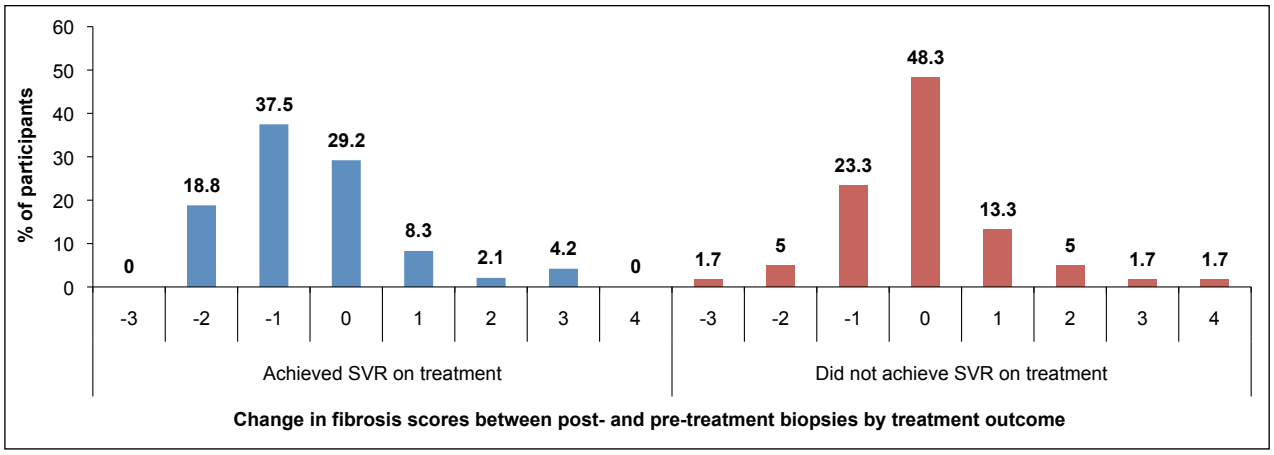

Figure 13. Changes in fibrosis scores (0-4) after treatment by SVR status for participants who had pre- and post-treatment biopsy results (n=108)

*All 0-6 scores standardised to 0-4 (see chapter 3 for description) to allow all biopsies to be analysed together.
Note: Numbers in some categories are very low and percentages should be interpreted with caution.

Deceased participants

One hundred and eighty eight participants had died by latest follow-up. This represents fifteen additional deceased participants compared to the first round of follow-up data collection. Five died in 2007, eight died in 2008 and the remaining two participants died several years ago but were not previously included in the database. All cause mortality rates varied significantly by RNA status: 16% of chronically infected participants were deceased by latest follow-up compared to 4% of participants who never became chronically infected (figure 14). Mortality rates were also higher in males or participants infected through blood transfusions or clotting factors, those who had high alcohol intake and participants who were older when infected.

Where death certificates were available (n=177), death was directly caused by liver disease for 48 participants. The underlying cause of death was coded to HCV infection for twenty, liver cell carcinoma for sixteen, hepatic failure for five, cirrhosis of the liver for three and other liver related conditions for four. HCV infection was one of the causes of death listed on the first part of the death certificate for thirty seven of the participants who died from liver-related causes. The first part of the death certificate details the chain of diseases or conditions leading directly to death.

Liver-related mortality rates were higher in participants who were chronically infected with HCV or had no RNA results compared to those who had no positive RNA results in their charts (figure 15). Thirty eight of those who died from liver-related causes were chronically infected, eight had no RNA results in their charts and the remaining two had RNA results in their charts, but had never tested RNA positive. High alcohol intake was a highly significant predictor of liver-related mortality. Information on alcohol consumption was available for 81% of those whose death was caused by liver disease. Forty nine percent had indicators of high levels of alcohol consumption in their medical charts. Liver-related mortality rates were also higher in males or participants infected through blood transfusions or clotting factors and participants who were older when infected.

The most common non-liver related causes of death for chronically infected participants were cancer, heart disease, renal disease and HIV/immunodeficiency (discussed in more detail in the section 'Participants infected through contaminated blood clotting factors').

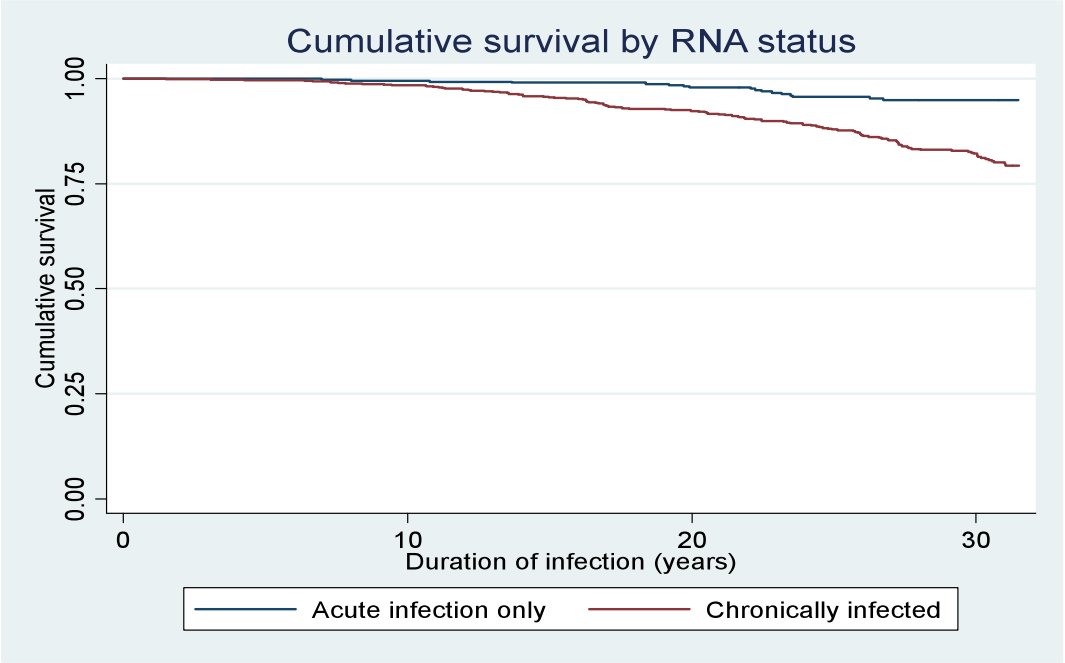

Figure 14. Comparison of survival for participants who ever tested hepatitis C RNA positive and those with RNA results in their chart but with no positive results

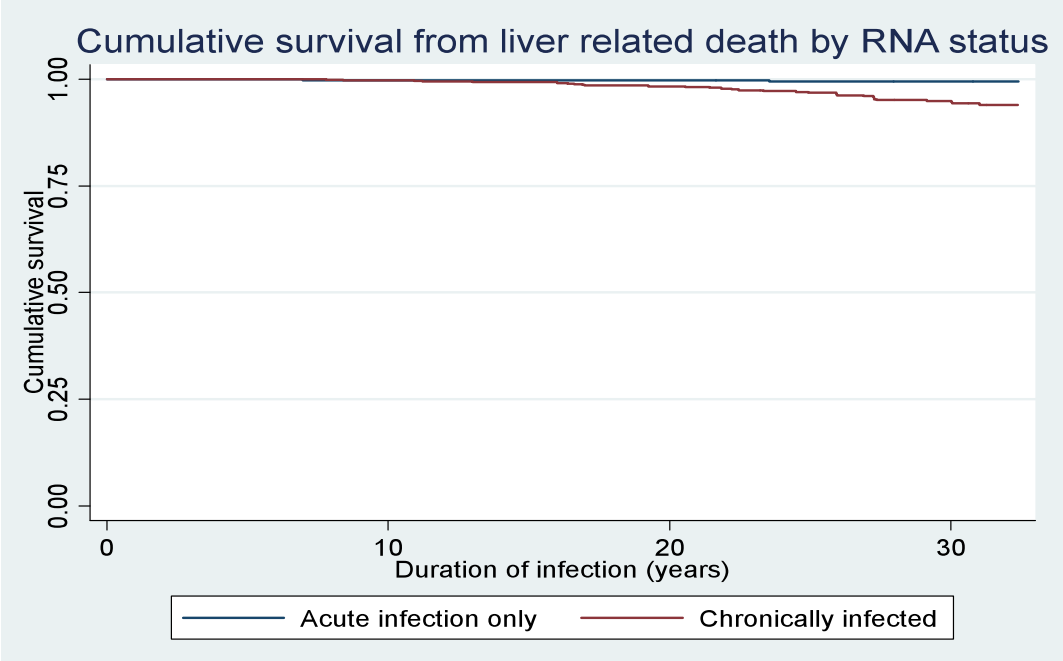

Figure 15. Comparison of survival from liver-related death for participants who ever tested hepatitis C RNA positive and those with RNA results in their chart but with no positive results

Table 21. Number and percentage of participants who died directly from liver-related disease, by source of infection

Source of infection	Died directly from liver-related disease *	% of participants who died directly from liver-related disease	% of chronically infected participants who died directly from liver-related disease
Anti-D	8	1	1.4
Transfusion/renal	21	6.4	7.5
Clotting factors	18	11.5	10.7
Total*	**48**	**3.7**	**4.8**

*One participant who died directly from liver-related disease was missing information relating to source of infection

Changes in the prevalence of the main liver-related outcomes since baseline data were collected

HCV disease progresses particularly after two to four decades of infection.[6] The median time since infection for the database population is now 30 years and the median duration of RNA positivity for those who became chronically infected is 29 years. This is our third round of data collection and we can clearly see increases in the prevalence of liver-related health outcomes since baseline data were collected (figure 16).

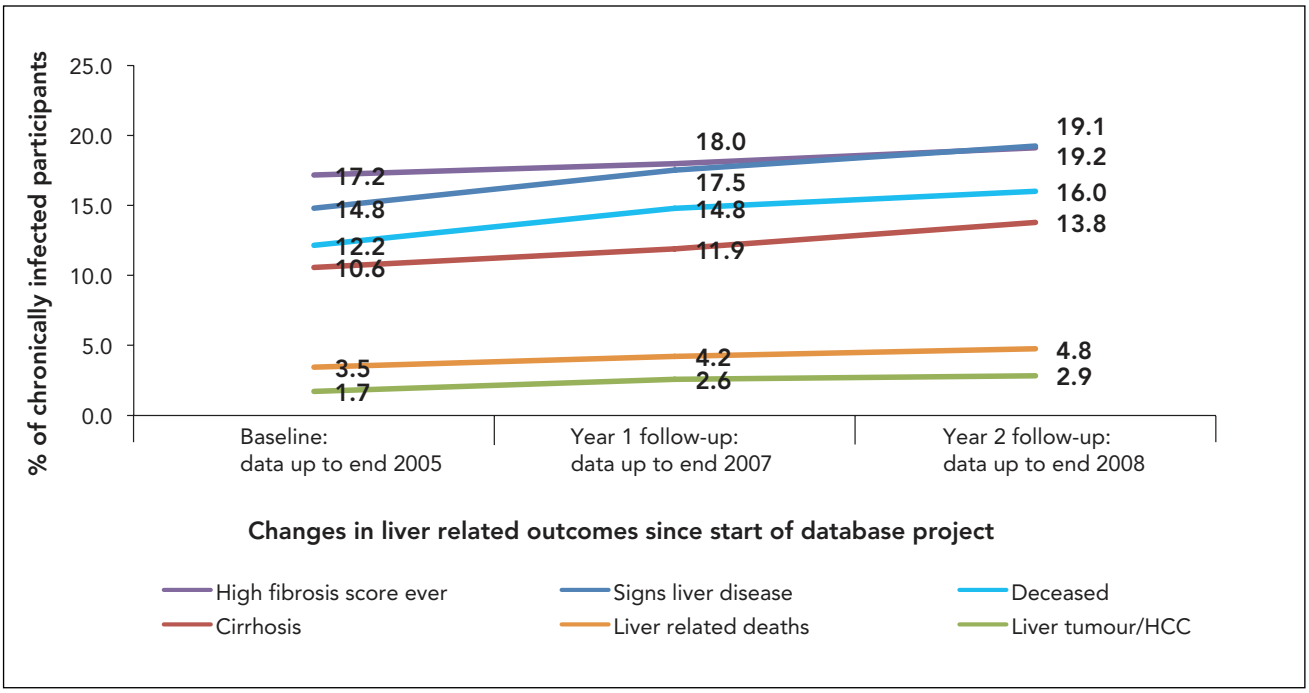

Figure 16. Changes in the prevalence of liver-related outcomes for chronically infected participants since baseline data were collected

Note: Percentages at baseline may differ slightly from baseline report due to slight changes in the way results are coded or analysed or where data are extracted from. The denominators may also have changed slightly due to the identification of several ineligible patients or duplicates.

Summary of disease progression and factors associated with disease severity

As there were several outcome measures that could be used to indicate HCV disease severity, a variable was created to summarise disease progression.

A participant was considered to have 'severe liver disease' if they had:

- Died from liver-related disease **or**
- Ever had one or more of the following signs of liver disease: cirrhosis, primary liver cancer, ascites, varices, decompensated liver disease, portal hypertension, encephalopathy, hepatomegaly or splenomegaly **or**
- Ever had a fibrosis score of 3 or 4 on a biopsy scored from 0 to 4 or a score between 4 and 6 on a biopsy scored from 0 to 6 (note: this is "worst" biopsy result, not necessarily most recent one; some patients may have improved on treatment)

A participant was considered to have 'moderate liver disease' if they had none of the above and had either:

- A fibrosis score of 2 on a biopsy scored from 0 to 4 or a score of 3 on a biopsy scored from 0 to 6 **or**
- Moderate or severe inflammation on any biopsy

All other participants were classified as having 'mild or no liver disease'.

Using these criteria, 27% (n=217) of chronically infected participants, 22% (n=11) of participants with no RNA results and 2% (n=7) of those who never tested RNA positive were classified as having severe liver disease by latest follow-up. A further 20% of chronically infected participants and 1% of those who never became chronically infected were classified as having moderate liver disease. By latest follow-up, 53% of chronically infected participants and 97% of participants who never became chronically infected were classified as having mild or no liver disease.

Tables 22 and 23 show the effects of some key host and virus characteristics on the odds of having severe liver disease. Only participants who tested RNA positive at some stage (ever chronically infected) were

included in these analyses as 92% of the 235 participants with severe disease had tested RNA positive and this approach allowed the effects of genotype to be assessed.

The determinants of having severe liver disease in the database cohort were high alcohol intake, older age at end of latest follow-up, male gender, longer duration of RNA positivity and HCV genotype 3 (table 22). Table 23 shows the same model with source of infection substituted for gender. These factors cannot be assessed together using a logistic regression model as gender is too closely linked to source of infection in the database population. This model indicates that participants infected through blood transfusions/ treatment for renal disease and those infected through clotting factors were more likely to have severe liver disease by latest follow-up compared to those infected through anti-D. All associations between these characteristics and severe liver disease were statistically significant and the influence of each of these factors on disease severity was independent of the effects of all of the other factors in the table.

The most important factor in disease progression was alcohol intake. Participants who had high alcohol intake had almost five times higher odds of having severe disease than those without. However, the number of chronically infected database participants with high alcohol intake was low (n=64) and due to its sensitivity, alcohol consumption data may be inaccurately reported. Figure 17 shows the prevalence of severe liver disease by duration of RNA positivity and alcohol intake.

Participants who were RNA positive for more than twenty years had approximately two fold higher odds of having severe liver disease compared to those infected for less than twenty years. The odds of having severe liver disease were almost three times higher for males compared to females. Participants who were aged 50 years or older at latest follow-up were more likely to have severe liver disease than younger participants.

Table 22. Factors associated with severe liver disease in chronically infected participants - logistic regression model (n=710)

Factors associated with having severe liver disease	Odds Ratio	P-value	95% Confidence interval
Alcohol consumption			
Non drinker/within recommended limits/moderately high	1	Reference	Reference
High (>40 units per week or alcohol abuse in chart)	4.96	<0.001	2.72 - 9.06
Age at end of latest follow-up			
<50 years	1	Reference	Reference
50 to 64 years	2.29	0.002	1.37 - 3.84
65+ years	3.29	<0.001	1.87 - 5.80
Gender			
Female	1	Reference	Reference
Male	2.85	<0.001	1.83 - 4.44
Genotype			
Genotype 1	1	Reference	Reference
Genotype 2	0.92	0.849	0.37 - 2.24
Genotype 3	2.00	0.008	1.20 - 3.34
Duration of RNA positivity			
<20 years	1	Reference	Reference
20+ years	1.88	0.016	1.12 - 3.14

Table 23. Factors associated with severe liver disease in chronically infected participants - logistic regression model (n=708)

Factors associated with having severe liver disease	Odds Ratio	P-value	95% Confidence interval
Alcohol consumption			
Non drinker/within recommended limits/moderately high	1	Reference	Reference
High (>40 units per week or alcohol abuse in chart)	4.65	<0.001	2.54 - 8.53
Age at end of latest follow-up			
<50 years	1	Reference	Reference
50 to 64 years	1.92	0.013	1.15 - 3.20
65+ years	2.26	0.005	1.28 - 4.00
Source of infection			
Anti-D	1	Reference	Reference
Transfusion/renal	3.08	<0.001	1.97 - 4.81
Clotting factors	2.25	0.015	1.17 - 4.34
Genotype			
Genotype 1	1	Reference	Reference
Genotype 2	0.64	0.330	0.26 - 1.57
Genotype 3	1.70	0.042	1.02 - 2.84
Duration of RNA positivity			
<20 years	1	Reference	Reference
20+ years	2.17	0.003	1.30 - 3.64

Explanatory note: The odds ratios shown are a measure of the odds of severe liver disease in one group (e.g. males) divided by the odds of severe disease in another group (the reference group e.g. females). An odds ratio of 1 indicates that severe liver disease is equally likely in both males and females and an odds ratio of more than 1 for males indicates that severe disease is more likely in males. P-values of <0.05 were taken to indicate a statistically significant difference between the distribution of severe disease in the category of the factor being assessed and the reference category of that factor.

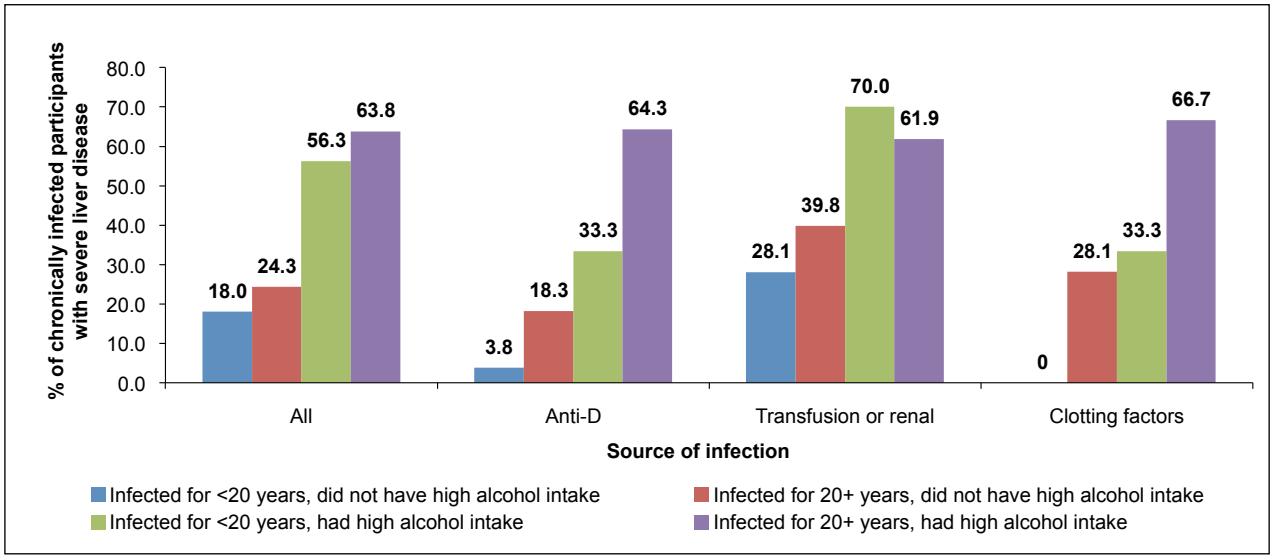

Figure 17. Percentage of chronically infected participants with severe liver disease by source of infection, duration of RNA positivity and alcohol consumption

Note: Numbers in some categories are very low and percentages should be interpreted with caution

Anti-viral treatment for hepatitis C

Almost 41% (n=329) of chronically infected participants had one or more courses of anti-viral treatment by latest follow-up. Participants stopping treatment early are included when calculating sustained virological response (SVR). The SVR rate has improved in recent years with the advent of combination therapy with pegylated interferon (Peg-IFN) and ribavirin (RBN) (figure 18). Tolerance of anti-viral treatment remains an issue, with 24% of all treatment courses stopped early due to side-effects. This was slightly higher for monotherapy with interferon (IFN) or Peg-IFN (28%) than for combination therapy (22%).

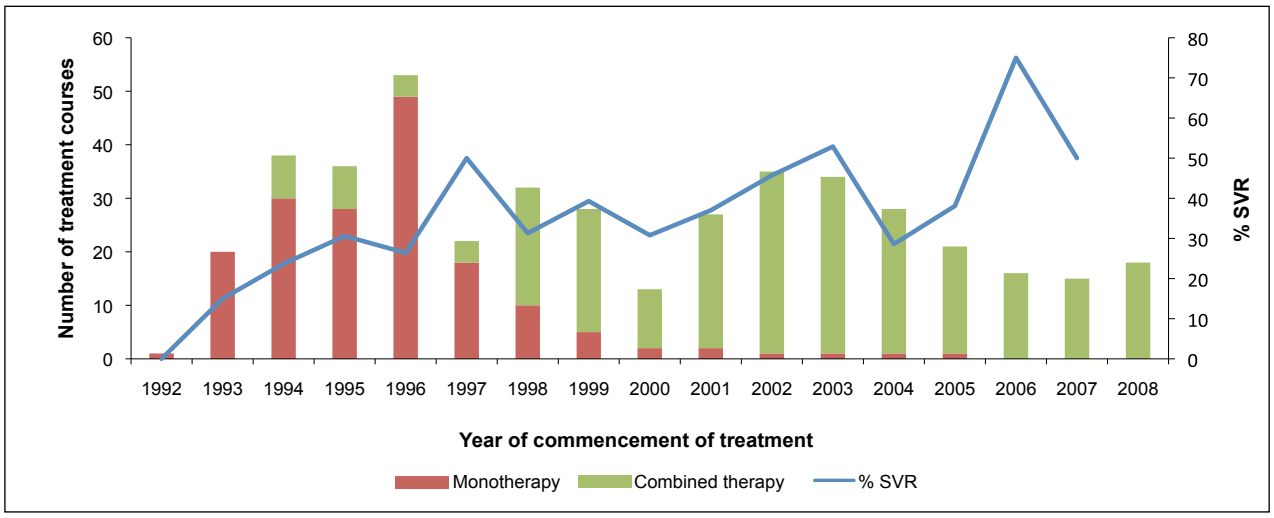

Figure 18.Treatment courses by type of treatment and percentage sustained virological response, 1992-2008

Note: Outcome awaited for 12 participants – not included when calculating SVR

Younger participants, those infected through blood transfusions or clotting factors, those with higher fibrosis scores and participants with genotype 2 or 3 infections were more likely to have been treated (table 24). However, of the 48 participants who commenced treatment between 2006 and 2008, 35 (73%) were genotype 1. This was their first course of treatment for 34, second course for 12 and third course for 2 participants. A high fibrosis score was recorded for 11 (23%) of these recently treated participants.

Table 24. Number and percentage of chronically infected participants treated, and percentage SVR, by fibrosis scores, hepatitis C genotype, source of infection and age at latest follow-up

Characteristic		Number treated	% treated	% SVR on first treatment	% SVR on last treatment
High fibrosis scores on any biopsy	Yes	95	61.7	19.2	31.5
	No	196	38.1	42.9	54.8
Hepatitis C genotype	1	194	33.2	22.5	31.7
	2	25	67.6	41.7	66.7
	3	100	70.4	56.6	72.2
Source of infection	Anti-D	142	33.0	34.1	45.1
	Transfusion/renal	135	50.2	38.1	48.9
	Clotting factors	52	50.0	33.3	51.0
Age at latest follow up	<60 years	236	48.0	41.2	54.2
	60+ years	93	29.6	21.7	31.5
All participants		**329**	**40.8**	**35.6**	**47.6**

Note: Genotype not available for 9 participants who were treated. Participants with genotypes 4/5 omitted from analysis of treatment data. Fibrosis scores not available for 38 of the participants who were treated. Treatment outcome awaited for 12 participants – these participants were not included when calculating SVR.

Treatment response

Treatment response for treatment naïve participants by genotype and type and duration of treatment are shown in figure 19. Seventy seven percent (n=10) of genotype 2 or 3 participants on combination therapy for 48 weeks or more achieved an SVR compared to 47% (n=23) of genotype 1 participants on the same treatment.

Treatment response rates on the most recent treatment with combination therapy by genotype and duration of treatment are shown in figure 20.

The factors associated with SVR on treatment were: treatment with combination therapy rather than monotherapy, having HCV genotypes 2 or 3 rather than genotype 1, longer duration of treatment, younger age at treatment, female gender and lower fibrosis scores on biopsy. Participants infected through clotting factors were also less likely to achieve SVR than those infected through anti-D or blood transfusions after taking account of treatment type, genotype, duration of treatment, age at treatment and fibrosis score. This may be partly explained by factors such as male gender, higher alcohol intake and high prevalence of HIV co-infection in the clotting factor group.

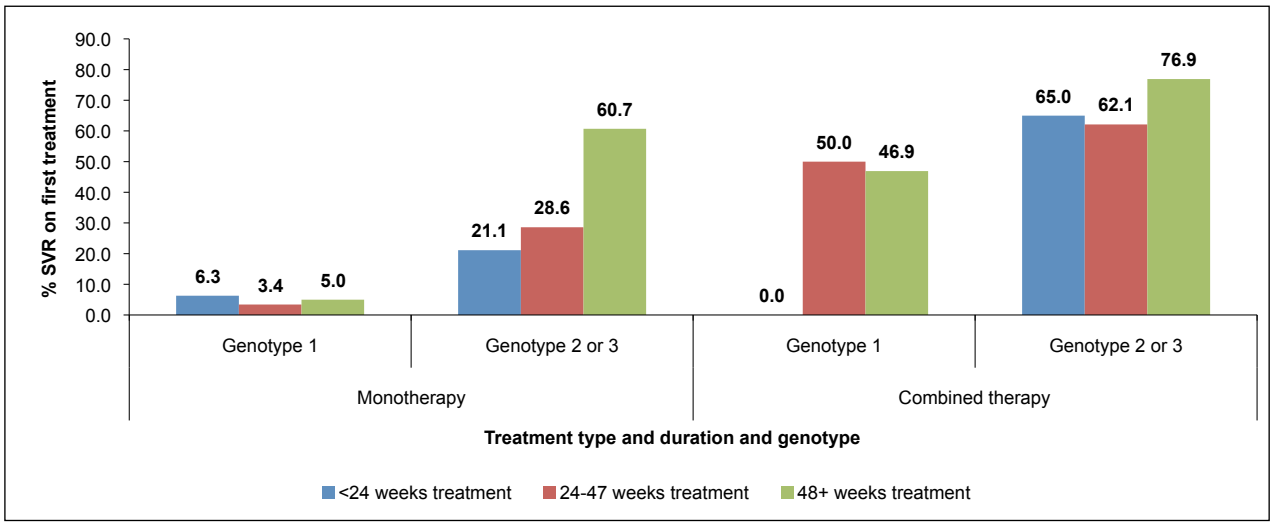

Figure 19. Percentage sustained virological response for treatment of naïve participants by genotype and duration of therapy for monotherapy with IFN (n=141) or Peg-IFN (n=1), and combined therapy with IFN and RBN (n=80) or Peg-IFN and RBN (n=88)

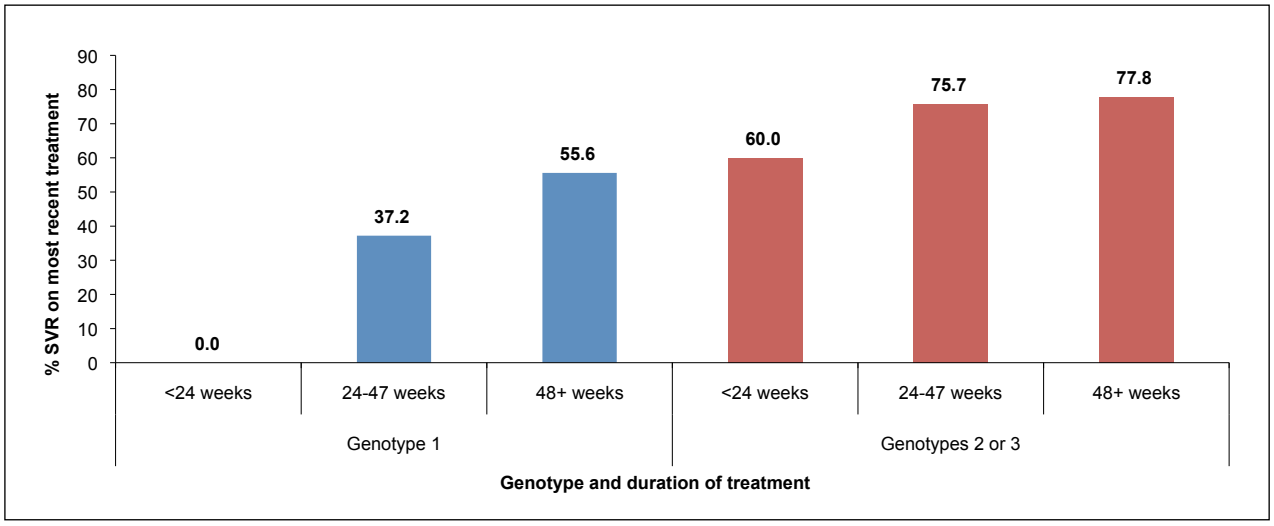

Figure 20. Percentage sustained virological response on last treatment using combined therapy with IFN and RBN (n=92) or Peg-IFN and RBN (n=12) by genotype and duration of treatment

Treatment response: previously treated participants

Eighty seven participants had at least two courses of treatment by end of latest follow-up. Three were still on treatment when follow-up data were collected. Of the 84 remaining participants, the second treatment was with monotherapy for 14 (most of these were in the 1990s) and with combination therapy for 70. The numbers involved were small but there was some success when participants were re-treated using combination therapy, with 31% of those with genotype 1 and 67% of those with genotypes 2 or 3 achieving SVR. Half (50%) of those achieving SVR on re-treatment with combination therapy had had a partial response to the previous course of treatment (initial response with breakthrough while still on treatment, or early relapse within six months of completion of treatment). In comparison, only 15% of those who did not achieve SVR on re-treatment had shown a partial response to previous treatment. This difference was statistically significant.

Liver transplants

Eighteen database participants had received twenty liver transplants by the end of 2008. Eleven received transplants in 2005 or earlier, three were transplanted in 2006, one in 2007 and three in 2008. The median age at transplant was 52.5 years (range: 29-66 years) and the median duration of HCV infection at transplant was 28.5 years (range: 1-41 years). All transplant recipients were RNA positive when transplanted and all of those tested post-transplant (n=14) remained RNA positive.

Histological staging was available for fourteen patients prior to their transplant and all had cirrhosis at this stage. Results were available for nine patients post-transplant. Eight patients had biopsy results within four years of transplant. In this time, two had developed mild fibrosis, one had developed moderate fibrosis, three had developed advanced fibrosis or cirrhosis and two had developed HCC. The remaining patient had cirrhosis on a biopsy carried out more than 15 years after the transplant.

Four of the liver transplant patients have since died, three from non-liver related causes and one from hepatocellular carcinoma. The median time between transplant and death for these patients was sixteen months.

Focus on the different patient groups

Database participants who became chronically infected with HCV through blood transfusions or treatment for renal disease had the highest prevalence of severe liver disease in spite of having the shortest median duration of RNA positivity at the end of latest follow-up. Thirty eight percent of transfusion/renal participants were classified as having severe liver disease, including 22% with cirrhosis, after a median duration of HCV RNA positivity by latest follow-up of 21 years. The prevalence of severe liver disease was also high in participants who were chronically infected through clotting factors, with 31% classified as having severe liver disease and 14% diagnosed with cirrhosis after a median duration of RNA positivity of 31 years. Chronically infected anti-D participants had better liver-related outcomes overall, with 19% classified as having developed severe liver disease, including 9% with cirrhosis, after a median duration of RNA positivity of 31 years.

There are several potential explanations for these differences in liver-related outcomes. Firstly, we would expect co-morbidities to be high in transfusion/renal participants in general, as many were infected with HCV as a result of treatment for serious medical conditions such as cancer. Transfusion/renal participants were also slightly older overall when infected with HCV, with a median age at infection of 32 years, compared to 28 years for anti-D participants and 14 years for participants infected through clotting factors. Gender may also be a factor as chronically infected female participants have a lower prevalence of serious liver-related outcomes than males in spite of having longer durations of RNA positivity. Alcohol intake also varies by gender and hence by source of infection, with 13% of chronically infected transfusion/renal participants and 17% of chronically infected clotting factor participants consuming high levels of alcohol at some stage, compared to 4% of anti-D participants.

Participants infected through anti-D

In spite of having the longest median duration of RNA positivity, database participants infected through anti-D have the lowest prevalence of serious liver-related outcomes. This is likely to be attributable, in part, to the fact that this group was entirely composed of females who were infected during or after

pregnancy and who were likely to have been in relatively good health when infected with HCV. Reported alcohol consumption was also lower for female database participants. Their median age at infection was 28 years, which makes them younger overall compared to the transfusion/renal group but significantly older than those infected through clotting factors.

Anti-D participants infected between 1977 and 1979 have had the lowest uptake of antiviral treatment to date (n=101, 27%). This is probably due to the relatively low prevalence of progressive fibrosis in this group, combined with published information showing poorer treatment responses in genotype 1 patients.[11,27] The SVR was 30% in participants infected during the 1977-79 anti-D outbreak and 34% in other genotype 1 database participants. Treatment uptake in participants infected during the second anti-D outbreak (1991-1994) has been extremely high (n=33, 89%). The percentage achieving SVR has also been very high (90%), even in comparison with other genotype 3 database participants (64%).

Demographic characteristics, liver-related outcomes and treatment data for participants infected during each anti-D outbreak period are shown in table 25.

Table 25. Summary of demographic characteristics, liver related outcomes and antiviral treatment data by anti-D outbreak

	1977-1979 Anti-D outbreak		1991-1994 Anti-D outbreak	
Characteristic	**Number**	**%**	**Number**	**%**
Hepatitis C genotype	**Genotype 1**		**Genotype 3**	
Chronically infected with hepatitis C	**376**	**56.2**	**37**	**54.4**
Median age at infection (years)	28		30	
Median age at end of follow up (years)	58		45	
Median years since infection at end of follow up	31		15	
Mean duration RNA positivity (years)	31		6	
Alcohol intake				
Alcohol data available - database study (highest reported alcohol used)	363		35	
≤14 units per week	334	92.0	31	88.6
15 to 40 units per week	14	3.9	2	5.7
>40 units per week or alcohol abuse in chart	15	4.1	2	5.7
Serum alanine aminotransferase levels				
Data available	374		35	
Normal	124	33.2	25	71.4
Slightly elevated (from upper normal limit to <2.5 times upper normal limit)	183	48.9	7	20.0
More highly elevated (≥2.5 times upper normal limit)	67	17.9	3	8.6
Liver disease severity				
Mild	208	55.3	21	56.8
Moderate	91	24.2	13	35.1
Severe	77	20.5	3	8.1
Outcomes				
Signs of liver disease	45	12	3	8.1
Cirrhosis	35	9.3	2	5.4
HCC	3	0.8	0	0
High fibrosis score on biopsy	66	17.6	2	5.4
Deceased	30	8	0	0
Liver-related disease directly caused death	6	1.6	0	0
Hepatitis C treatment				
Treated	101	26.8	33	89.2
Treated and treatment response available	95	25.2	31	83.8
SVR on last treatment with monotherapy	23	17.4	16	100
SVR on last treatment with combined therapy	72	31.9	15	80
Overall SVR on last treatment		29.8		90.3

Participants infected through blood transfusions or treatment for renal disease

Database participants infected through blood transfusions or treatment for renal disease had the highest rate of HCV chronicity at diagnosis. RNA results were missing for three, but where results were available, 82% (n=269) were chronically infected and 18% (n=61) had cleared the HCV virus by this time.

The group of participants infected through blood transfusions or treatment for renal disease were the only patient cohort with a wide age distribution and significant proportions of both males and females, and both genotype 1 and 3 infections. These characteristics make this patient population a good one for examining the host and virus characteristics associated with liver disease severity. Logistic regression was used to model the factors that were independently and significantly associated with severe liver disease in this population (table 26).

High alcohol intake, older age at the end of latest follow-up, male gender, HCV genotype 3 and longer duration of infection were all found to be independently associated with severe liver disease in chronically infected blood transfusion/renal patients (table 26). It would be interesting to also examine the effects of factors such as BMI, steatohepatitis and insulin resistance on disease severity, but our data are not currently sufficient to allow for this. We hope to be able to improve on this in future rounds of data collection if the relevant data are recorded in the patient charts.

Table 26. Factors associated with severe liver disease in chronically infected participants infected through blood transfusions/treatment for renal disease - logistic regression model (n=228)

Factors associated with having severe liver disease	Odds Ratio	P-value	95% Confidence interval
Alcohol consumption			
Non drinker/within recommended limits/moderately high	1	Reference	Reference
High (>40 units per week or alcohol abuse in chart)	3.19	0.007	1.37 - 7.42
Age at end of latest follow up			
<50 years	1	Reference	Reference
50+ years	3.05	0.002	1.49 - 6.26
Gender			
Female	1	Reference	Reference
Male	2.60	0.003	1.39 - 4.86
Genotype			
Genotype 1	1	Reference	Reference
Genotype 2	0.77	0.619	0.27 - 2.18
Genotype 3	2.59	0.004	1.36 - 4.93
Duration of RNA positivity			
<20 years	1	Reference	Reference
20+ years	2.15	0.016	1.15 - 4.01

Participants infected through contaminated blood clotting factors

Of the 161 database participants infected through blood clotting factors, 65% (n=104) were chronically infected with HCV at diagnosis and 23% (n=37) had no RNA results in their charts (figure 21). These patients had all died prior to RNA testing but had similar prevalence of serious liver-related outcomes to the chronically infected participants and it is likely that they were chronically infected with HCV when they died. The remaining 12% (n=20) had RNA results in their charts but had never tested positive. These participants showed no signs of serious liver-related disease by latest follow-up.

Thirty five percent (n=36) of the chronically infected participants and 84% (n=31) of those with no HCV RNA results were co-infected with HIV. It was difficult to ascertain the true effects of HIV co-infection on HCV disease progression as 66% (n=44) of the co-infected participants had died many years previously. However, 33% (n=22) of those who were HIV positive had signs of serious liver disease by latest follow-up compared to 16% (n=12) of those who were HIV negative, even though they had a shorter median

duration of follow-up (25 years compared to 28 years) (figure 21). Where data were available (77%, n=99), high alcohol intake was also found to be associated with severe liver disease. Fifty six percent of HIV negative participants with high alcohol consumption were classified as having severe liver disease by latest follow-up compared to 16% of those who had not had high alcohol intake. The effects of alcohol on liver disease severity was much less pronounced and not statistically significant in HIV positive participants, with 50% of those with high alcohol consumption classified as having severe disease compared to 42% of those without. However, because a significant proportion of these participants were deceased, they had been followed up for a shorter duration of time and were younger at the time of latest follow-up or death.

Death certificates were available for 41 of the 44 HIV positive participants who had died. The underlying cause of death was liver-related disease for nine and directly related to HIV infection for twelve. A further ten had causes of death relating to immunodeficiency, but the term HIV was not specifically mentioned on their death certificate. The underlying cause of death was classified as directly liver-related for 9 of the 22 HIV negative participants who had died, not liver-related for 12 and the death certificate was missing for the remaining patient.

Forty one participants infected through blood clotting factors had received combination therapy for HCV by latest follow-up. The number treated was too low to reliably assess if treatment response varied with HIV status, but the response rates by type of treatment and genotype were not statistically worse in the co-infected participants. Of the twenty six genotype 1 participants treated, 33% of those who were co-infected with HIV achieved SVR compared to 41% of those who were not. Of the fifteen genotype 2 or 3 participants treated, 86% of those who were co-infected with HIV achieved SVR compared to 75% of those who were not. These SVR rates were also comparable to those achieved by participants infected through other means (36% SVR for genotype 1 and 69% for genotype 3).

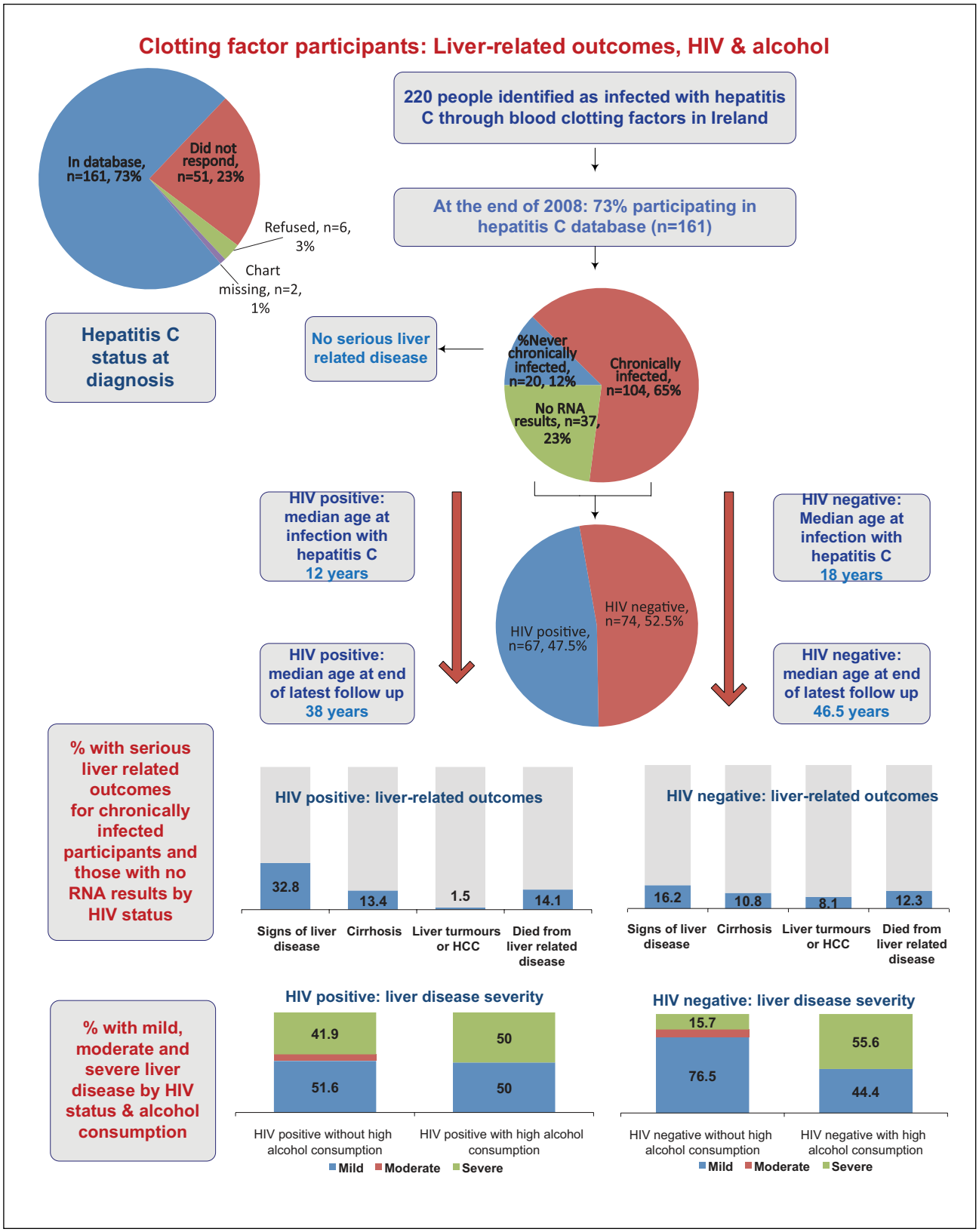

Figure 21. Summary of hepatitis C infection and disease progression in clotting factor participants by HIV status

Clinical management and health service usage

Long term medications other than anti-viral treatment

The most common long-term medications used were drugs for acid-related disorders, drugs used to treat depression, anxiety or sleep disorders, cardiovascular drugs and anti-inflammatory and anti-rheumatic drugs (table 27). The proportion of chronically infected participants taking long-term medications to treat depression, anxiety or diabetes was significantly higher than that for participants who never became chronically infected.

Table 27. Most common long-term medications recorded in medical charts

Medication type	All participants		Chronically infected		Never chronically infected	
	Number	%	Number	%	Number	%
Drugs for acid related disorders	296	22.7	216	26.8	75	16.8
Psychoanaleptics	243	18.6	180	22.3	60	13.4
Psycholeptics	200	15.3	147	18.2	48	10.7
Analgesics	187	14.4	125	15.5	56	12.5
Beta blocking agents	184	14.1	136	16.9	47	10.5
Mineral supplements	180	13.8	133	16.5	47	10.5
Agents acting on the renin-angiotensin system	161	12.4	115	14.3	46	10.3
Diuretics	152	11.7	114	14.1	38	8.5
Serum lipid reducing agents	151	11.6	78	9.7	73	16.3
Antiinflammatory and antirheumatic products	139	10.7	88	10.9	51	11.4
Drugs for treatment of bone diseases	128	9.8	90	11.2	38	8.5
Thyroid therapy	114	8.7	80	9.9	33	7.4
Antithrombotic agents	111	8.5	75	9.3	36	8.1
Calcium channel blockers	95	7.3	74	9.2	21	4.7
Drugs for obstructive airway diseases	88	6.8	60	7.4	27	6
Antianemic preparations	79	6.1	56	6.9	18	4
Sex hormones and modulators of the genital system	79	6.1	49	6.1	28	6.3
Drugs used in diabetes	77	5.9	58	7.2	17	3.8
Corticosteroids for systemic use	62	4.8	55	6.8	5	1.1
Vitamins	58	4.5	49	6.1	8	1.8
Antiepileptics	51	3.9	35	4.3	15	3.4
Immunosuppressive agents	48	3.7	45	5.6	3	0.7
Antihemorrhagics	45	3.5	36	4.5	7	1.6
Antivirals for systemic use	43	3.3	31	3.8	1	0.2
Antihypertensives	41	3.1	30	3.7	11	2.5
Drugs for functional gastrointestinal disorders	40	3.1	29	3.6	9	2

Visits to the hepatology unit

Seventy seven percent of all living database participants had attended their hepatology unit in 2007 or 2008 and a further 3% had been followed up through other services within the same hospital in this time period. The frequency of attendance at the hepatology units varied with RNA status. Eighty eight percent of participants who had ever been chronically infected attended their unit in 2007 or 2008 and a further two percent were followed up through other services in the hospital. Participants who had never become chronically infected were less likely to have attended recently, with 60% attending in 2007 or 2008 and an additional 3% attending other services in the hospital. For participants who had attended hepatology services on an out-patient basis since last follow-up, the median number of visits was two for those who were ever chronically infected and one for those who had never become chronically infected.

After accounting for RNA status, anti-D participants were more likely to have attended their hepatology unit in 2007 or 2008 than participants infected through clotting factors or blood transfusions/treatment for renal disease. However, there was no difference in the proportion of participants with some follow-up data from 2007 or 2008 by source of infection, indicating that the transfusion/renal and clotting factor participants were just more likely to be followed up through other hospital services in addition to, or instead of, their hepatology unit. There was no difference in follow-up by severity of liver disease after accounting for RNA status.

Twenty two percent of living participants who were ever chronically infected and 11% of those who were never chronically infected had visited hospital on an in-patient basis since last follow-up. The median number of in-patient visits was one for both. Sixty eight percent of admissions were not liver-related. Liver

biopsies were the main liver-related reason for hospital admission (21% of all admissions). Other liver-related reasons for admission include initiation of HCV treatment (n=8) and liver transplant (n=3).

Specialist health services and procedures

Since last follow-up, 42% (n=286) of ever chronically infected living participants and 23% (n=99) of those who were never chronically infected attended one or more specialist hospital services other than hepatology. The most common services used by chronically infected participants were haematology (10%), psychiatry/psychology/counselling (6.9%), endocrinology (6.2%) and rheumatology (5.8%) (table 28). As expected, a high proportion of participants infected through clotting factor attended haematology and physiotherapy services and a very high proportion of participants infected as a result of treatment for renal disease attended nephrology services.

Table 28. Most common specialist services, other than hepatology, attended by living participants since the last round of follow-up data collection

Most common services attended	Ever chronically infected		Never chronically infected	
	Number	%	Number	%
Haematology	70	10.3	16	3.7
Rheumatology	39	5.8	19	4.4
Endocrinology	42	6.2	15	3.5
Physiotherapy	35	5.2	21	4.9
Psychiatry/psychology/counselling	47	6.9	5	1.2
Surgical	31	4.6	15	3.5
Cardiology	21	3.1	13	3.0
Dermatology	23	3.4	5	1.2
Dietician/nutritionist	19	2.8	9	2.1
Nephrology	20	3.0	6	1.4
Orthopaedic	16	2.4	9	2.1
Neurology	14	2.1	9	2.1
Respiratory	13	1.9	6	1.4
Obstetrics/Gynaecology	12	1.8	5	1.2
Ophthalmology	12	1.8	4	0.9
Dental	12	1.8	3	0.7

Since last follow-up, 57% (n=385) of ever chronically infected living participants and 28% (n=122) of those who were never chronically infected underwent one or more procedures aside from liver biopsies. The most common liver-related procedures were ultrasounds (37% of chronically infected living participants) and CT scans (6% of chronically infected living participants) (table 29). The number of biopsies being carried out has been decreasing in recent years. Because ultrasounds are less invasive and more acceptable to patients, it is likely that they are increasingly being used to monitor disease progression where possible (figure 11). Some of the hepatology units have also started to use fibroscans to assess liver elasticity.

Table 29. Most common procedures undergone by living participants since the last round of follow-up data collection

Most common procedures	Ever chronically infected		Never chronically infected	
	Number	%	Number	%
Ultrasound (liver or liver related)	252	37.2	29	6.8
X-ray (not liver related)	135	19.9	66	15.4
Upper GI endoscopy	49	7.2	16	3.7
CT Scan (liver or liver related)	39	5.8	10	2.3
Colonoscopy/ileoscopy	23	3.4	21	4.9
Ultrasound (not liver related)	35	5.2	8	1.9
CT Scan (not liver related)	27	4.0	8	1.9
MRI (not liver related)	21	3.1	12	2.8
ECG	11	1.6	5	1.2
MRI (liver or liver related)	8	1.2	0	0.0

If health services or procedures are availed of privately and not discussed with a participant's hepatologist they will not be recorded in a participant's medical chart and will be under-represented in the database. Services known to be commonly attended on a private basis include counselling, physiotherapy, chiropody and complementary and alternative therapies.

Complementary and alternative therapies

Information recorded in the medical charts of participants indicates that 6% used one or more complementary or alternative therapies. The most common therapies used were herbal remedies or supplements (3%), acupuncture (2%), massage therapy (1%) and reflexology (1%). However, data from the HSE relating to the use of health services for HAA cardholders indicate very high usage of complementary and alternative therapies (personal communication: Michele Tait, HSE). In 2009, approximately 3,600 complementary therapy sessions were recorded. Therapies included in this are reflexology, massage, aromatherapy, hydrotherapy and acupuncture. Reflexology and massage are the most commonly used. All of these are accessed on a private basis. In 2009, approximately 850 physiotherapy sessions were recorded. Both complementary therapies and physiotherapy are funded under the HAA only on the recommendation of the patient's GP or consultant hepatologist.

Chapter 5 Discussion

The information presented in this report is based on the third round of data collection on over 1,300 people infected with HCV through blood or blood products administered in Ireland. The database participants represent over three quarters of the total number of people identified as having been infected in this way. The collection of their medical information on a regular basis allows us to follow the natural history of HCV infection, their response to treatment and their use of health services. The number of eligible people participating in the database has continued to rise, with some previous non-responders now giving consent, and with the identification of small numbers of newly eligible people each year.

Viral clearance

It is estimated that between 19% and 36% of the database population had spontaneous clearance of HCV, depending on whether the total population includes all those with any antibody positive result or only those with positive confirmatory tests. This finding is in keeping with the generally accepted range of 55-85% for development of chronic infection.[5,6] Females were significantly more likely to have cleared the virus by the time of their diagnosis than males. The gender bias in viral clearance is supported by a systematic review of 31 studies of acute HCV infection which found a mean spontaneous viral clearance rate of 26% and that viral clearance was significantly higher in females (42%) compared to males (20%).[19]

Disease progression

This is a crucial time to follow the progress of disease, as the database participants have now been infected for an average of 30 years and the majority are now aged over 50 years. In HCV infection, the association between both duration of infection and age, with fibrosis progression, has been well described, and it has been estimated that up to 20% of patients will progress to cirrhosis over 20-25 years after infection.[1,9]

The overall impression from this latest round of data collection is that, although there is evidence of progression of disease in some people, the majority of the database population, even those chronically infected, do not have any evidence of serious liver disease. The vast majority of those who did not become chronically infected have no signs of liver disease. Since baseline data collection about three years ago, an increase of 11-37% has been seen in the prevalence of the main liver-related outcomes among those chronically infected (high fibrosis scores, signs of liver disease, cirrhosis, death, liver-related death). The rise in HCC has been greater, but the numbers of HCC are small. The prevalence of these outcomes will be monitored closely in the coming years.

Cirrhosis

There has been a slight increase in the prevalence of cirrhosis, with 14% of chronically infected participants now having developed cirrhosis. Over a quarter of chronically infected participants with cirrhosis had high alcohol use. Cirrhosis was also significantly associated with infection through blood transfusion/renal treatment and clotting factors, rather than anti-D. The cohort of participants who were infected through anti-D in the 1977-79 outbreak have a low rate of cirrhosis at 9.3%, despite an average duration of infection of 31 years. A Canadian study looking at the prognosis of patients infected with HCV through receipt of contaminated blood products found that approximately 10% had developed cirrhosis after 20 years of infection. This study also predicted that 37% of haemophiliac patients and 23% of non-haemophiliac patients would develop cirrhosis after 40 years of infection.[28]

Our method of estimating the rate of fibrosis progression was similar to that used by Poynard et al in a large-scale study looking at fibrosis progression in people infected with HCV.[29] They estimated the time from infection to cirrhosis to be 24 years in people with high alcohol consumption and 42 years in females who were infected when less than 40 years of age and who did not have high levels of alcohol

consumption. Our findings were of longer periods of progression, at 27 years and 80 years respectively. However, as Poynard et al point out, these results should not be interpreted as meaning that progression to cirrhosis is universal and inevitable. Based on their estimated average rate of fibrosis progression and without treatment, the median expected time to cirrhosis was 30 years; 33% of patients had an expected median time to cirrhosis of less than 20 years and 31% will never progress to cirrhosis or will not progress for at least 50 years. A recent meta-analysis of a large number of published studies of HCV natural history reported an estimated prevalence of cirrhosis to be 16% at 20 years after infection and nearly three-fold higher at 30 years. The predicted estimates varied by study design, setting, population, age at infection and duration of infection. The progression of fibrosis appears to be non-linear with particularly high progression in the third decade of infection.[30]

HCC and deaths

Since the previous round of data collection an additional three people have developed HCC and there have been an additional 15 deaths, five of which were directly caused by liver disease.

Severe liver disease

We created a summary measurement of disease progression to describe those having any evidence of severe liver disease: 27% of those chronically infected were thus described as having severe liver disease compared to 2% of those who were never chronically infected. It is not possible to determine what proportion of this amount of liver disease is due to HCV rather than other factors which may damage the liver.

The same factors were repeatedly found to be related to the poorer outcomes of chronic HCV infection in the database population. These were high alcohol intake, male gender, older age at the time of follow-up, and longer duration of infection. Associations between these factors and HCV disease progression have been described in many other studies.[1,6,9,29,31-34] Infection through blood transfusion/renal treatment or through clotting factors, rather than anti-D, was also related to poorer outcomes in the database population.

Genotype 3

The finding that participants infected with HCV genotype 3 had higher odds of severe disease than those with genotype 1 HCV has not been commonly reported. Although it is well established that HCV genotype is an important determinant of response to treatment, less evidence exists regarding an association between HCV genotypes and differences in the natural course of disease. The published data on the impact of HCV genotypes on fibrosis progression rates, development of cirrhosis, and the risk for HCC, have been conflicting.[35] However, a recent study on a large dataset, the Swiss Hepatitis C Cohort, found that HCV genotype 3 was associated with accelerated fibrosis.[36] There is a possible mechanism for genotype 3 to influence disease progression as there is a biological association between genotype 3 and steatosis independently of BMI. Steatosis has also been found to be associated with fibrosis progression.[37] However, it is also possible that this finding regarding genotype 3 could be explained by residual confounding or the potential confounding effects of another factor not included in the model. For instance, we could not examine the effects of BMI on disease progression in the database cohort as BMI data were only available for a minority of participants. In addition, it is possible that the distribution of co-morbidities varied by genotype and this has not been accounted for. Conflicting results were reported from the UK HCV Register which found that type 1 infection is associated with greater aggressiveness than type 2 or 3 infections, with type 1 infection being independently associated with more advanced stages of liver disease on biopsies carried out by the Registry.[38] They also found that HCV genotype 1 infection is more likely to be associated with spontaneous clearance than non-1 infection.

Alcohol

The importance of alcohol consumption deserves highlighting. Alcohol is known to be an important co-factor in the progression of HCV liver disease to cirrhosis and hepatocellular carcinoma.[1,5,9] Alcohol use during therapy also adversely affects response to treatment. Safe levels of alcohol consumption are still unclear and even moderate levels of consumption may accelerate disease progression in some patients.[5] In the database, alcohol intake was found to be the most important factor in disease progression, with participants who had high alcohol intake having almost five times higher odds of having severe liver disease than those without. Unfortunately, although there was information about alcohol consumption available in the medical records of the majority of participants, in many cases there was no recent information recorded. Alcohol consumption is also likely to be under-reported. This may explain why, although the results did demonstrate a relationship between high alcohol consumption and unfavourable outcomes, no such relationship was seen for moderately high consumption. Given the unequivocal findings from the database, supported by international literature, of the association between high alcohol consumption and negative outcomes in HCV infected people, it is essential that information on current alcohol intake is available in the database. We will continue to encourage the recording of this at all outpatient hepatology visits.

Overweight

Overweight is known to be a risk factor for disease progression, perhaps reflecting the higher rate of hepatic steatosis and steatohepatitis, a precursor to fibrosis, observed among overweight patients. The association between obesity and virological response to treatment is less clear-cut with conflicting results from different studies.[39] We record body mass index (BMI) in the database wherever this information is available in the medical chart but to date this has been available in only a minority of cases. We hope that it will be possible to have body weight recorded as a routine at each clinic visit in the future so that we can investigate any association between overweight and disease progression or response to treatment in this group.

Medical conditions

Although medical conditions that are recorded in participants' medical charts are entered into the database, the interpretation of these data is difficult without having a comparison group against which to compare the frequency of their occurrence. These conditions may be best studied by separate research but data contained in the database may provide the stimulus to investigate certain conditions. A health and lifestyle survey that was carried out on HAA card recipients in 2009 will be published later this year and will compare results in HCV infected people with those in the general population.

Treatment uptake and response

The database provides interesting information on the use of and response to antiviral treatment of participants. Almost 41% of chronically infected participants have been treated, with significant numbers still commencing treatment each year. This figure is high compared to that reported in other cohorts where only a small sub-set of those infected and diagnosed have been treated.[40] However, lack of access to specialist care has been found to be a factor in low levels of treatment in some settings and this would not apply to the database population because of their access to health services facilitated by the HAA scheme. By the end of 2008, 70% of genotype 2 and 3 participants have received antiviral treatment, and 33% of genotype 1. Participants commencing treatment in recent years include greater proportions of genotype 1. Their response to completion of treatment will be followed with interest in the coming years.

Currently, the recommended therapy of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin.[5,11,41] Successful response to treatment, as measured by SVR, has been similar in the database participants to that reported in the international literature following combination treatment. Large-scale clinical trials have reported SVR rates of 76-82% in genotype 3 patients and 42-46% in genotype 1 patients on this treatment regime.[11,42,43] The treatment outcomes for database patients who have been treated with these regimes have been comparable at 77% and 47% respectively.

A successful response to treatment in database participants has been associated with genotype (genotype 2 or 3), younger age at treatment, female gender and lower fibrosis scores. This is in keeping with the findings of international studies.[39,41]

Pre-treatment viral load

Large clinical trials have also demonstrated that, in addition to HCV genotype, pre-treatment viral load is a major predictor of SVR following combination treatment.[41] Patients with high baseline viral loads >800,000 IU/ml are less likely to achieve an SVR than those with lower viral loads.[39] We have not been able to assess this association in the database due to lack of standardisation in the quantification of viral loads. In the past, different laboratories have used different tests and reported results in different units of measurement. However, the recent adoption of international units (IU/ml) for measuring viral load by the relevant laboratories in Ireland will allow us in the coming years to look at the association between pre-treatment viral load and SVR, and between early virological response (EVR)/rapid virological response (RVR) and SVR, in database participants.

EVR and RVR

Early sustained suppression of HCV replication has been shown to be a good predictor of SVR. The likelihood that a patient will fail to achieve an SVR can be predicted by the virological response at 12 weeks of treatment (EVR) and probably even earlier. A patient not demonstrating an EVR (a decrease in serum HCV RNA by 2 logs or more at treatment week 12) has a less than 3% chance of achieving SVR. Of patients who do show an EVR, 67% to 80% achieve an SVR.[44,45]

An RVR (HCV RNA undetectable at week 4 of treatment) is now emerging as another milestone in patient care.[46] In general, RVR is a robust predictor of SVR, and studies suggest that patients infected with genotype 2 or 3 who attain RVR may be candidates for a shortened duration of therapy.[27,47] A recent study has demonstrated that the ultimate response to treatment can be identified within the first 24 hours by a decline in viral load that is more marked in responders than non-responders.[48]

Clinical outcome of treatment

Although SVR is used as an indicator of successful treatment, improved clinical outcomes following treatment have also been demonstrated in many studies. Several large studies have suggested that successful treatment with pegylated interferon and ribavirin (as evidenced by SVR) may halt and even reverse hepatic fibrosis.[49,50] SVR to treatment has also been shown to be associated with improved clinical outcomes, mainly prevention of liver failure, in patients with chronic HCV infection and advanced fibrosis.[51] Viral eradication is sometimes accompanied by reversal of cirrhosis, and histopathologically documented regression of cirrhosis has been shown to be associated with decreased disease-related morbidity and improved survival.[52] We will continue to follow these clinical outcomes in the database population, both treated and untreated.

In the database participants, 22% of treatment courses with combination therapy have been stopped early due to side effects. Internationally, the numbers demonstrating premature withdrawal from therapy due to side effects are now lower than in earlier studies at 10-20%, suggesting improved understanding and management of adverse events.[10] In the next round of data collection we plan to record the details of side effects leading to premature cessation of treatment.

Liver transplants

By the end of 2008, 18 of the database participants had received liver transplants. Where post-transplant information was available, many of them showed accelerated disease progression with fibrosis, cirrhosis or HCC. HCV re-infection is known to occur in almost all patients after liver transplantation and to lead to a more rapid course post-transplant than in immune-competent individuals.[10] A large American study looking at post-transplant outcomes after liver transplantation found that the natural history of HCV cirrhosis was accelerated post-transplant. In this study, 18% (n=88) of 502 HCV infected patients

developed cirrhosis within 3.7 years of transplantation.[53] Another study looking at survival post-transplant found that, of 200 patients with HCV infection who underwent liver transplantation, 95% were still alive after 1 year and 79% were still alive after seven years. They also found that approximately half of their patients experienced significant early fibrosis recurrence post-transplant.[54]

Focus on different groups

The participants in the National Hepatitis C Database, although all infected with HCV through administration of blood and blood products within Ireland, are not a homogeneous group. There are several sub-groups within this population, differing in their age and sex breakdown, mode of acquisition of HCV, co-morbidities and other factors. In analysing data by the different sub-groups, it is apparent that they vary also in their clinical outcomes to date and in their response to treatment. We plan to continue to monitor the outcomes separately in these three groups in the years ahead.

Anti-D group

In general, those infected through anti-D immunoglobulin have fared better that those infected by other means. In spite of having the longest average duration of infection, they have the lowest prevalence of serious liver-related outcomes. This may be explained by the fact that they are female, were younger at the time of infection, and in general they did not have co-morbidities. They also have lower alcohol consumption. There are two distinct anti-D groups: 1977-79 outbreak (genotype 1) and 1991-94 outbreak (genotype 3). Those in the smaller, more recent outbreak group, infected with genotype 3, have better outcomes to date, which is to be expected as they have a shorter duration of infection, and greater numbers have been treated and have had a successful response to treatment.

Blood transfusion/renal group

Database participants infected through blood transfusions or treatment for renal disease had the highest prevalence of severe liver disease despite having the shortest average duration of infection. This is likely to be attributable to the fact that many of them had co-morbidities; they are also older than the anti-D group and had a higher prevalence of high alcohol consumption.

Blood clotting factor group

Of those infected through clotting factors, over 40% were co-infected with HIV. Those who were HIV positive were twice as likely to have signs of serious liver disease compared to those who were HIV negative. Compared with HCV mono-infected patients, co-infected patients are known to have an increased risk of developing cirrhosis and decompensated liver disease.[55] Although the success of treatment of HCV and HIV co-infection with pegylated interferon and ribavirin has been demonstrated in several randomised trials, the overall SVR rates were lower than in patients with HCV mono-infection. Important predictors of response in these trials included HCV genotype, pre-treatment HCV RNA level, and presence of RVR and EVR.[56-58] However, among database participants infected through clotting factors, 51% of those treated have attained an SVR, and those with HIV co-infection achieved a similar response to those with HCV mono-infection. Good virological outcomes to treatment in HCV/HIV co-infected haemophiliac patients in Ireland have been reported previously.[59]

Use of services

The majority of chronically infected participants have continued to attend regularly for out-patient visits. These hospital services and resulting referrals to other health services are provided free of charge under the Health (Amendment) Act 1996. As expected, those who never became chronically infected were less likely to have attended recently and some have been effectively discharged from their units. However, in analysing the database data, the models take account of duration of infection at last follow-up and age at last follow-up. The next round of data collection will collect information on when the patient is next scheduled to attend for an out-patient appointment, or whether they have been discharged or lost to follow-up.

The number of biopsies being carried out has declined in recent years. Some of the hepatology units have started to use fibroscans (transient elastography) to quantify liver fibrosis. This is a new, non-invasive method that uses both ultrasound and low frequency elastic waves to assess liver elasticity.[60-62] Fibroscan results, where available in the hepatology units, will be captured in the next round of data collection.

Complementary and alternative therapies

Although the database does record information about usage of complementary and alternative therapies where these are mentioned in patient charts, we acknowledge that this is not a reliable source of this information. Patients may not mention their use of these treatments to their hospital consultant or this information may not be recorded in the chart. The figure of 6% of participants using such therapies is likely to be a significant under-estimate, given the usage quoted under the HAA scheme, and information from other studies. According to a recent study carried out in Ireland, and in line with international studies, the use of complementary therapy is high, and increasing, in the general population in Ireland with an increase from 20% to 27% between 1998 and 2002.[63] Numerous studies indicate that most complementary and alternative therapy users do not attend practitioners and are more likely to self prescribe.[63] The health and lifestyle survey carried out in 2009, mentioned above, is likely to provide more useful information on HAA cardholders use of complementary and alternative therapies.

Conclusion

The National Hepatitis C Database project has progressed in both participation rate and quality of data since its establishment six years ago. The ongoing support of participants, support groups and health professionals is essential to its success. Eligible people who have not yet participated may join at any time through their hepatology unit.

The regular collection of data from the hospital records of participants will continue. We would encourage hepatology unit staff to record body weight/BMI and alcohol consumption information as a routine at clinic visits. In the next round of data collection, additional information, where available, will be collected on: insulin resistance, steatosis, fibroscans, details of adverse effects of treatment, both starting and finishing treatment doses, and clinic follow-up/discharge status of patients. We look forward to carrying out more detailed analysis of viral load data, recorded now in a standardised format, before, during and after treatment.

The data in the database are available for use by researchers and by the participating hepatology units. The policy and procedures for accessing information contained in the database are outlined in a document which is available on the database website or through the project team at HPSC. All publications based on data from the database must acknowledge the National Hepatitis C Database and the participating hepatology units.

We welcome any comments and suggestions that participants, health professionals or other interested people may have on ways in which we could improve the database and the use of the information contained in it.

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Glossary of definitions, terms and abbreviations

Definitions

Case of hepatitis C for the purpose of this database
Any patient with one or more positive test results for hepatitis C, including positive RNA (PCR), line-immunoassay (RIBA/INNO-LIA) or EIA results, indeterminate line-immunoassay results and weak positive EIA results.

Confirmed positive case of hepatitis C
Any patient who had at least one positive RNA (PCR) result or at least one positive line-immunoassay (RIBA/INNO-LIA) result.

Ever hepatitis C RNA positive (PCR positive)
Any patient who had at least one positive RNA (PCR) result

Definition of alcohol use in excess of recommended limits
More than 14 units (standard drinks) per week for females
More than 21 units (standard drinks) per week for males

A standard drink in Ireland today equals 10gms of alcohol and is equal to a half pint of beer or a single measure of spirits or a small glass of wine. The limits of 14 and 21 standard drinks (spread out over the week) for women and men respectively are used as a general guide for low risk drinking (Strategic Task Force on Alcohol. Second Report. Sept 2004).

Terms

Anti-D
Antibodies against rhesus D antigens. A small amount of the baby's blood can enter the mother's circulation during pregnancy, or larger amounts can enter during delivery. If the mother is negative for rhesus proteins and the baby is rhesus positive, the mother produces antibodies against the rhesus D antigens. These antibodies can pass through the placenta and damage the baby. The risk of disease is higher with subsequent pregnancies with rhesus positive babies. Anti-D immunoglobulin given during or after pregnancy prevents this.

Ascites
The accumulation of fluid in the spaces between tissues and organs in the abdominal cavity.

Autoantibody tests
Autoantibody tests detect antibodies, which normally fight infections and other foreign substance within the body, but are mistakenly attacking the body's own cells, tissues or organs.

Blood clotting disorders (as used in this report)
Inherited blood disorders in which there is a defect in a factor essential for the clotting mechanism of the blood. These include haemophilia A (deficient in factor VIII), haemophilia B (deficient in factor IX), von Willebrand disease (deficient in von Willebrand factor) and deficiencies of factors V, VII or X.

Cirrhosis
Widespread replacement of liver tissue by fibrotic scar tissue and regenerative nodules, leading to progressive loss of liver function.

Complementary and alternative medicine
A group of diverse medical and health care systems, practices and products that are not currently considered to be part of conventional medicine. The term includes herbalism, aromatherapy, homeopathy,

acupuncture, massage and reflexology. Complementary medicine is used together with conventional medicine. Alternative medicine is used in place of conventional medicine.

Confidence interval for an odds ratio
The width of a confidence interval provides a range of plausible values for the odds ratio in the population from which the data were sampled and gives an idea of the degree of confidence about the accuracy of an odds ratio.

Database
A systematically arranged collection of computer data, structured so that it can be automatically retrieved or manipulated.

Early Virological Response (EVR)
Undetectable HCV RNA (< 50 IU/mL) by qualitative PCR or a ≥2 log drop in HCV RNA at week 12 by quantitative PCR

Extrahepatic manifestations of hepatitis C
Outside of, or unrelated to, the liver. Extrahepatic manifestations associated with hepatitis C include cryoglogulinaemia syndrome, glomerulonephritis, neuropathy, lymphoma, Sjögren syndrome, porphyria cutanea tarda, diabetes.

Fibrosis
Liver fibrosis refers to the accumulation of tough fibrous scar tissue in the liver.

Genotype testing
Hepatitis C genotype tests are used to determine which of the genetically distinct types of hepatitis C virus are present in the patient's blood. Hepatitis C genotype is important in predicting response to anti-viral therapy.

Health Amendment Act (HAA) card
The HAA card is given to people who contracted hepatitis C from the administration within the state of blood or blood products. They are entitled to a range of services under the Health (Amendment) Act 1996.

Hepatic encephalopathy
Neuropsychiatric abnormality in the setting of liver failure. It is caused by toxic substances, which are normally removed by the liver, travelling in the blood to the brain.

Hepatitis C EIA (Enzyme Immunoassay)/ELISA (Enzyme-Linked Immunosorbent assay)
An assay that detects antibodies to specific hepatitis C antigens in a patient's blood. The hepatitis C EIA test is usually used as an initial screening test for hepatitis C antibodies.

Hepatitis C PCR test (Polymerase Chain Reaction)
Test used to detect the presence of hepatitis C virus RNA (genetic material). A positive PCR result indicates an active infection with replicating virus.

Hepatocellular carcinoma (HCC)
Primary malignancy (cancer) of the liver.

Hepatomegaly
Enlarged liver.

Liver biopsy
A liver biopsy is a medical procedure involving the removal of a small piece of liver using a special needle. This is then examined under a microscope for signs of liver abnormality.

Liver function tests (LFTs)
Liver function tests are a group of blood tests which provide information about how the patient's liver is functioning and may act as indicators of liver injury.

Mean (average)
The mean is a measure of central value that is used when values are normally distributed. The mean is calculated by dividing the sum of all the observations by the total number of observations.

Median
The median is a measure of central value that is used when values are not normally distributed (skewed to one side). The median is obtained by arranging observations from lowest value to highest value and picking the middle value (divides the observations in half).

Meta-analysis
A meta-analysis combines the result of several studies on a particular topic to give an overall summary measure of effect.

Multivariate logistic regression
Logistic regression is used to determine if the presence of, or level of, other characteristics affect the likelihood of a specific outcome of interest occurring. In a multivariate logistic regression model, each factor in the model is adjusted for the effect of the other factors on the outcome.

Odds ratio
The odds ratio is a measure of the odds of an event occurring in one group divided by the odds of it occurring in another group. An odds ratio of 1 indicates that the event is equally likely in both groups.

Oesophageal varices
Abnormally dilated and lengthened sub-mucosal veins in the oesophagus. These are usually a consequence of portal hypertension and may bleed.

Portal hypertension
High blood pressure in the portal vein that carries blood from the digestive tract to the liver. The most common cause is cirrhosis. Consequences can include ascites, hepatic encephalopathy, oesophageal varices and splenomegaly.

P-value
In statistics, a result is deemed significant if it is unlikely to have occurred by chance. The p-value is the probability of obtaining a result at least as extreme as the result obtained in the analysis, by chance alone. A p-value of 0.05 indicates that there was a 5% (or 1 in 20) chance of obtaining the result by chance alone. If you are comparing the occurrence of a characteristic in two groups, a low p-value (<0.05) indicates that it is likely that there is a true difference in the value of, or odds of the occurrence of a characteristic in the two groups.

Rapid Virological Response (RVR)
HCV RNA undetectable at week 4 of treatment

Recombinant immunoblot assay (RIBA)
An additional test for hepatitis C specific antigens in a patient's blood. RIBA tests are usually performed after a positive EIA result and are used to confirm the presence of antibodies to the hepatitis C virus. A positive RIBA result is generally considered confirmation that a patient has been infected with hepatitis C, but cannot differentiate between past infection and current infection.

Renal
The term renal refers to the kidney.

Sicca/Sjögren's syndrome
A chronic inflammatory disease that is characterized by dryness of mucous membranes especially of the eyes and mouth and by infiltration of the affected tissues by immune cells. There is a strong epidemiological association between Sjögren's syndrome and hepatitis C infection.

Splenomegaly
Enlarged spleen.

Sustained virological response (SVR)
The absence of detectable hepatitis C RNA in the serum as shown by a qualitative hepatitis C RNA assay with lower limit of detection of 50 IU/ml or less at 24 weeks after the end of treatment.

Abbreviations

ALT	Alanine aminotransferase (a liver enzyme)
Anti-HCV	Antibody to hepatitis C virus
EIA	Enzyme immunoassay, a screening test for hepatitis C
EVR	Early Virological Response
HAA	Health (Amendment) Act
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPSC	Health Protection Surveillance Centre, formerly known as the National Disease Surveillance Centre
HSE	Health Service Executive
IBTS	Irish Blood Transfusion Service, formerly known as the Blood Transfusion Service Board
NDSC	National Disease Surveillance Centre, now known as the Health Protection Surveillance Centre
NICE	National Institute for Clinical Excellence
PCR	Polymerase chain reaction
RIBA	Recombinant immunoblot assay, a more specific hepatitis C test
RNA	Ribonucleic acid
RVR	Rapid Virological Response
SVR	Sustained virological response
WHO	World Health Organization

Appendix A

Members of the National Hepatitis C Database Steering Committee

Dr Declan Bedford, Health Service Executive, Dublin North East

Ms Emer Bolger, Beaumonty Hospital.

Dr Barbara Coughlan, UCD School of Nursing

Ms Joanne Deveney, Positive Action

Ms Anne Duffy, Irish Haemophilia Society

Ms Susan Gaughran, Transfusion Positive

Professor John Hegarty, St Vincent's University Hospital (Alternate: Prof Suzanne Norris, St James's Hospital)

Ms Lara Hynes, Department of Health and Children

Ms Maura Long, Transfusion Positive

Mr Mark Murphy, Irish Kidney Association

Ms Niamh Murphy, Health Protection Surveillance Centre

Ms Michele Tait, Hepatitis C National Co-ordinator, Health Service Executive (Chair)

Dr Lelia Thornton, Health Protection Surveillance Centre

Ms Noeleen White, Positive Action

Appendix B

Members of the National Hepatitis C Database Scientific and Technical Group

Prof Billy Bourke, Our Lady's Children's Hospital, Crumlin

Prof Garry Courtney, St Luke's Hospital, Kilkenny

Dr Orla Crosbie, Cork University Hospital

Prof John Crowe, Mater Misericordiae University Hospital

Prof John Hegarty, St Vincent's University Hospital

Dr John Lee, University College Hospital, Galway

Ms Carol McNulty, St Vincent's University Hospital

Ms Niamh Murphy, Health Protection Surveillance Centre

Prof Frank Murray, Beaumont Hospital

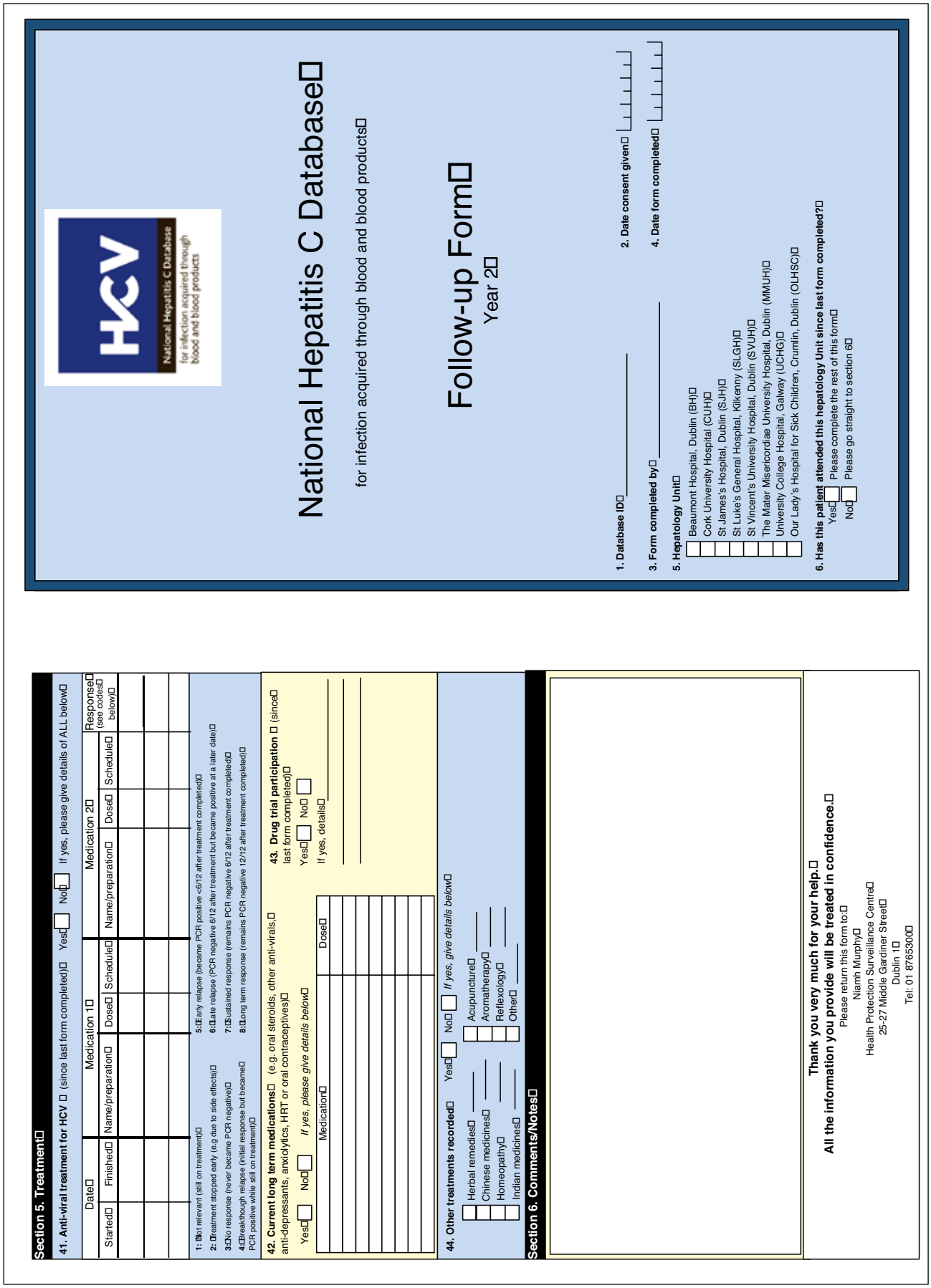
Dr Niamh Nolan, St Vincent's University Hospital

Prof Suzanne Norris, St James's Hospital

Prof Cliona O'Farrelly, Trinity College Dublin

Dr Lelia Thornton, Health Protection Surveillance Centre

Appendix C Data collection form for second year of follow-up



National Hepatitis C Database

for infection acquired through blood and blood products

Follow-up Form

Year 2

1. Database ID _____ 2. Date consent given ___/___/___

3. Form completed by _____ 4. Date form completed ___/___/___

5. Hepatology Unit
- Beaumont Hospital, Dublin (BH)
- Cork University Hospital (CUH)
- St James's Hospital, Dublin (SJH)
- St Luke's General Hospital, Kilkenny (SLGH)
- St Vincent's University Hospital, Dublin (SVUH)
- The Mater Misericordiae University Hospital, Dublin (MMUH)
- University College Hospital, Galway (UCHG)
- Our Lady's Hospital for Sick Children, Crumlin, Dublin (OLHSC)

6. Has this patient attended this hepatology Unit since last form completed?
Yes: Please complete the rest of this form
No: Please go straight to section 6

Section 5. Treatment

41. Anti-viral treatment for HCV (since last form completed) Yes No If yes, please give details of ALL below

Date Started	Date Finished	Medication 1 Name/preparation	Medication 1 Dose	Medication 1 Schedule	Medication 2 Name/preparation	Medication 2 Dose	Medication 2 Schedule	Response (see codes below)

1: Not relevant (still on treatment)
2: Treatment stopped early (e.g due to side effects)
3: No response (never became PCR negative)
4: Breakthough relapse (initial response but became PCR positive while still on treatment)
5: Early relapse (became PCR positive <6/12 after treatment completed)
6: Late relapse (PCR negative 6/12 after treatment but became positive at a later date)
7: Sustained response (remains PCR negative 6/12 after treatment completed)
8: Long term response (remains PCR negative 12/12 after treatment completed)

42. Current long term medications (e.g. oral steroids, other anti-virals, anti-depressants, anxiolytics, HRT or oral contraceptives)
Yes No *If yes, please give details below*

Medication	Dose

43. Drug trial participation (since last form completed)
Yes No
If yes, details _____

44. Other treatments recorded Yes No *If yes, give details below*
- Herbal remedies _____
- Chinese medicines _____
- Homeopathy _____
- Indian medicines _____
- Acupuncture _____
- Aromatherapy _____
- Reflexology _____
- Other _____

Section 6. Comments/Notes

Thank you very much for your help.
All the information you provide will be treated in confidence.

Please return this form to:
Niamh Murphy
Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin 1
Tel: 01 8765300

Database ID _____ Date last form completed _____

Section 1. Patient Details

7. Patient initials _____ **8. DOB** (dd/mm/yy) _____ **9. Height** _____ **10. Weight** _____

11. BMI _____ **12. Sex** Male ☐ Female ☐ **13. County of residence** _____

14. Occupation (as recorded in medical records) _____

15. Birth history (if female)
Number of pregnancies since last form completed _____
Number of live births since last form completed _____

16. Alcohol intake at last visit (units/week)

	Non-Drinker	<=14	15-40	>40
Females	☐	☐	☐	☐
Males	☐	<=21	22-40	>40

17. Smoking status at last visit (cigarettes/day) Non-Smoker ☐ 1-20 ☐ >20 ☐

18. Patient's death recorded since last form completed? Yes ☐ No ☐
If yes: date of death (dd/mm/yy) _____ **Cause of death** _____

19. Other significant viral infection(s) (diagnosed since last form completed) ? Yes ☐ No ☐
If yes, please specify _____

20. Other known liver disease (diagnosed since last form completed) ? Yes ☐ No ☐
If yes, please specify _____

21. Other significant medical conditions (diagnosed since last form completed) ? Yes ☐ No ☐
If yes, please specify

Section 2. Clinical Status

22. Signs of HCV related liver disease (diagnosed since last form completed)
Yes ☐ No ☐
If yes, please specify below
- ☐ Ascites
- ☐ Varices/Bleeding Varices
- ☐ Cirrhosis
- ☐ Liver tumour/HCC
- ☐ Encephalopathy
- ☐ Other (please specify) _____

23. Extrahepatic manifestations of HCV infection (diagnosed since last form completed)
Yes ☐ No ☐
If yes, please specify below
- ☐ Cryoglobulinaemia
- ☐ Glomerulonephritis
- ☐ Porphyria
- ☐ Cutaneous vasculitis
- ☐ Other (please specify) _____
- ☐ Neuropathy
- ☐ Lymphoma
- ☐ Sicca / Sjögren syndrome
- ☐ Diabetes

Section 3. Clinical Management

24. Date of most recent visit for HCV related care (dd/mm/yy) _____

25. Hepatology related care since last form completed
☐ Outpatient
Number of appointments attended _____
☐ Inpatient (including day care). Please give details of each episode:
Main reason for admission _____ Length of stay (nights)* _____
_____ _____
_____ _____
_____ _____
* for day cases please record the number of nights as 0

26. Procedures undergone since last form completed

Procedure	No. of times	Procedure site
☐ Diagnostic gastroscopy		
☐ Therapeutic Banding gastroscopy		
☐ Therapeutic injection gastroscopy		
☐ TIPPS		
☐ Ultrasound		
☐ CT		
☐ MRI		
☐ Hepatic angiography		

Other, specify procedure and number of times _____
Please specify type of ultrasound _____

27. Other medical/surgical/psychiatric services attended (since last form completed)
_____

28. Other specialist healthcare services (including physiotherapy & dental) attended (since last form completed)
_____

Database ID _____ Date last form completed _____

29. Liver transplant recipient (since last form completed) Yes ☐ No ☐
If yes, Date (dd/mm/yy) _____
If no, have they been put on the waiting list? Yes ☐ No ☐
Are they currently on the waiting list? Yes ☐ No ☐

Section 4. Test Results

30. Liver function tests (LFTs) (most recent)
Date (dd/mm/yy) _____
Results: ALT _____ AST _____ Bilirubin _____ Albumin _____ INR _____ PTR _____ AFP _____ Alk Phos _____ Gamma GT _____ Glucose _____

31. Fibroscan result (most recent)
Date (dd/mm/yy) _____
Fibroscan result (Kpa) _____

32. Hepatitis B test results (most recent)
Date (dd/mm/yy) _____

	Pos	Neg	Not tested/Unknown
HBsAg	☐	☐	☐
HBeAg	☐	☐	☐
Anti-HBs	☐	☐	☐
Anti-HBc	☐	☐	☐
Anti-HBe	☐	☐	☐

33. INNO-LIA HCV score (please record banding pattern of most recent OR if banding not available record results as pos/neg/ind)
Date (dd/mm/yy) _____ C1 ___ C2 ___ E2 ___ NS3 ___ NS4 ___ NS5 ___ OR ☐ Pos. ☐ Neg. ☐ Ind. ☐

34. RIBA (please record banding pattern of most recent OR if banding not available record results as pos/neg/ind)
Date (dd/mm/yy) _____ C100 ___ C33 ___ C22 ___ NS5 ___ OR ☐ Pos. ☐ Neg. ☐ Ind. ☐

35. HCV antibody tests
EIA (earliest recorded) Date of test (dd/mm/yy) _____ Pos. ☐ Neg. ☐ Weak ☐

36. HCV genotype/sequence information:
Genotype/subtype _____
Sequence information ☐ 1977 ☐ 1991

37. HLA type

Class I		Class II	
A	/☐	DR	/☐
B	/☐	DQ	/☐
C	/☐	DP	/☐

38. HCV PCR (ALL since last form completed)

Date of test (dd/mm/yy)	Pos.	Neg.	International Unit/ml (IU/ml) OR copies/ml

39. Autoantibodies (most recent)
Date (dd/mm/yy) _____

	Pos.	Neg.	Titre
ANF	☐	☐	
AMA	☐	☐	
SMA	☐	☐	
RF	☐	☐	
DNA	☐	☐	
LKM	☐	☐	

40. Liver biopsy Yes ☐ No ☐ If yes, give details of ALL since last form completed below:

Laboratory reference no.	Date of biopsy (dd/mm/yy)	Chronic hepatitis: Normal	Mild	Moderate	Severe	Fibrosis score	Scoring system	Cirrhosis	HCC
		☐	☐	☐	☐			☐	☐

Appendix D Biopsy scoring

Fibrosis scoring systems

Score	Original HAI or Knodell[15]	Modified HAI or Modified Knodell or Ishak[16] or Desmet[17]	Scheuer[18]	International group of Hepatopathologists
0	No fibrosis	No fibrosis	None	No fibrosis
1	Fibrosis portal expansion	Fibrosis expansion of some portal areas, with or without short fibrous septa	Enlarged, fibrotic portal tracts	Fibrous portal expansion
2		Fibrosis expansion of most portal areas, with or without short fibrous septa	Periportal or portal-portal septa with intact architecture	Portal septa with normal vascular relationships
3	Bridging fibrosis (portal-portal or portal-central linkage)	Fibrosis expansion of most portal areas, with occasional portal to portal bridging	Fibrosis with architectural distortion but no obvious cirrhosis	Distorted structure or incomplete cirrhosis (focal nodules)
4	Cirrhosis	Fibrosis expansion of portal areas, with marked bridging (portal to portal as well as portal to central)	Probable or definite cirrhosis	Cirrhosis, probable or definite
5		Marked bridging with occasional nodules (incomplete cirrhosis)		
6		Cirrhosis, probable or definite		

The grade of inflammation on biopsy was categorised as:Normal, mild inflammation, moderate inflammation or severe inflammation

Appendix E Contact Information

Support Groups

Positive Action
56 Fitzwilliam Square, Dublin 2. Tel: 01-676 2853, Fax: 01-662 0009

Transfusion Positive
3 Clanwilliam Square, Dublin 2. Tel: 01-639 8855. Fax: 01-639 8856

Irish Haemophilia Society
First Floor, Cathedral Court, New St, Dublin 8. Tel:01-657 9900, Fax: 01-657 9901,
Email: info@haemophilia.ie, Website: www.haemophilia-society.ie

Irish Kidney Association
Donor House, Block 43a Park West, Dublin 12. Tel: 01-620 5306, Fax: 01-620 5366, Locall: 1890-543 639,
E-mail: info@ika.ie, Website: www.ika.ie

Specialist Centres

Beaumont Hospital
Hepatology Unit, Beaumont Road, Dublin 9. Tel: 01-809 2220/01-809 3000

Mater Misericordiae University Hospital
Hepatology Unit, 55 Eccles St., Dublin 7. Tel:01-803 2048/01-803 2000

St James's Hospital
Hepatology Unit, James's St., Dublin 8. Tel: 01-410 3417/01-410 3000

St Vincent's University Hospital
Hepatology Unit, Elm Park, Dublin 4. Tel: 01-209 4248/01-269 4533

Our Lady's Children's Hospital
Hepatology Unit, Crumlin, Dublin 12. Tel: 01-409 6742/01-409 6100

Cork University Hospital
Hepatology Unit, Wilton, Cork. Tel: 021 492 2274/021-454 6400

University College Hospital
Hepatology Unit, Newcastle Road, Galway. Tel: 091-544 370/091-524 222

St Luke's Hospital
Hepatology Unit, Kilkenny. Tel: 056-778 5329/056-778 5000

Liaison Officers

HSE Dublin North East

Dublin NW/N
Mr Larry Bathe, Health Service Executive, Mill Lane, Palmerstown, Dublin 20. Tel: 01 620 1758

Cavan, Louth, Meath and Monaghan
Ms Barbara Leech, Health Service Executive, Primary Care Unit, Railway Street, Navan, Co Meath.
Tel: 046 907 6451

HSE Dublin/Mid Leinster

Dublin SW/W/S/Kildare Wicklow
Ms Anne Tiernan/Ms Valerie Whelan, Health Service Executive, Primary Care Unit, Block E, Westland Park, Nangor Road, Dublin 12. Tel: 01 460 9671

Dublin SE/Dun Laoghaire/Bray/Wicklow
Mr John Fennell, Health Service Executive, Civic Centre, Main Street, Bray, Co Wicklow. Tel: 01 274 4257

Laois, Longford, Offaly, Westmeath
Ms Elaine Barry, Primary Care Unit, Health Service Executive,, Springfield, Mullingar, Co Westmeath. Tel: 044 938 4429

HSE West

Clare/Limerick/Tipperary North
Mr Michael Griffin, Primary Care Unit Manager, Health Service Executive, Ballycumin Avenue, Raheen Business Park, Limerick. Tel: 061 464 004

Leitrim/Sligo/Donegal
Ms Phil Mulligan/Ms Sadie Flanagan, Community Care Service, Health Service Executive, Iona Office Block, Main Street, Ballyshannon, Co Donegal. Tel: 071 9834000

Galway/Mayo/Roscommon
Mr Richard Broderick, Health Service Executive Primary Care Unit, Merlin Park Regional Hospital, Galway. Tel: 091-775673

HSE South

Carlow/Kilkenny/Tipperary South/Waterford/Wexford
Mr Cathal O'Reilly/Ms Breda Aylward, Health Service Executive, Lacken, Dublin Rd, Kilkenny. Tel: 056-778 4113

Cork/Kerry
Mr Donal Murphy, Primary Care Unit, 26/27 South Mall, Cork. Tel: 021 492-1872/ 021-492 1871

For all queries that cannot be resolved at local level and within the hospital services:
Ms Michele Tait, Health Service Executive, Mill Lane, Palmerstown, Dublin 20. Tel: 01 620 1750

Relevant National Agencies

Health Protection Surveillance Centre,
25-27 Middle Gardiner St, Dublin 1. Tel: 01-8765300. Email: hcvdatabase@hpsc.ie
Website: www.hpsc.ie, Database website: www.hcvdatabase.ie

National Centre for Hereditary Coagulation Disorders (NCHCD)
St James's Hospital, James's St., Dublin 8. Tel: 01-416 2141
Irish Blood Transfusion Service
National Blood Centre, James's St., Dublin 8. Tel: 01-432 2800

National Virus Reference Laboratory
UCD, Belfield, Dublin 4. Tel: 01-716 1323

Consultative Council on Hepatitis C
2nd Floor HSE Offices, Mill Lane, Palmerstown, Dublin 20. Tel: 01-620 1708
Email: cchepc@health.irlgov.ie, Website: http://www.consultativecouncilonhepc.ie/

Factors found to be linked to more severe hepatitis C disease

- Testing PCR positive
- High alcohol consumption
- Male gender
- Older age at infection or at last visit
- Longer duration of infection
- Genotype 3 infection
- Elevated alanine aminotransferase levels (ALT – liver enzyme)

Being overweight/obese has also been found to be linked to faster disease progression in other studies. Unfortunately, height and weight were not recorded in the charts of the majority of database participants so we could not look at this.

What you can do to improve your health

- Anti-viral treatment for hepatitis C, if recommended by your doctor
- Decrease or give up alcohol
- Healthy weight
- Healthy lifestyle

Areas we hope to improve upon in the database

- Obtain weight and height data for most participants
- Obtain recent alcohol data
- Increase database participation

Please contact your hepatology unit if you have not consented and would like to. If you have any queries about the database or you would like us to look at specific issues please contact HPSC or the patient support groups. We welcome all suggestions.

Support & Contact Information

Support Groups

Positive Action
Tel: 01-676 2853 Fax: 01-662 0009
Email: info@positiveaction.ie
Website: www.positiveaction.ie

Transfusion Positive
Tel: 01-639 8855 Fax: 01-639 8856
Email: transfusionpositive@eircom.net
Website: www.transfusionpositive.ie

Irish Haemophilia Society
Tel:01-657 9900 Fax: 01-657 9901
Email: info@haemophilia.ie,
Website: www.haemophilia.ie

Irish Kidney Association
Tel: 01-620 5306 Fax: 01-620 5366
Locall: 1890-543 639
E-mail: info@ika.ie, Website: www.ika.ie

HPSC: HCV Project Staff

Dr Lelia Thornton, Project Co-ordinator

Ms Niamh Murphy, Surveillance Scientist

Ms Paula Flanagan, Research Nurse

Ms Margaret McIver, Surveillance Assistant

HPSC-Health Protection Surveillance Centre
Tel: 01 8765 300
Email: hcvdatabase@hpsc.ie
Website: www.hpsc.ie
Database website: www.hcvdatabase.ie

National Hepatitis C Database

Database News

Newsletter of the National Hepatitis C Database Issue 2 June 2009

Contents

Health Protection Surveillance Centre,

25-27 Middle Gardiner St, Dublin 1.
Tel: 01-8765300

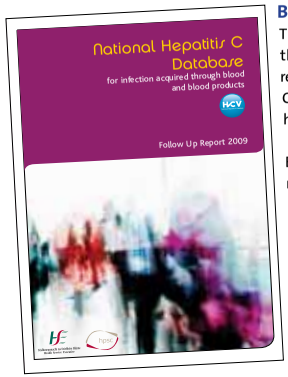
Email:
hcvdatabase@hpsc.ie

Website:
www.hpsc.ie

Database website:
www.hcvdatabase.ie

Welcome to Database News

Welcome to the second edition of Database News, the newsletter of the National Hepatitis C Database. Thank you to everyone who consented to participate in the database. We hope you find the results to date useful. We are also very grateful to all the Hepatology Units and patient support groups who have given their full support since the database project started in 2004.



Background to the database

The National Hepatitis C Database was set up by the Health Protection Surveillance Centre (HPSC) in response to a recommendation by the Consultative Council on Hepatitis C. Its aim is to learn more about hepatitis C and its effects on patients.

Baseline data was collected in 2005 and 2006 and a report on this was published in 2007. The first round of follow-up data was collected in 2007 and the follow up report was published recently. Both reports are available in the Hepatology Units, from the hepatitis C liaison officers and at www.hcvdatabase.ie.

Everyone infected by blood and blood products can take part in the database

Everybody who was infected with hepatitis C through blood or blood products in Ireland is eligible to participate in the database. We are collecting information on people who still have circulating virus (PCR or RNA positive) and people who cleared the virus or have undetectable virus levels (antibody positive, but not PCR/RNA positive).

What information is collected?

The information collected includes details of the source of the hepatitis C infection, current state of health, use of health services, liver biopsy and other test results, and treatment information. A research nurse from HPSC collects this information from the hospital medical records of people who have agreed to take part or those who have died. There is no direct contact with patients. Names and addresses are not recorded in the database.

Participation in the database

The total number of participants so far is 1,275, which is 75% of those who are eligible to participate. This is already a very good participation rate, but a higher participation rate will mean better information about the whole group of people infected with hepatitis C through blood and blood products in Ireland. Eighty five people have been added to the database since the baseline data collection. If you are eligible and have not yet agreed to take part, but would like to participate, consent forms are available in the hepatology units. You can consent at any time. If you are unsure whether or not you consented already, just ask your hepatology nurse or consultant.

Main findings so far

Database population

- 78% of database participants are women, due to the large number infected with hepatitis C through contaminated anti-D, 787 of whom are included in the database (figure 1)
- Over half of participating men are haemophiliacs who were infected through contaminated clotting factors (figure 1)
- The average age at follow up data collection was 56 years for women and 46 years for men
- On average, women had been infected for 29 years and men for 22 years when the follow up data was collected
- 46% of those who are still alive remain hepatitis C PCR positive and 54% no longer test positive for circulating virus (figure 2)

Alcohol consumption

- Information on alcohol consumption was infrequently recorded except at the first visit
- 12% of patients reported moderately high or high alcohol intake
- Men were much more likely to report excess alcohol consumption (figure 3)
- High alcohol intake was found to be associated with severe liver disease - 62% of PCR positive patients with high alcohol intake had severe liver disease, compared to 22% of those who reported moderately high alcohol intake or alcohol consumption within recommended limits

Signs of liver disease

- 148 database participants (12%) had clinical signs of serious liver disease
- PCR positive patients (18%) were more likely to have serious liver disease than PCR negative (or virus undetectable) patients (1%)

Cirrhosis

- 97 patients had developed cirrhosis of the liver by latest follow up
- 93 were PCR positive (12% of PCR positive patients) and 4 had no PCR results in their charts
- Cirrhosis was more common in patients with high alcohol consumption – 27% of patients with cirrhosis had high alcohol consumption compared to 5% of those without cirrhosis
- Men and older participants were more likely to have developed cirrhosis

Biopsy results

- 763 database participants had one or more liver biopsies
- 141 PCR positive patients (18%) had a high fibrosis score on biopsy
- Characteristics associated with having high fibrosis scores included being PCR positive, older age, male gender and high alcohol intake

Other medical conditions

- Almost all patients had medical conditions other than hepatitis C recorded in their charts. We do not know if the percentage of database participants with these conditions is different from the general population. However, if a condition is strongly linked to hepatitis C infection, we would expect to see it occurring more frequently in PCR positive patients compared to those who have been PCR negative (or virus undetectable) for a long time
- 369 patients had depression or anxiety recorded in their medical charts. Long term medications commonly used to treat depression, anxiety or sleep disorders were noted in the charts of more than half of these. Depression or anxiety were more likely to be recorded for PCR positive patients (34%) than for PCR negative patients (22%)
- Osteoporosis and osteopaenia were also more likely to be recorded for PCR positive database participants (16%)
- Other commonly reported medical conditions included fatigue and lethargy (31%), arthralgia/joint pain (24%), hysterectomies (22%) and fibromyalgia (11%)
- HPSC has recently sent a health and lifestyle questionnaire to all HAA card holders to see whether these and other medical conditions differ between the database population and the general population. Results will be compared to a similar study carried out in the general population in Ireland

Deceased participants

- 173 participants had died by latest follow-up
- Death certificates were available for 95%
- Death was directly caused by liver disease for 43 participants: 33 were PCR positive, 8 had no PCR results in their charts and the remaining 2 had PCR results in their charts, but had never tested PCR positive
- The cause of death was hepatitis C for 19, liver cell carcinoma for 12, liver failure for 3, cirrhosis of the liver for 3 and other liver related conditions for 6
- Information on alcohol consumption was available for 34 of the participants who died from liver disease and 53% of these had high alcohol consumption

Anti-viral treatment

- Almost 40% (n=309) of PCR positive participants had one or more courses of anti-viral treatment by the latest follow-up
- Patients with higher fibrosis scores, those with hepatitis C genotypes 2 or 3 and those infected through clotting factors or blood transfusions were more likely to have been treated
- Response to treatment has improved dramatically since the introduction of combined therapy with pegylated interferon and ribaviri. Sustained virological response (viral clearance) is now being achieved for almost half of genotype 1 patients and approximately 70% of patients with genotypes 2 or 3 (figure 4)

Changes in biopsy results post treatment

- 106 PCR positive participants had liver biopsies before and after treatment
- Fibrosis scores had improved for 61% (n=23) of those who achieved SVR
- A significant proportion of those who were treated but did not achieve SVR also showed improvements in biopsy scores after treatment (n=21, 31%)

Liver transplants

- Fifteen patients had received liver transplants
- The average age at transplant was 51 years and the average duration of infection at transplant was 27 years
- All transplant recipients were PCR positive when transplanted

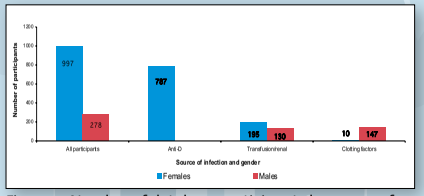


Figure 1. Number of database participants by source of infection and gender (source=other for 6 patients)

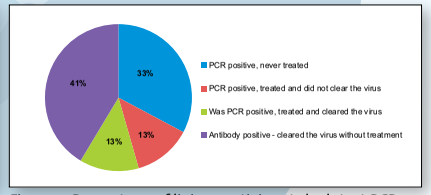


Figure 2. Percentage of living participants by latest PCR status

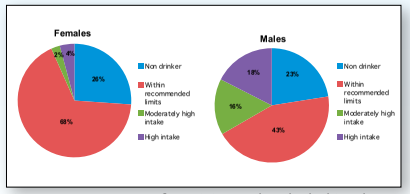


Figure 3. Percentage of participants by alcohol intake and gender

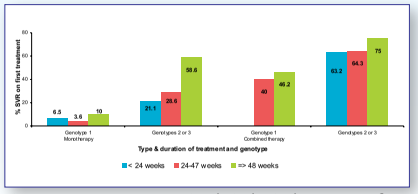


Figure 4. Percentage sustained virological response after first treatment course by genotype and duration of therapy for monotherapy with Interferon, and combined therapy with Interferon and ribarvirin or pegylated interferon and ribavirin

Report prepared by the Health Protection Surveillance Centre
on behalf of the Consultative Council on Hepatitis C

Report prepared by the
Health Protection Surveillance Centre
on behalf of the Consultative Council on Hepatitis C

Health Protection Surveillance Centre
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