National Hepatitis C Database

for infection acquired through blood and blood products

2015 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 very pleased to introduce the 2015 report from the National Hepatitis C Database. This is the fifth report to be produced from the database. It is based on information collected during the years 2010 – 2013 inclusive and describes the main findings from this data.

2014 was a very significant year in that it marked 20 years since the announcement by the then Blood Transfusion Service Board that anti-D immunoglobulin, which was known to have been infected with the hepatitis C virus, had been administered in Ireland to many women. In the months and years that followed, many individuals including men, women and children in Ireland were found to have been infected with hepatitis C through the receipt of contaminated blood, anti-D and other blood products.

Since 1994 we have seen the establishment of eight designated centres of care in the hospital setting, in addition to many other services for those individuals infected with hepatitis C through contaminated blood and blood products. It is now 10 years since the National Hepatitis C Database was established. The database has allowed us to track the progression of the hepatitis C virus so that we can continue to learn more about the disease and the population affected. Information gained through the database has been invaluable both in terms of looking at how the virus behaves over time and how people respond to treatment, and also in terms of helping us to know what services will be needed in the future.

I would like to acknowledge the work of Dr Lelia Thornton and her colleagues in the Health Protection Surveillance Centre who manage the database. This report presents four years of data relating to the years 2010 to 2013 and includes some initial data on patients who have undergone anti-viral therapy using the new triple therapy containing direct acting anti-viral agents. There have been huge developments in the area of therapeutic drug treatment for hepatitis C in the last number of years and we are now entering into an era where complete eradication of the hepatitis C virus is a real possibility.

Ireland's cohort of patients who were infected through contaminated blood and blood products are of particular interest as most people's date of infection is known and so therefore the behaviour of the virus and its impact over a period of time can be closely monitored. Therefore I would like to thank most sincerely all those who have given their consent to be included in the database and also those who have actively encouraged and continue to encourage participation through the hepatology units and the patient support groups. Over three quarters of those known to have been infected with hepatitis C through contaminated blood and blood products have their information included in the database which really improves the level of quality data that can be collected and then used when monitoring disease progression and the impact of treatment.

The collection of this data will continue to be of vital importance in the coming years, especially with the advancements in treatments available to people with hepatitis C. We already know from the existing data that the success rate for those who have been on treatment is high among the Irish population. Although many of the participants in the database do not show evidence of having liver disease, a significant number of those with chronic infection have developed serious liver disease including cirrhosis and liver cancer, some of whom have died.

We look forward to continuing to work with the project over the coming years and in particular to analysing the data which will emerge at a time when treatments are constantly advancing and greatly improving the outcomes for those who are living with the disease.

Michele Tait
Chair
National Hepatitis C Database Steering Committee

Acknowledgements

We wish to thank all those people who have consented to participate in the national hepatitis C database. We would like to acknowledge the contribution of all staff in each of the eight hepatology units, particularly the consultant hepatologists, hepatitis C nurse specialists, consultant histopathologists, and administrative staff, especially those who organised the retrieval of patient medical notes.

We would also like to acknowledge the support of:

The patient support groups: Positive Action, Transfusion Positive, Irish Haemophilia Society, and Irish Kidney Association.

Members of the Database Steering Committee (Appendix A)

Members of the Database Scientific and Technical Group (Appendix B)

Dr Elizabeth Kenny, Chair of the Consultative Council on Hepatitis C (until 2012)

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Staff of the General Register Office (GRO)

Hepatitis C Liaison Officers

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Executive Summary

Hepatitis C infection is a major cause of chronic liver disease and death throughout the world. Hepatitis C virus (HCV) is transmitted by blood and now occurs primarily through injecting drug use. Transfusion-related HCV infection is rare since the introduction of routine screening of blood for HCV antibodies in the early 1990s.

Between 55% and 85% of those infected develop chronic infection and are at risk of progressive liver disease. Up to 20% of chronically infected individuals will develop cirrhosis of the liver over a 20 to 25 year period. Approximately 3% to 4% of patients with cirrhosis will develop hepatocellular carcinoma (HCC) per year.

There have been major advances in hepatitis C treatments in recent years with the arrival of direct acting antivirals which have been shown to achieve very high rates of viral clearance.

The National Hepatitis C Database was set up in 2004 to collect data on people infected with HCV through the receipt of contaminated blood and blood products in Ireland. Approximately 1,700 people were infected through anti-D immunoglobulin, blood transfusion, blood clotting factors or treatment for renal disease. The purpose of the database project is to follow the natural history of infection, evaluate the outcomes of treatment, provide information for planning of services, and serve as a resource for research. Information is gathered from the participants' medical records in the eight participating hepatology units. This report is based on the fifth round of data collection and includes data on database participants up to the end of 2013.

Main findings

Profile of participants

- There are 1,320 database participants, a participation rate of 77%.
- 1,060 were still alive at the end of 2013.
- The source of infection in participants was anti-D immunoglobulin (61%), blood transfusion or treatment for renal disease (26%) and blood clotting factors (13%).
- The average age at last follow-up was 60 years.
- Participants included 1025 females and 295 males.
- The average time interval from infection to last follow-up was 32 years.

Hepatitis C status

- The spontaneous viral clearance rate in this population is between 20% and 36% (depending on whether participants with no confirmatory antibody results are included in the denominator).
- 390 database participants (36.8%) were still alive and chronically infected at the end of 2013, at an average age of 63 years.
- 261 of these were infected through anti-D, 99 through blood transfusion and 28 through blood clotting factors.
- The most common genotype in participants is genotype 1 (77%), followed by genotype 3 (18%).

Alcohol consumption

- Alcohol consumption in excess of recommended levels was recorded for 17% of those with chronic infection.
- This was higher in males and in younger people.

Body mass index (BMI)

- BMI was available for only 44% of participants.
- The findings may not be representative of the whole population as BMI is more likely to be recorded for those who are overweight or underweight.
- 37% were categorised as overweight and a further 30% were obese.

Diabetes mellitus

- Diabetes was recorded in 8% of database participants.
- The prevalence of diabetes was higher in those who developed chronic infection (9.6%) than in those who never developed chronic infection (5.5%).

Outcomes

Liver-related disease was rare in those who never developed chronic infection so the focus of the results is those participants who developed chronic infection.

Clinical signs of severe liver disease

- 29% (n=233) of those who were chronically infected had clinical signs of severe liver disease (such as cirrhosis, oesophageal varices, portal hypertension and ascites) recorded at the last follow-up, an increase from 22% four years ago.
- The factors associated with having signs of serious liver disease were longer duration of infection, male sex, older age, high alcohol intake, and genotype 3 infection.
- Those with high alcohol consumption had >5 times higher odds of having serious liver disease compared to those without.
- Participants infected through blood transfusion or treatment for renal disease were more likely to have signs of serious liver disease compared to anti-D participants.

Cirrhosis

- 22% (n=181) of those who ever developed chronic infection had developed cirrhosis by latest follow-up. This is an increase from 17% four years ago.
- Cirrhosis developed at an average age of 55 years and average duration of infection of 26 years.
- Older age, longer duration of infection, high alcohol intake, and male sex were all independently associated with higher prevalence of cirrhosis on multivariate logistic regression analysis.
- Participants infected through blood transfusion or treatment for renal disease were more likely to have developed cirrhosis compared to those infected through anti-D.

Hepatocellular carcinoma (HCC)

- HCC had developed in 44 (5%) of those who ever had chronic infection, at an average duration of infection of 30 years and an average age of 63 years. This was an increase of 12 cases since four years ago.
- Current chronic infection rather than past chronic infection, male sex, and genotype 3 rather than genotype 1 were independently associated with HCC on multivariate logistic regression analysis.

Deaths

- By the end of 2013, 260 participants had died. This is an increase of 48 deaths in the past four years.
- Among participants who ever developed chronic infection, 23% had died, compared to 8% among those who never became chronically infected.
- Death from liver disease occurred in 73 participants, 63 of whom had been chronically infected and 8 of whom had no RNA results (had died before RNA testing began).
- The factors associated with liver-related mortality on multivariate regression analysis were high alcohol intake, male sex, and current chronic infection compared with past chronic infection.
- Those infected through blood transfusion or clotting factors were more likely to have died from liver-related causes than the anti-D participants.

Anti-viral treatment

- 48% (n=390) of chronically infected participants had received at least one course of anti-viral treatment. This is an increase from 42% four years ago.

- Those who were more likely to have been treated were those who were younger, those infected in the 1991-1994 anti-D outbreak or through blood transfusion or clotting factors, those with higher fibrosis scores and participants with genotype 2 or 3 infections.
- A sustained virological response (SVR) was more likely to be achieved in younger participants, those with genotypes 2 or 3, those who were not cirrhotic prior to treatment and those who did not have high levels of alcohol intake.
- SVR rates for treatment naïve participants who received the standard of care course of pegylated interferon (Peg-IFN) and ribavirin (RBV) was 75% for genotypes 2 and 3 and 59% for genotype 1.
- Thirty seven genotype 1 participants were treated with either telaprevir or boceprevir, in combination with Peg-IFN and RBV, by the end of 2013. Treatment response was available for 21 of these, of whom 17 (81%) achieved an SVR. All those who received at least 24 weeks of treatment (n=15) achieved an SVR.

Liver transplants

- Twenty two database participants had received a liver transplant. The average age at transplant was 54 years and the average duration of infection was 29 years.
- All those tested post-transplant were RNA positive.
- Eleven of the liver transplant recipients had died by the end of 2013. The average time between transplant and death for these patients was 29 months.

Focus on three individual patient groups

Detailed descriptions of the three patient groups are provided in Chapter 5.

Summary tables

Please see summary tables 1-12 and figure 1 for further details of main outcomes and infection status, by individual patient groups.

Conclusion

This report shows the current or last known health status of 1,320 people infected with HCV through the administration of blood or blood products in Ireland. More than half the database population are now in their fourth decade since they acquired HCV infection. It is clear that those who did not develop chronic HCV infection do not show signs of liver-related disease. Among those who developed chronic infection, the majority have not been shown to have signs of liver-related disease. However, a significant number have developed serious liver disease such as cirrhosis and liver cancer, some of whom have died. There has also been a clear progression in the prevalence of adverse health outcomes overall since the last round of data collection four years ago. Of the total database population, 390 people were alive and still HCV infected at the end of the current data collection period.

The rapidly shifting therapeutic landscape for HCV infection, with the arrival of new highly effective drug regimens, of shorter duration and fewer side effects, offers a more optimistic future for those who still have chronic infection.

The participation rate in the database project is high at 77%. The ongoing support of participants, support groups and health professionals is essential to the success of this work. Eligible people who are not yet participants in the database may join at any time by contacting their hepatology unit. The database project team invites participants, health professionals and researchers to contact us with suggestions for further development or improvement of the database, and requests for information from the database.

Summary tables

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

Outcomes	All (n=1320)		Ever chronically infected* (n=813)		Currently chronically infected† (n=562)		Alive & currently chronically infected (n=390)		Chronically infected in the past (n=251)‡		Never chronically infected (n=458)§		No RNA results (n=49)	
All participants	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease‖	246	18.6	233	28.7	186	33.1	91	23.3	47	18.7	6	1.3	7	14.3
Cirrhosis	188	14.2	181	22.3	144	25.6	65	16.7	37	14.7	2	0.4	5	10.2
Liver tumours or HCC	46	3.5	44	5.4	43	7.7	9	2.3	1	0.4	0	0	2	4.1
High fibrosis score on biopsy¶	186	14.1	179	22.0	125	22.2	68	17.4	54	21.5	5	1.1	2	4.1
Deceased	260	19.7	185	22.8	172	30.6			13	5.2	35	7.6	40	81.6
Died from liver disease**	73	5.6	63	7.9	60	10.9			3	1.2	2	0.4	8	17.8

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

† RNA positive on last test. This includes participants who are deceased

‡ At least one positive hepatitis C RNA result, now testing RNA negative, indicates viral clearance spontaneously (small numbers) or through anti-viral treatment

§ Positive or indeterminate line-immunoassay results (RIBA/INNO-LIA) or positive/weak positive EIA/ELISA results, RNA tests done but none were positive. These participants cleared the hepatitis C virus spontaneously and are likely to have done so within a year of infection

‖ Signs of liver disease refer to clinical signs of serious liver disease and include the following: cirrhosis, HCC, varices, portal hypertension, ascites, decompensated liver disease, encephalopathy, splenomegaly, hepatomegaly, hepatosplenomegaly, hypersplenism, hepatopulmonary syndrome, hepatic synthetic dysfunction, hepatorenal syndrome and portal gastropathy

¶ 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. Denominator is all participants (includes those who did not have biopsy results). The proportion of chronically infected participants who had biopsies was significantly higher than that for participants who did not become chronically infected. Fewer biopsies have been carried out in recent years, due to the greater use of less invasive techniques, so severity of fibrosis, based on biopsy results, is likely to be underestimated

** Liver-related disease directly caused death. Denominator for this is all participants, minus the 23 participants who have died but whose cause of death was not available (n=1297)

Table 2. Current RNA status for all participants

RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	%	Num	%	Num	%
Chronically infected*, never treated	396	30.0	279	26.3	117	45.0
Chronically infected, treated, no SVR	165	12.5	110	10.4	55	21.2
Chronically infected, treated, awaiting outcome, last RNA test positive	1	0.1	1	0.1	0	0
Past chronic infection†, treated, SVR	201	15.2	194	18.3	7	2.7
Past chronic infection, treated, awaiting response, but last RNA test negative	21	1.6	21	2.0	0	0
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	2	0.2	0	0	2	0.8
Past chronic infection, spontaneous resolution	27	2.1	23	2.2	4	1.5
Never chronically infected, confirmed positive‡	199	15.1	178	16.8	21	8.1
Never chronically infected, not confirmed positive§	259	19.6	245	23.1	14	5.4
No RNA results in chart, confirmed positive	3	0.2	1	0.09	2	0.8
No RNA results in chart, not confirmed positive	46	3.5	8	0.75	38	14.6
Total	**1320**	**100**	**1060**	**100**	**260**	**100**

* Hepatitis C RNA positive on most recent test

† At least one positive hepatitis C RNA result, most recent RNA test results were negative

‡ Positive line-immunoassay results (RIBA/INNO-LIA). RNA tests done but none were positive. These participants cleared the hepatitis C virus spontaneously and are likely to have done so within a year of infection

§ Positive/weak positive EIA/ELISA results or indeterminate line-immunoassay results (RIBA/INNO-LIA). RNA tests done but none were positive

By source of infection

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

Outcomes	All* (n=811)		Ever chronically infected (n=428)		Currently chronically infected (n=312)		Alive and currently chronically infected (n=261)		Chronically infected in the past (n=116)		Never chronically infected (n=373)	
Anti-D all	Num	%	Num	%	Num	%	Num	%	Num	%	Num	%
Signs of liver disease	99	12.2	94	22.0	74	23.7	44	16.9	20	17.2	4	1.1
Cirrhosis	79	9.7	77	18.0	59	18.9	34	13.0	18	15.5	1	0.3
Liver tumours or HCC	7	0.9	7	1.6	7	2.2	2	0.8	0	0.0	0	0
High fibrosis score on biopsy	90	11.1	86	20.1	63	20.2	42	16.1	23	19.8	3	0.8
Deceased	81	10.0	55	12.9	51	16.4			4	3.5	25	6.7
Died from liver disease†	20	2.5	18	4.3	18	5.8			0	0	1	0.3

* There were no RNA results in the charts of 10 participants. These are included under all, but not under ever or never chronically infected.
This table includes participants infected in non-anti-D outbreak years (n=50) and those infected in outbreak years (1991-1994), but who did not have the relevant outbreak genotype (n=6).

† Denominator for this is all participants minus nine participants who have died but whose cause of death was not available (n=802)

Table 4. Current RNA status for all anti-D participants

RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	%	Num	%	Num	%
Chronically infected, never treated	230	28.4	198	27.1	32	39.5
Chronically infected, treated, no SVR	82	10.1	63	8.6	19	23.5
Past chronic infection, treated, SVR	92	11.3	90	12.3	2	2.5
Past chronic infection, treated, awaiting response, but last RNA test negative	9	1.1	9	1.2	0	0
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	1	0.1	0	0	1	1.2
Past chronic infection, spontaneous resolution	14	1.7	13	1.8	1	1.2
Never chronically infected, confirmed positive	152	18.7	137	18.8	15	18.5
Never chronically infected, not confirmed positive	221	27.3	211	28.9	10	12.3
No RNA results in chart, confirmed positive	1	0.1	1	0.1	0	0
No RNA results in chart, not confirmed positive	9	1.2	8	1.1	1	1.2
Total	**811**	**100**	**730**	**100**	**81**	**100**

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

Outcomes	All* (n=682)		Ever chronically infected (n=374)		Currently chronically infected (n=298)		Alive and currently chronically infected (n=247)		Chronically infected in the past (n=76)		Never chronically infected (n=302)	
Anti-D 1977-1979	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	92	13.5	87	23.3	70	23.5	40	16.2	17	22.4	4	1.3
Cirrhosis	74	10.9	72	19.3	56	18.8	31	12.6	16	21.1	1	0.3
Liver tumours or HCC	7	1.0	7	1.9	7	2.4	2	0.8	0	0	0	0
High fibrosis score on biopsy	87	12.8	83	22.2	62	20.8	41	16.6	21	27.6	3	1.0
Deceased	79	11.6	53	14.2	51	17.1			2	2.6	25	8.3
Died from liver disease†	20	3.0	18	4.9	18	6.1			0	0	1	0.3

* 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 eight participants who have died but whose cause of death was not available (n=674)

Table 6. Current RNA status for anti-D participants infected between 1977 and 1979

RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	**%**	**Num**	**%**	**Num**	**%**
Chronically infected, never treated	222	32.6	190	31.5	32	40.5
Chronically infected, treated, no SVR	76	11.1	57	9.5	19	24.1
Past chronic infection, treated, SVR	55	8.1	54	9.0	1	1.3
Past chronic infection, treated, awaiting response, but last RNA test negative	9	1.3	9	1.5	0	0
Past chronic infection, spontaneous resolution	12	1.8	11	1.8	1	1.3
Never chronically infected, confirmed positive	141	20.7	126	20.9	15	19.0
Never chronically infected, not confirmed positive	161	23.6	151	25.0	10	12.7
No RNA results in chart	6	0.9	5	0.8	1	1.3
Total	**682**	**100**	**603**	**100**	**79**	**100**

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

Outcomes	All* (n=73)		Ever chronically infected (n=37)		Never chronically infected (n=32)	
Anti-D 1991-1994	Num	%	Num	%	Num	%
Signs of liver disease	5	6.9	5	13.5	0	0
Cirrhosis	3	4.1	3	8.1	0	0
Liver tumours or HCC	0	0	0	0	0	0
High fibrosis score on biopsy	2	2.7	2	5.4	0	0
Deceased	1	1.4	1	2.7	0	0
Died from liver disease†	0	0	0	0	0	0

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

† Denominator for this is all participants minus one participant who has died but whose cause of death was not available (n=72)

Note: 6 participants who were infected during this anti-D outbreak period, but who did not have this outbreak genotype are excluded from this table.

Four participants remain currently chronically infected and alive and 33 were chronically infected in the past. Liver-related outcomes are not shown for these patients to ensure that they are not identifiable.

Table 8. Current RNA status for anti-D participants infected between 1991 and 1994

RNA status based on most recent RNA results	All		Currently alive	
	Num	%	Num	%
Chronically infected, never treated	1	1.4	1	1.4
Chronically infected, treated, no SVR	3	4.1	3	4.2
Past chronic infection, treated, SVR	31	42.5	30	41.7
Past chronic infection, spontaneous resolution	2	2.7	2	2.8
Never chronically infected, confirmed positive	5	6.9	5	6.9
Never chronically infected, not confirmed positive	27	37.0	27	37.5
No RNA results in chart	4	5.5	4	5.6
Total	**73**	**100**	**72**	**100**

Note: 6 participants who were infected during this anti-D outbreak period, but who did not have this outbreak genotype are excluded from this table.

One participant was deceased. Further details are not shown for this patient to ensure that they are not identifiable.

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

Outcomes	All* (n=337)		Ever chronically infected (n=274)		Currently chronically infected (n=186)		Alive and currently chronically infected (n=99)		Chronically infected in the past (n=88)		Never chronically infected (n=61)	
Blood transfusion/renal	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	102	30.3	99	36.1	79	42.5	36	36.4	20	22.7	2	3.3
Cirrhosis	84	24.9	82	29.9	64	34.4	27	27.3	18	20.5	1	1.6
Liver tumours or HCC	27	8.0	27	9.9	26	14.0	5	5.1	1	1.1	0	0
High fibrosis score on biopsy	83	24.6	80	29.2	54	29.0	24	24.2	26	29.6	2	3.3
Deceased	104	30.9	93	33.9	87	46.8			6	6.8	9	14.8
Died from liver disease†	32	9.8	31	11.6	28	15.6			3	3.4	1	1.7

* There were no RNA results in the charts of 2 participants (both deceased). These are included under all, but not under ever or never chronically infected

† Denominator for this is all participants minus nine participants who have died but whose cause of death was not available (n=328)

Table 10. Current RNA status for blood transfusion/renal participants

RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	**%**	**Num**	**%**	**Num**	**%**
Chronically infected, never treated	122	36.2	63	27.0	59	56.7
Chronically infected, treated, no SVR	64	19.0	36	15.5	28	26.9
Past chronic infection, treated, SVR	72	21.4	68	29.2	4	3.8
Past chronic infection, treated, awaiting response, but last RNA test negative	7	2.1	7	3.0	0	0
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	1	0.3	0	0	1	1.0
Past chronic infection, spontaneous resolution	8	2.4	7	3.0	1	1.0
Never chronically infected, confirmed positive	28	8.3	22	9.4	6	5.8
Never chronically infected, not confirmed positive	33	9.8	30	12.9	3	2.9
No RNA results in chart	2	0.6	0	0	2	1.9
Total	**337**	**100**	**233**	**100**	**104**	**100**

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

Outcomes	All (n=165)		Ever chronically infected (n=107)		Currently chronically infected (n=61)		Alive and currently chronically infected (n=28)		Chronically infected in the past (n=46)		Never chronically infected (n=21)		No RNA results (n=37)	
Blood clotting factors	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	44	26.7	39	36.5	32	52.5	11	39.3	7	15.2	0	0	5	13.5
Cirrhosis	24	14.6	21	19.6	20	32.8	4	14.3	1	2.2	0	0	3	8.1
Liver tumours or HCC	12	7.3	10	9.4	10	16.4	2	7.1	0	0	0	0	2	5.4
High fibrosis score on biopsy†	12	7.3	12	11.2	8	13.1	2	7.1	4	8.7	0	0	0	0
Deceased	74	44.9	36	33.6	33	54.1			3	6.5	1	4.8	37	100
Died from liver disease*	20	12.5	13	12.4	13	21.7			0	0	0	0	7	20.6

* Denominator for this is all participants minus five participants who have died but whose cause of death was not available (n=160)

†Liver biopsy on only 42% of ever chronically infected

Table 12. Current RNA status for blood clotting factor participants

RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	**%**	**Num**	**%**	**Num**	**%**
Chronically infected, never treated	42	25.5	17	18.7	25	33.8
Chronically infected, treated, no SVR	19	11.5	11	12.1	8	10.8
Past chronic infection, treated, SVR	36	21.8	35	38.5	1	1.4
Past chronic infection, treated, awaiting response, but last RNA test negative	5	3.0	5	5.2	0	0
Past chronic infection, spontaneous resolution	5	3.0	3	3.3	2	2.7
Never chronically infected, confirmed positive	17	10.3	17	18.7	0	0
Never chronically infected, not confirmed positive	4	2.4	3	3.3	1	1.4
No RNA results in chart, confirmed positive	1	0.6	0	0	1	1.4
No RNA results in chart, not confirmed positive	36	21.8	0	0	36	48.6
Total	**165**	**100**	**91**	**100**	**74**	**100**

By sex

Table 13. Summary of main outcomes by hepatitis C RNA status for females

Outcomes	All (n=1025)		Ever chronically infected (n=591)		Currently chronically infected (n=419)		Alive & currently chronically infected (n=324)		Chronically infected in the past (n=172)		Never chronically infected (n=421)		No RNA results (n=13)	
Females	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	152	14.8	145	24.5	116	27.7	64	19.8	29	16.9	5	1.2	2	15.4
Cirrhosis	125	12.2	122	20.6	95	22.7	51	15.7	27	15.7	1	0.2	2	15.4
Liver tumours or HCC	18	1.8	18	3.1	18	4.3	4	1.2	0	0	0	0	0	0
High fibrosis score on biopsy	134	13.1	128	21.7	92	22.0	57	17.6	36	20.9	4	1.0	2	15.4
Deceased	135	13.2	103	17.4	95	22.7			8	4.7	28	6.7	4	30.8
Died from liver disease*	38	3.8	35	6.0	34	8.3			1	0.6	2	0.5	1	7.7

* Denominator for this is all participants minus fourteen participants who have died but whose cause of death was not available (n=1011)

Table 14. Current RNA status for females

RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	**%**	**Num**	**%**	**Num**	**%**
Chronically infected, never treated	297	29.0	236	26.5	61	45.2
Chronically infected, treated, no SVR	121	11.8	87	9.8	34	25.2
Chronically infected, treated, awaiting outcome, last RNA test positive	1	0.1	1	0.1	0	0
Past chronic infection, treated, SVR	136	13.3	131	14.7	5	3.7
Past chronic infection, treated, awaiting response, but last RNA test negative	14	1.4	14	1.6	0	0
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	1	0.1	0	0	1	0.7
Past chronic infection, spontaneous resolution	21	2.0	19	2.1	2	1.5
Never chronically infected, confirmed positive	172	16.8	154	17.3	18	13.3
Never chronically infected, not confirmed positive	249	24.3	239	26.9	10	7.4
No RNA results in chart, confirmed positive	1	0.1	1	0.1	0	0
No RNA results in chart, not confirmed positive	12	1.2	8	0.9	4	3.0
Total	**1,025**	**100**	**890**	**100**	**135**	**100**

Table 15. Summary of main outcomes by hepatitis C RNA status for males

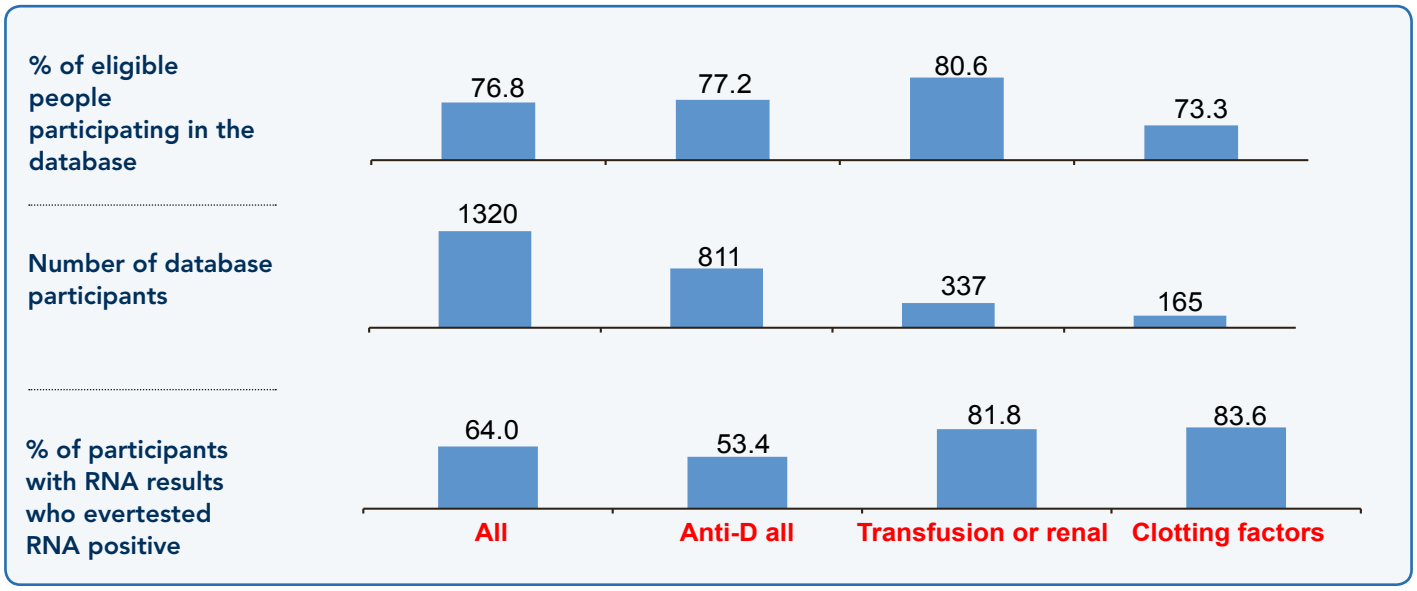
Outcomes	All (n=295)		Ever chronically infected (n=222)		Currently chronically infected (n=143)		Alive & currently chronically infected (n=66)		Chronically infected in the past (n=79)		Never chronically infected (n=37)		No RNA results (n=36)	
Males	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	94	31.9	88	39.6	70	49.0	27	40.9	18	22.8	1	2.7	5	13.9
Cirrhosis	63	21.4	59	26.6	49	34.3	14	21.2	10	12.7	1	2.7	3	8.3
Liver tumours or HCC	28	9.5	26	11.7	25	17.5	5	7.6	1	1.3	0	0	2	5.6
High fibrosis score on biopsy	52	17.6	51	23.0	33	23.1	11	16.7	18	22.8	1	2.7	0	0
Deceased	125	42.4	82	36.9	77	53.9			5	6.3	7	18.9	36	100
Died from liver disease*	35	12.2	28	12.9	26	18.7			2	2.6	0	0	7	21.9

* Denominator for this is all participants minus nine participants who have died but whose cause of death was not available (n=286)

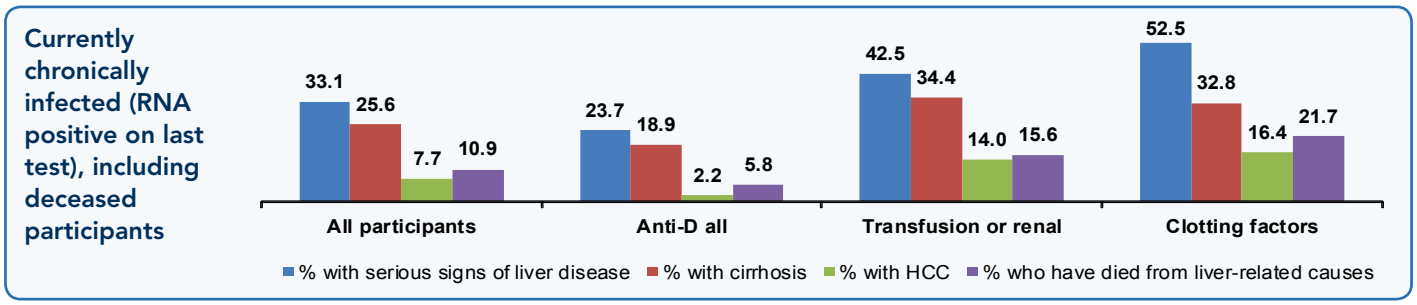
Table 16. Current RNA status for males

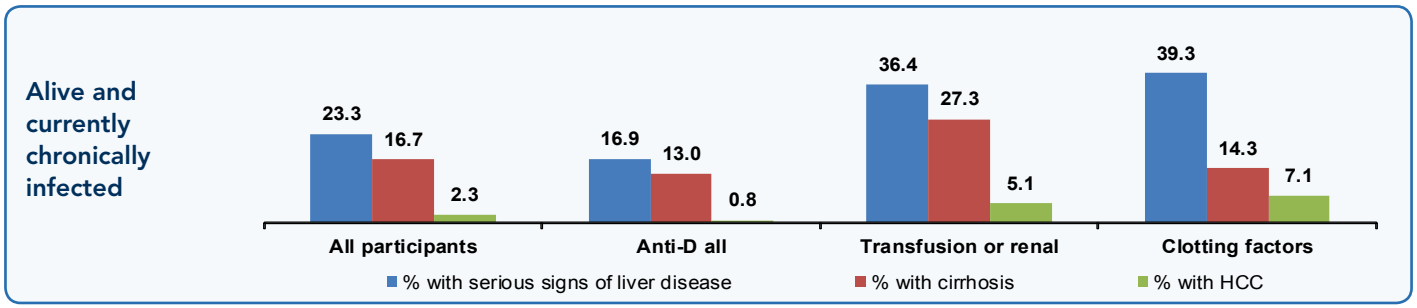
RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	**%**	**Num**	**%**	**Num**	**%**
Chronically infected, never treated	99	33.6	43	25.3	56	44.8
Chronically infected, treated, no SVR	44	14.9	23	13.5	21	16.8
Past chronic infection, treated, SVR	65	22.0	63	37.1	2	1.6
Past chronic infection, treated, awaiting response, but last RNA test negative	7	2.4	7	4.1	0	0
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	1	0.3	0	0	1	0.8
Past chronic infection, spontaneous resolution	6	2.0	4	2.4	2	1.6
Never chronically infected, confirmed positive	27	9.2	24	14.1	3	2.4
Never chronically infected, not confirmed positive	10	3.4	6	3.5	4	3.2
No RNA results in chart, confirmed positive	2	0.7	0	0	2	1.6
No RNA results in chart, not confirmed positive	34	11.5	0	0	34	27.2
Total	295	100	170	100	125	100

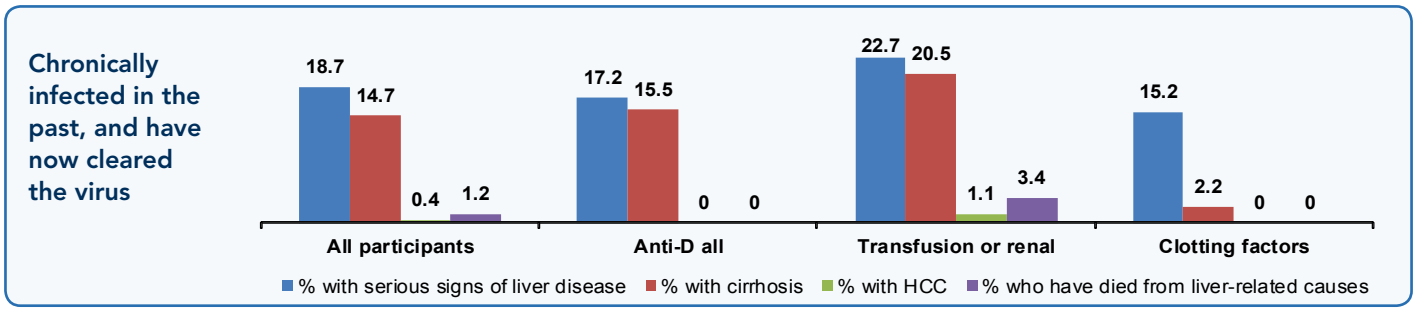
Hepatitis C RNA status and disease outcomes



Liver-related outcomes







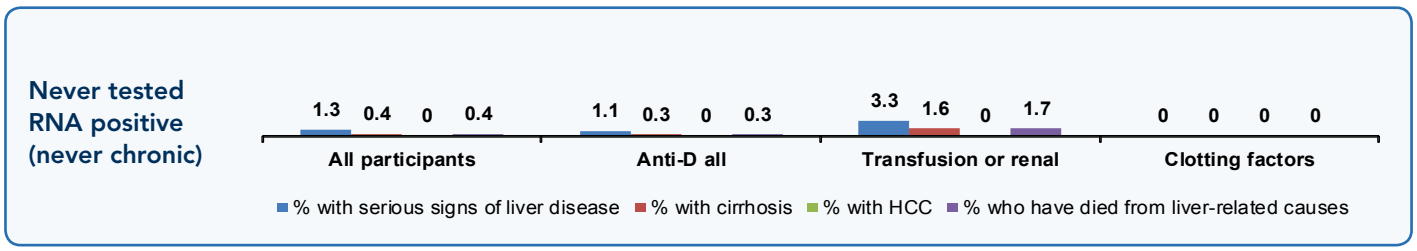


Figure 1. Summary of database participation, RNA status, and disease progression by RNA status, for all participants and by source of infection

Chapter 1. Hepatitis C virus infection

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 mother to infant 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 people developing symptoms or clinically evident acute infection.[2] In most people who become infected with HCV, viremia persists, that is, virus continues to be present in the circulation. 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] Spontaneous resolution of chronic hepatitis C is relatively rare, but can occur.[9]

Chronically infected people are at risk of 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. Approximately 3% to 4% of patients with cirrhosis will develop HCC per year.[10] Factors that have been shown to be associated with progression of liver fibrosis include older age at infection, male sex, genetic factors, metabolic factors (steatosis, diabetes and obesity), co-infection with human immunodeficiency virus (HIV) or hepatitis B, duration of infection, and alcohol intake.[1,4,6,10]

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]

Recently, there have been major advances in hepatitis C treatments. Until 2011, the standard of care was a combination of pegylated interferon (PegIFN) and ribavirin (RBV) for 24 to 48 weeks, depending on the genotype. This resulted in a successful response to treatment (SVR - sustained virological response) in more than 75% of patients with genotypes 2 and 3 HCV infection, and 40-50% of those with genotype 1.[11,12]

In 2011, telaprevir and boceprevir were licensed for HCV genotype 1 infection and came into use in Ireland in 2012. These two protease inhibitor drugs are first generation direct acting antivirals (DAAs) and are used in combination with PegIFN and RBV. This combination has been shown to achieve higher SVR rates than the previous regimen, but with additional side effects.[13] Three new HCV DAAs were licensed in the EU in 2014, for use as part of combination therapies for HCV infection: sofosbuvir, simeprevir and daclatasvir. Each of these can be used in combination with PegIFN and RBV, yielding SVR rates of 60-100%. These new DAAs, and others which have since been approved, are now also used in interferon-free combinations, initially as part of early access programmes in patients with advanced liver disease, and have been shown to achieve very high SVR rates and to be well tolerated.[13]

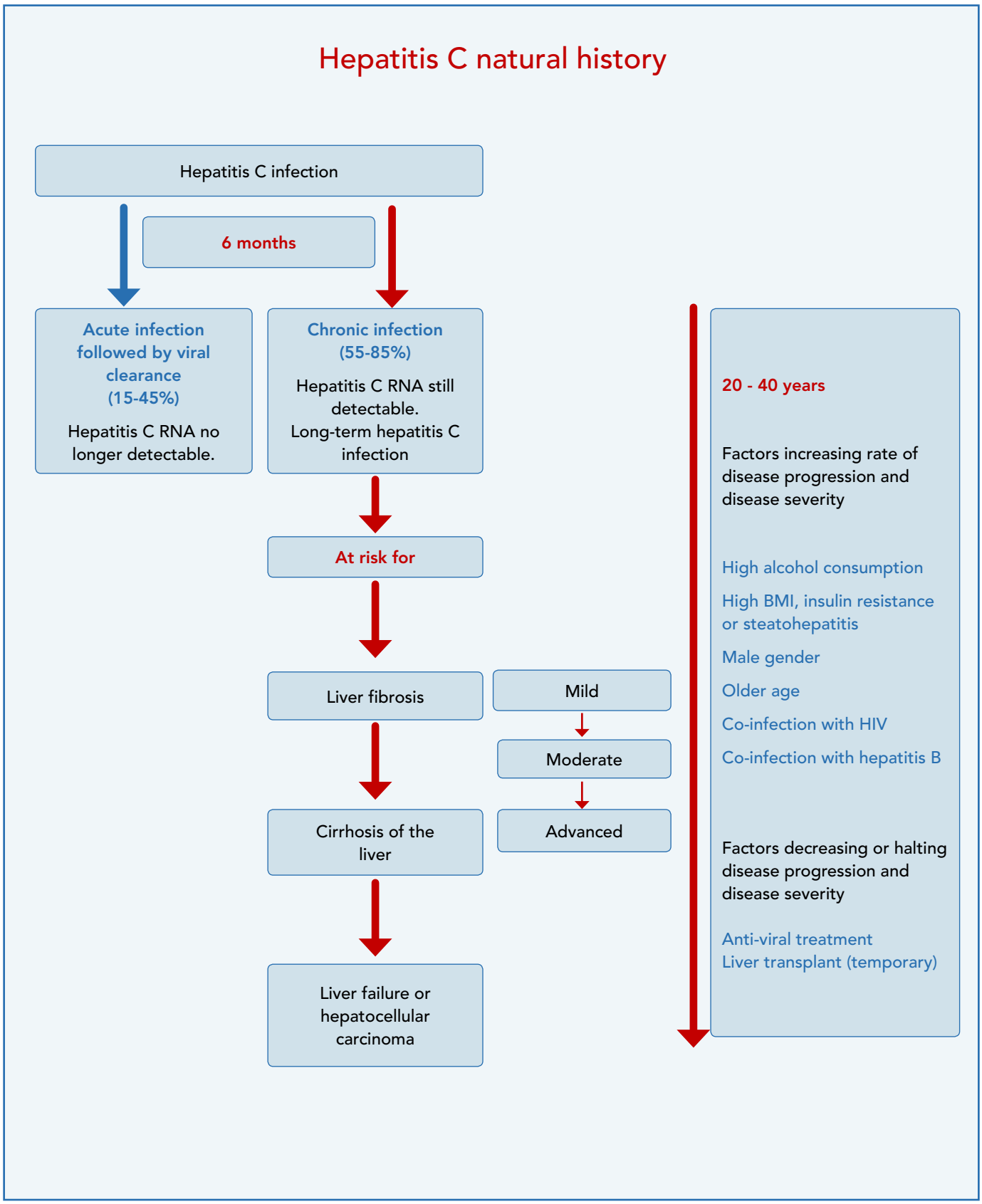


Figure 2. Summary of natural history of hepatitis C infection

Chapter 2. National Hepatitis C Database

2.1 Background to the database

The National Hepatitis C Database was set up in 2004 by the HSE-Health Protection Surveillance Centre (HPSC) in association with eight specialist hepatology units to collect data on people who were 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 transfusions, people with haemophilia and other blood clotting disorders and people who received treatment for renal disease.[14] Specialist hepatology services were set up in eight designated hospitals to provide services for this group, which numbers approximately 1,700 people. Those infected are also entitled to a range of additional hospital and primary care services under the Health (Amendment) Act, 1996 (HAA).

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).

2.2 The objectives of the database are:

1. To follow the natural history of infection in people infected with hepatitis C 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

2.3 Data collection and reporting

Baseline data were collected in 2005 and 2006 and included all relevant data from the date of diagnosis on all consented participants and those who had died. A baseline report[15] describing these data was published in October 2007. Three follow-up reports have been published since baseline data collection, in 2009, 2010 and 2012.[16,17,18] This is the fourth follow-up report and includes information on all participants up to the end of 2013. 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).

2.4 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.[15]

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 tested 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.

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 the time of suspected infection, having had documented exposure to HCV, and some of these may have cleared the virus and since sero-reverted. HCV antibody levels have been demonstrated to drop below detection limits in some patients.[19,20,21]

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.

2.5 Source of data

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

2.6 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. Methods: Data period 2010-2013

3.1 Data Collection

The fourth round of follow-up data collection began in January 2014 and captured data on patients up to 31st December 2013. Data were extracted from the participants' medical notes by a HPSC research nurse. Information collected included clinical, demographic and lifestyle data which had been added to the participants' medical records between the date of last data collection (up to the end of 2009) and the date of follow-up data collection (up to 31st December 2013). 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, additional data fields were included in the latest follow-up data collection form (appendix C).

3.2 Recruitment of new participants

Recruitment of new participants to the database is ongoing and new participants are welcome to join at any time. These include people who did not consent to database participation when first invited to do so in 2004, and those who have been 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.

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

3.4 Assigning dates of diagnosis of cirrhosis and hepatocellular carcinoma (HCC)/liver cancer

Variables were created to indicate if participants had cirrhosis or HCC on biopsy, ultrasound, CT, MRI or fibroscans, or mentioned elsewhere in their medical charts or death certificates. The earliest date mentioned in relation to a diagnosis of cirrhosis or HCC was used as a date of diagnosis. In some cases, particularly where cirrhosis or HCC were recorded in a patient's medical records when baseline data collection was done, the only information available was a diagnosis recorded when the patient first or last attended the hepatology unit and these dates may not accurately reflect when a patient developed cirrhosis or HCC.

3.5 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 hepatology visit/last test result 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.

3.6 Interpretation and presentation of HCV test results

3.6.1 HCV tests and their meaning

RNA tests are used to test for circulating virus. Positive results indicate current infection. Antibody tests indicate if a person has ever been HCV infected, even if they no longer have circulating virus. 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.

3.6.2 Chronic HCV infection

As the vast majority of participants were diagnosed some years after infection, "ever testing RNA positive" can be taken to indicate that the person had developed chronic long-term infection. 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.

3.6.3 Spontaneous viral clearance

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.[22,23]

3.6.4 Categorisation by RNA status

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 small number of 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. Results for the ever RNA positive group are also presented separately for those who remain chronically infected (currently chronically infected) and those who were chronically infected in the past and have since cleared the virus (chronically infected in past), mostly as a result of anti-viral treatment.

3.7 Categorisation of alcohol consumption

At the time of setting up this database, the low-risk drinking guidelines for the general population in Ireland defined an upper limit of 21 units (standard drinks) per week for males and 14 units per week for females.[24] (Note: Low-risk drinking guidelines have been revised and are now defined as 17 standard drinks for men and 11 standard drinks for women, per week.[25]) Participants consuming above these limits (21 for males, 14 for females) and under 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 the number of units of alcohol consumed per week were available for 94% 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 (i.e. alcoholic liver disease, alcohol abuse or >40 units per week).

3.8 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 of the patient.

3.9 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.

3.10 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:[26] fibrosis scored from 0-4
- Modified Knodell system,[27,28] also known as the Ishak or the modified HAI system: fibrosis scored from 0-6
- Scheuer system:[29] 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.

3.11 Fibroscan results

Fibroscan results provide useful indicators of advanced fibrosis and cirrhosis, but are not as accurate at distinguishing mild to moderate fibrosis. Results may also vary depending on the success rate of the scan and physiological features of the patient, particularly high BMI and abdominal adiposity. We interpreted scores of 9.5-14.4 kPa as indicating that the patient may have advanced fibrosis and scores of 14.5 kPa or higher as indicating that the patient may have cirrhosis.[30]

3.12 Data analysis

Data analysis was done using Microsoft Access 2010, Microsoft Excel 2010 and Stata/SE version 11.2. 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. Logistic regression was used to investigate which patient and virus characteristics were independently associated with key liver-related outcomes. The logistic regression models were mostly used to examine the determinants of key liver-related outcomes in participants who were ever chronically HCV infected and generally initially included sex, alcohol consumption, age at end of follow-up, duration of infection, HCV genotype and BMI. Models were also created with source of infection instead of sex as these two variables were too closely linked for the effect of both to be examined in the same model. Cox regression was used in survival analyses and survival curves were derived using the Kaplan Meier method. All statistical tests were 2-tailed and a p-value of <0.05 was taken as statistically significant.

Chapter 4. Main Findings

The summary tables 1-12 at the beginning of this report provide details of RNA status and outcomes by source of infection group

4.1 Participation rates and representativeness of the database cohort

The overall participation rate in the database is now 77%, including people who have died, and the consent rate is 74% (figure 3). Six people have consented and been added to the database since the last round of data collection and one person removed (found to be ineligible), bringing the total number of participants to 1,320. Figure 3 details the response rate by source of infection.

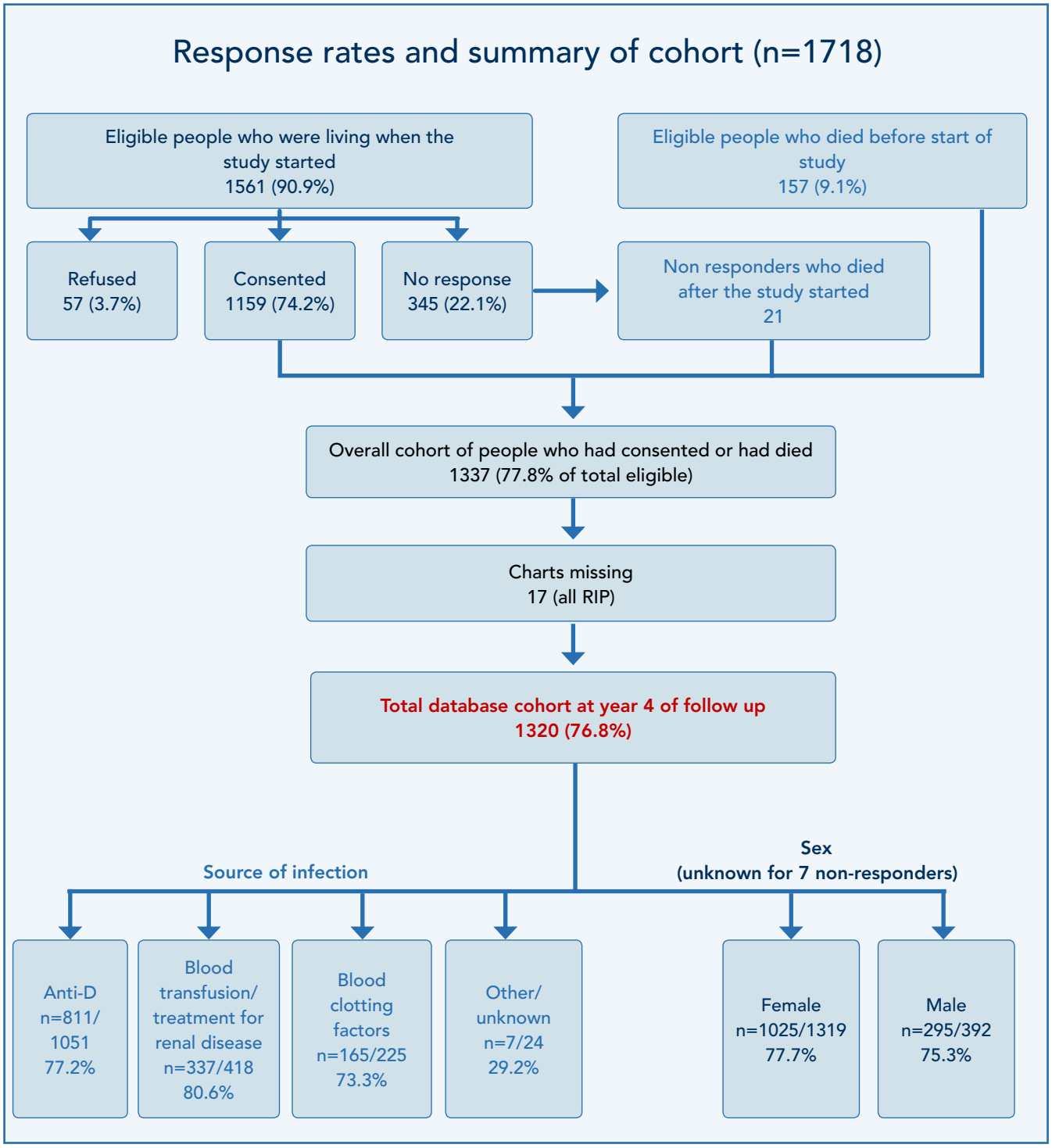


Figure 3. Summary of database cohort and participation rates by source of infection and sex

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

Database participation increased with increasing age up to the mid-60s and declined slightly thereafter. This difference was statistically significant and was also evident when deceased patients were excluded from the analysis (consenting persons only). There was no significant difference in participation rate for females and males: 78% of females (n=1025) and 75% of males (n=295). People infected through blood clotting factors (73%) were significantly less likely to be included in the database compared to blood transfusion/renal patients (81%).

4.2 Hepatitis C infection status and RNA results

4.2.1 Hepatitis C test results

See Methods section 3.6 regarding interpretation of HCV test results.
Overall, 62% (n=813) of database participants had at least one positive RNA result in their charts and a further 15% (n=202) had positive confirmatory tests for HCV antibodies (e.g. RIBA/INNO-LIA) but no positive RNA results (figure 4). The remaining 23% (n=305) tested either ELISA/EIA positive or weak positive, or RIBA/INNO-LIA indeterminate, and had no other positive HCV results.

Twenty two percent (n=37) of participants infected through clotting factors had no RNA test results in their charts. All were deceased and most had died in the early to mid 1990s. RNA tests were only commonly used from 1994 onwards in Ireland. It is likely that a large proportion would have been RNA positive if they had been tested prior to their death.

4.2.2 Viral clearance rate

Once participants with no RNA results were excluded (n=49), the overall spontaneous viral clearance rate, as determined by testing RNA negative at the time of first diagnosis, was 36% (458/1271). This varied by sex and source of infection. Females (n=421, 42%) were significantly more likely to have cleared the virus by the time of their diagnosis than males (n=37, 14%) (figure 4). This sex imbalance remained but was significantly lessened when anti-D participants were excluded (23% for females compared to 14% for males).

As stated above, some participants did not have positive confirmatory results for HCV. A 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, 20% (199/1012) had cleared the virus spontaneously by the time they were diagnosed. Therefore the true spontaneous viral clearance rate after the acute infection is likely to be between 20 and 36%, with 64%-80% of infections becoming chronic.

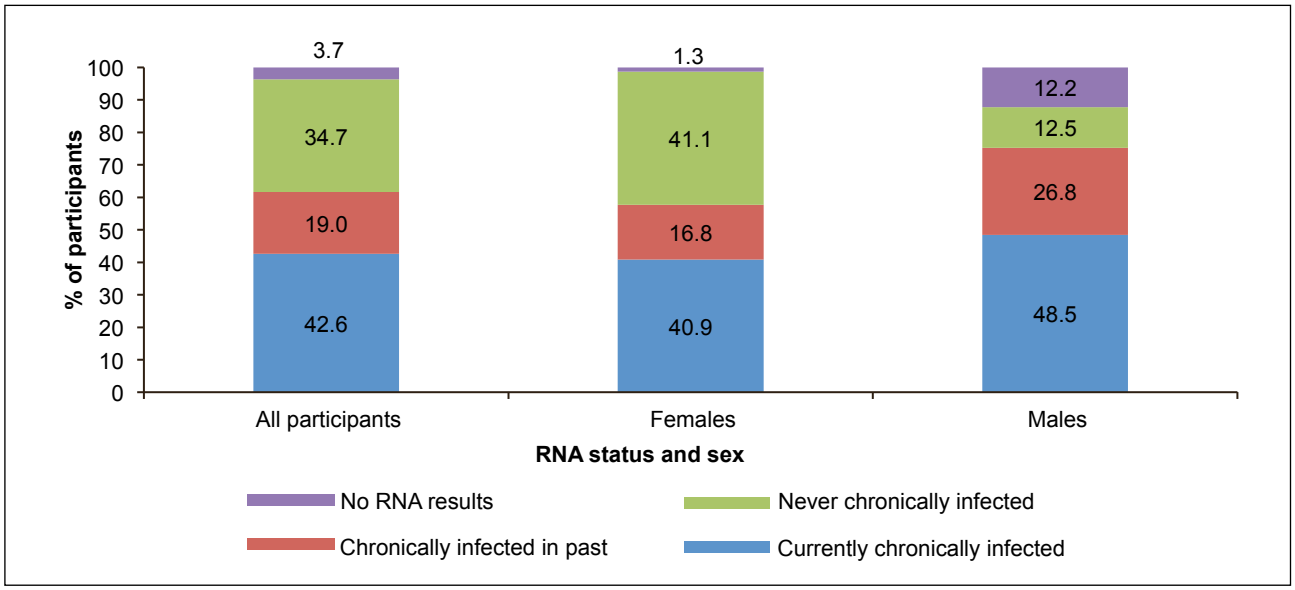


Figure 4. Hepatitis C RNA results for all participants and by sex

4.3 End of latest follow-up

Data up to the end of 2013, 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 last test result or their date of death, as this is the last date when information was recorded in their medical charts.

Sixty three percent of all living database participants had attended their hepatology unit in 2012 or 2013 and a further 6% had been followed up through other services within the same hospital in this time period. Attendance at the hepatology units varied with RNA status. Seventy six percent of participants who remained chronically infected attended their unit in 2012 or 2013 and a further four percent were followed up through other services in the hospital. Seventy three percent of participants, who were chronically infected in the past and had cleared the virus, attended their unit in 2012 or 2013 and a further eight percent of these participants were followed up through other services in the hospital. Participants who had never become chronically infected were less likely to have attended recently, with 46% attending in 2012 or 2013 and an additional 8% attending other services in the hospital. It should be considered that 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. Thirty four living participants have been discharged from their hepatology unit. Twenty two never tested RNA positive, five had no RNA results in their charts, seven were chronically infected in the past but have since cleared the virus.

4.4 Database participants: entire cohort

Date of infection and demographic characteristics for the entire database cohort are shown in figure 5 and table 17.

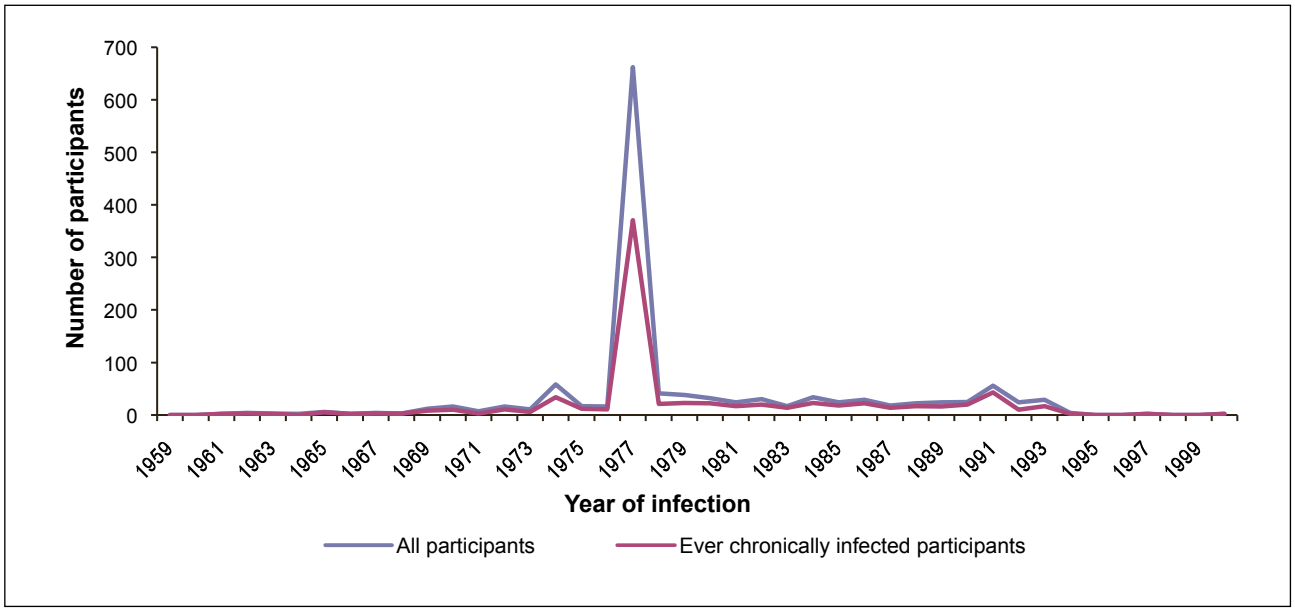


Figure 5. Number of database participants by year of HCV infection and RNA status

Table 17. Summary of demographic and virus characteristics for database participants by RNA status (n=1320)

All participants	All*		Ever chronically infected		Currently chronically infected		Alive & currently chronically infected		Chronically infected in the past		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%	Num	%	Num	%
All participants	**1320**		**813**		**562**		**390**		**251**		**458**	
Sex (n=1320)												
Females	1025	77.7	591	72.7	419	74.6	324	83.1	172	68.5	421	91.9
Males	295	22.3	222	27.3	143	25.4	66	16.9	79	31.5	37	8.1
Age at infection (n=1320)												
Median	**28**	**0-77**	**28**	**0-77**	**29**	**0-77**	**28**	**0-72**	**26**	**0-66**	**28**	**0-63**
<20	212	16.1	145	17.8	80	14.2	58	14.9	65	25.9	43	9.4
20-24	228	17.3	138	17.0	88	15.7	64	16.4	50	19.9	82	17.9
25-29	338	25.6	180	22.1	128	22.8	102	26.2	52	20.7	153	33.4
30-34	259	19.6	152	18.7	103	18.3	81	20.8	49	19.5	104	22.7
35-39	136	10.3	88	10.8	70	12.5	48	12.3	18	7.2	44	9.6
40+	147	11.1	110	13.5	93	16.5	37	9.5	17	6.8	32	7.0
Age at end of follow-up (n=1320)												
Median	**60**	**12-91**	**61**	**16-91**	**62**	**18-91**	**63**	**21-90**	**57**	**16-83**	**59**	**15-91**
0-44	187	14.2	104	12.8	56	10.0	28	7.2	48	19.1	52	11.4
45-49	98	7.4	54	6.6	28	5.0	12	3.1	26	10.4	41	9.0
50-54	160	12.1	92	11.3	53	9.4	37	9.5	39	15.5	64	14.0
55-59	200	15.2	125	15.4	83	14.8	61	15.6	42	16.7	73	15.9
60-64	268	20.3	152	18.7	111	19.8	85	21.8	41	16.3	111	24.2
65-69	215	16.3	144	17.7	109	19.4	88	22.6	35	13.9	69	15.1
70+	192	14.5	142	17.5	122	21.7	79	20.3	20	8.0	48	10.5
Time since infection (n=1320)												
Median	**32**	**1-52**	**34**	**1-52**	**34**	**1-52**	**36**	**7-52**	**32**	**10-51**	**32**	**4-48**
<20 years	165	12.5	85	10.5	63	11.2	12	3.1	22	8.8	59	12.9
20-29 years	368	27.9	209	25.7	127	22.6	63	16.2	82	32.7	135	29.5
30+ years	787	59.6	519	63.8	372	66.2	315	80.8	147	58.6	264	57.6
Duration RNA positivity (n=813)												
Median	**31**	**1-52**	**31**	**1-52**	**34**	**1-52**	**36**	**7-52**	**22**	**1-45**	**n/a**	
<20 years	169	20.8	169	20.8	63	11.2	12	3.1	106	42.2		
20-29 years	207	25.5	207	25.5	127	22.6	63	16.2	80	31.9		
30+ years	437	53.8	437	53.8	372	66.2	315	80.8	65	25.9		
Highest alcohol intake (n=1207)												
Non drinker	289	23.9	177	23.1	131	24.9	85	22.5	46	19.3	106	25.1
Within recommended limits	741	61.4	455	59.5	301	57.1	240	63.7	154	64.7	278	65.7
Moderately high	85	7.0	60	7.8	35	6.6	25	6.6	25	10.5	24	5.7
High†	92	7.6	73	9.5	60	11.4	27	7.2	13	5.5	15	3.5
HCV genotype (n=781)												
Genotype 1	598	76.6	598	76.6	465	85.3	348	89.5	133	56.4	n/a	
Genotype 2	37	4.7	37	4.7	16	2.9	8	2.1	21	8.9		
Genotype 3	142	18.2	142	18.2	61	11.2	32	8.2	81	34.3		
Genotype 4	2	0.3	2	0.3	2	0.4	1	0.3	0	0.0		
Genotype 5	2	0.3	2	0.3	1	0.2	0	0	1	0.4		
Body mass index (n=585)												
Normal or underweight	194	33.2	131	32.9	98	35.5	84	34.9	33	27.0	63	33.7
Overweight	216	36.9	151	37.9	107	38.8	94	39.0	44	36.1	65	34.8
Obese	175	29.9	116	29.1	71	25.7	63	26.1	45	36.9	59	31.6

*49 database participants had no RNA results in their medical records. They are included in the data for the "All" category, but not in the breakdown by RNA status.

† High alcohol intake includes alcohol abuse or alcoholic liver disease recorded in participant's medical record. The alcohol breakdown represents the highest recorded alcohol intake for each participant. No alcohol data were available for 113 database participants.

n/a: not applicable

4.4.1 Sex, age and duration of infection

See Methods section 3.3 for assumptions about year of infection.

Of the 1320 database participants, 62% (n=813) were chronically HCV infected at diagnosis. Due to the large anti-D cohort, females predominate and account for 73% (n=591) of those who ever became chronically infected and 83% (n=324) of those who remained chronically infected and alive at the end of latest follow-up. The median age at infection for ever chronically infected participants was 28 years, the median age at end of follow-up was 61 years and the median duration of RNA positivity was 31 years. Those remaining chronically infected and alive at the latest follow-up (n=390) are now a median age of 63 years and have been infected for a median duration of 36 years (table 17). Eighty one percent of these have been HCV RNA positive for 30 years or longer.

4.4.2 Alcohol consumption

See Methods section 3.7 for categorization of alcohol consumption.

Moderately high alcohol intake was recorded in the medical charts of 8% of ever chronically infected participants for whom data were available, and high alcohol consumption was recorded for 10% (table 17). Males and females differed in their reported exposure to alcohol with 34% (n=68) of chronically infected males having moderately high or high alcohol intake compared to 12% (n=65) of females (figure 6). Younger participants were also more likely to drink excessively. Alcohol consumption also differed significantly by source of infection with participants infected through anti-D (11%) (table 19) less likely to consume alcohol in excess of recommendations compared to those infected through blood transfusion or treatment for renal disease (21%) (table 20) and those infected through clotting factors (35%) (table 21). However, this is largely attributable to the differences in age and sex distribution by source of infection.

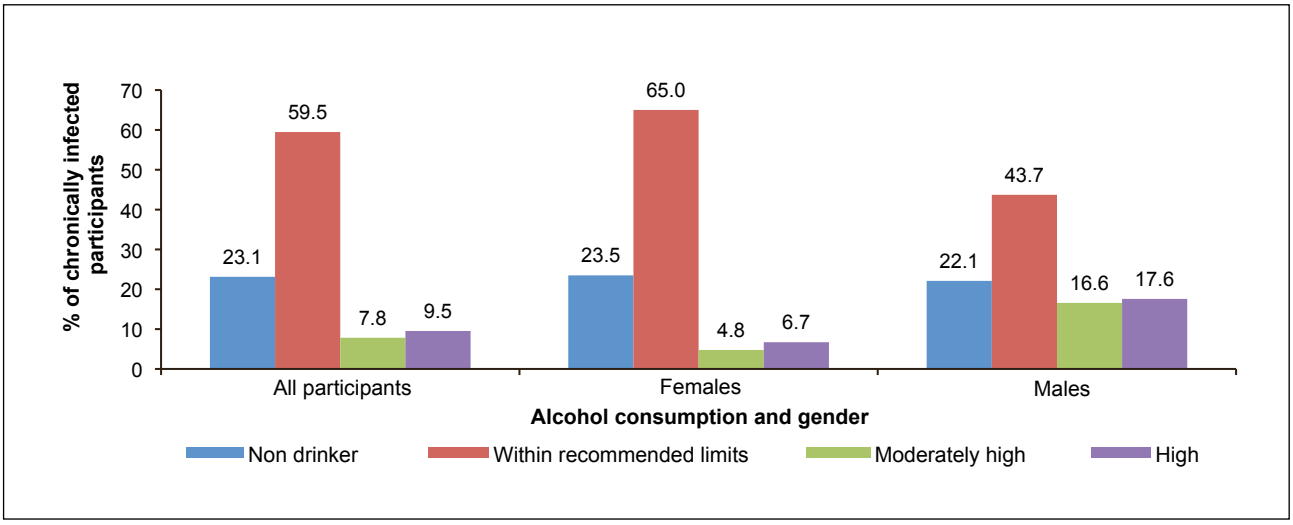


Figure 6. Distribution of highest reported alcohol consumption by sex for participants who became chronically infected (n=765)

4.4.3 HCV genotype

The HCV genotype was available for nearly all of the database participants who became chronically infected (n=781, 96%). Genotype 1 predominated: 77% (n=598) were infected with genotype 1, 18% (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 (table 17).

4.4.4 Body mass index (BMI)

BMI data were available for 44% (n=585) of all database participants and 49% (n=398) of ever chronically infected participants. Overall, 37% (n=216) were overweight and a further 30% (n=175) were obese (table 17). These data may not be representative of all participants as it is likely that BMI data are recorded more often for those who are either overweight or underweight. BMI did not vary significantly by sex or source of infection, but did vary by age at end of latest follow-up, with participants aged between 50 and 64 years more likely to be obese than both younger and older participants. BMI did not vary by HCV RNA status except for patients who were chronically infected and have now cleared the virus. These patients were more likely to be obese than currently chronically infected participants and those who never became chronically infected. However, this may be associated with HCV genotype as genotype 3 patients were more likely to be obese and were also more likely to have been successfully treated compared to genotype 1 patients. It could also indicate that people who had not yet cleared the virus had adopted healthier diets with the knowledge that obesity can accelerate liver disease progression. Alternatively, this could be a data anomaly due to greater BMI data completeness for genotype 1 participants (53% compared to 39% for genotype 3 participants, p=0.002).

4.4.5 Diabetes mellitus and steatosis

Diabetes was recorded in the medical charts of 8% (n=105) of database participants. The prevalence varied by RNA status, with those who became chronically infected more likely to have diabetes than those who never developed chronic infection (9.6% compared to 5.5%, p=0.009) (table 18). The prevalence of diabetes increased significantly with increasing BMI only for participants who were never chronically infected, and obesity and older age were the only demographic factors independently associated with diabetes in this population on logistic regression analysis. For chronically infected participants, the prevalence of diabetes varied by age and sex, with males and older people (≥50 years) more likely to be diabetic. There was no significant variation in diabetes by HCV genotype or BMI. However, BMI data were only available for 49% of chronically infected participants, so this finding may be due to poor data completeness.

A further sixteen participants did not have a diagnosis of diabetes recorded in their medical records but did have test results indicating potential diabetes: six had haemoglobin A1c results of 48 mmol/mol or greater, five had fasting blood glucose levels ≥7 mmol/l and five had random blood glucose levels ≥11.1 mmol/l. Eleven were chronically HCV infected and five were never chronically infected.

Table 18. Comparison of the prevalence of diabetes mellitus in ever and never chronically infected participants *(chi-square test), by BMI, sex, source of infection, age at end of follow-up and HCV genotype*

Diabetes	Ever chronically infected		Never chronically infected		p-value
	Num	%	Num	%	
All participants (n=1271)	**78**	**9.6**	**25**	**5.5**	**0.009**
BMI category (n=585)					
Underweight or normal	11	8.4	0	0	**0.018**
Overweight	17	11.3	4	6.2	0.245
Obese	15	12.9	12	20.3	0.200
Sex (n=1271)					
Females	51	8.6	22	5.2	**0.039**
Males	27	12.2	3	8.1	0.476
Source of infection (n=1313)					
Anti-D all	40	9.4	18	4.8	**0.014**
Anti-D 77-79	37	9.9	16	5.3	**0.027**
Anti-D 91-94	2	5.4	0	0	0.182
Transfusion or renal	31	11.3	6	9.8	0.739
Clotting factors	7	6.5	1	4.8	0.758
Age at end of latest follow-up (years) (n=1271)					
0-49	7	4.4	0	0.0	**0.040**
50-64	39	10.6	10	4.0	**0.003**
65+	32	11.2	15	12.8	0.643

Note: Two database participants with diabetes did not have RNA results recorded and are not included in this table

Steatosis was recorded in the medical records of 15% (n=120) of participants who were ever chronically infected with HCV, and of 19% (n=73) of those who remained chronically infected and alive at latest follow-up. This is likely to be an underestimate as steatosis may remain undiagnosed in patients who have not had recent ultrasounds, biopsies, MRI or CT scans. Sixty two percent (n=227) of participants who remain chronically infected and alive, and had not previously been diagnosed with steatosis, had one or more of these procedures in the past four years. Twenty percent (n=46) were diagnosed with steatosis as a result. In those who remain chronically infected and alive, steatosis was significantly associated with being overweight or obese and with having high fibrosis scores on biopsy on multivariable logistic regression analysis. Steatosis was not independently associated with sex, high alcohol consumption or HCV genotype once BMI and fibrosis scores were taken into account.

4.5 Description of database participants by source of infection

4.5.1 Participants infected through contaminated anti-D immunoglobulin (n=811)

The anti-D group is entirely composed of females who were infected during their child-bearing years (median age at infection: 28 years) (figure 7, table 19). 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.[27] Batches from the first donor were contaminated with genotype 1 HCV and were distributed between 1977 and 1979. Eighty four percent (n=682) 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 nine percent (n=73) of participating anti-D participants. The genotype for six additional participants infected between 1991 and 1994 did not match the outbreak genotype. The estimated year of infection for the remaining fifty participants was outside of the two outbreak periods and sixty six percent of these (n=33) did not have positive confirmatory results for HCV. The source of their infection is unclear. By latest follow-up, 32% (n=261) of anti-D participants remained chronically infected and alive. The median age of this subset of the population was 63 years and their median duration of RNA positivity was 36 years. Ninety four percent had been RNA positive for 30 years or longer. Detailed results by each outbreak are contained in Table 32.

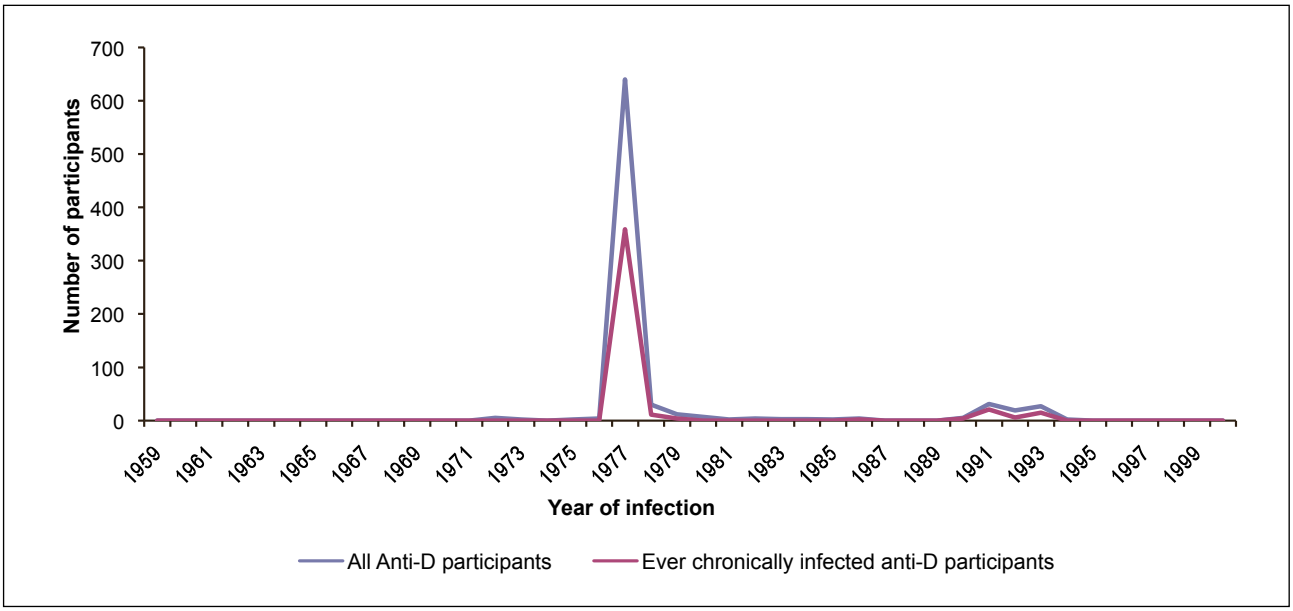


Figure 7. Number of anti-D participants by year of HCV infection and RNA status

Table 19. Summary of demographic and virus characteristics for all anti-D database participants by RNA status (n=811)

Anti-D all	All*		Ever chronically infected		Currently chronically infected		Alive & currently chronically infected		Chronically infected in the past		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%	Num	%	Num	%
All participants	**811**		**428**		**312**		**261**		**116**		**373**	
Sex (n=811)												
Females	811	100	428	100	312	100	261	100	116	100	373	100
Males	0	0	0	0	0	0	0	0	0	0	0	0
Age at infection (n=811)												
Median (range)	**28**	**17-44**	**28**	**17-44**	**28**	**17-44**	**28**	**17-44**	**27.5**	**17-39**	**28**	**17-43**
<20	45	5.5	24	5.6	18	5.8	15	5.7	6	5.2	21	5.6
20-24	176	21.7	98	22.9	64	20.5	54	20.7	34	29.3	73	19.6
25-29	279	34.4	136	31.8	101	32.4	87	33.3	35	30.2	140	37.5
30-34	200	24.7	103	24.1	73	23.4	66	25.3	30	25.9	96	25.7
35-39	90	11.1	58	13.6	47	15.1	32	12.3	11	9.5	31	8.3
40+	21	2.6	9	2.1	9	2.9	7	2.7	0	0.0	12	3.2
Age at end of follow-up (n=811)												
Median (range)	**61**	**26-80**	**62**	**31-79**	**63**	**33-79**	**63**	**34-79**	**59**	**31-75**	**60**	**26-80**
0-44	51	6.3	16	3.7	6	1.9	4	1.5	10	8.6	31	8.3
45-49	53	6.5	20	4.7	11	3.5	4	1.5	9	7.8	32	8.6
50-54	106	13.1	45	10.5	25	8.0	20	7.7	20	17.2	59	15.8
55-59	149	18.4	84	19.6	60	19.2	49	18.8	24	20.7	64	17.2
60-64	211	26.0	111	25.9	82	26.3	70	26.8	29	25.0	98	26.3
65-69	159	19.6	101	23.6	81	26.0	72	27.6	20	17.2	58	15.5
70+	82	10.1	51	11.9	47	15.1	42	16.1	4	3.4	31	8.3
Time since infection (n=811)												
Median	**35**	**4-52**	**36**	**9-52**	**36**	**9-52**	**36**	**9-52**	**35**	**10-37**	**34**	**4-48**
<20 years	57	7.0	18	4.2	5	1.6	3	1.1	13	11.2	36	9.7
20-29 years	165	20.3	60	14.0	33	10.6	14	5.4	27	23.3	101	27.1
30+ years	589	72.6	350	81.8	274	87.8	244	93.5	76	65.5	236	63.3
Duration RNA positivity (n=428)												
Median	**35**	**1-52**	**35**	**1-52**	**36**	**9-52**	**36**	**9-52**	**23**	**1-36**	n/a	
<20 years	57	13.3	57	13.3	5	1.6	3	1.1	52	44.8		
20-29 years	60	14.0	60	14.0	33	10.6	14	5.4	27	23.3		
30+ years	311	72.7	311	72.7	274	87.8	244	93.5	37	31.9		
Highest alcohol intake (n=777)												
Non drinker	169	21.8	80	19.1	60	19.6	48	18.7	20	17.9	88	24.9
Within recommended limits	541	69.6	292	69.9	211	69.0	186	72.4	81	72.3	246	69.7
Moderately high	35	4.5	22	5.3	16	5.2	13	5.1	6	5.4	13	3.7
High	32	4.1	24	5.7	19	6.2	10	3.9	5	4.5	6	1.7
HCV genotype (n=423)												
Genotype 1	380	89.8	380	89.8	304	98.4	256	98.1	76	66.7	n/a	
Genotype 2	2	0.5	2	0.5	0	0.0	0	0.0	2	1.8		
Genotype 3	41	9.7	41	9.7	5	1.6	5	1.9	36	31.6		
Genotype 4												
Genotype 5												
Body mass index (n=410)												
Normal or underweight	133	32.4	76	30.4	59	30.9	50	28.7	17	28.8	57	35.6
Overweight	153	37.3	97	38.8	80	41.9	74	42.5	17	28.8	56	35.0
Obese	124	30.2	77	30.8	52	27.2	50	28.7	25	42.4	47	29.4

*10 Anti-D database participants had no RNA results in their medical records. They are included in the data for the "All" category, but not in the breakdown by RNA status. Eleven genotype 1 anti-D participants, 2 genotype 2 anti-D participants and 4 genotype 3 anti-D participants either had a genotype that did not match that of their outbreak periods or were infected outside of outbreak periods
n/a: not applicable

4.5.2 Participants infected through contaminated blood transfusions or treatment for renal disease (n=337)

This group was the most heterogeneous in terms of age and sex (table 20). They had the highest median age at infection (32), but this ranged from 0 to 77 years. Fifty nine percent of chronically infected participants were female and forty one percent were male, making this the only group with sizeable proportions of each sex. Using the assumptions outlined in Methods section 3.3, most of the blood transfusion/renal participants were infected in the late 1970s and 1980s. At latest follow-up, the median age of transfusion/renal participants who remained chronically infected and alive (29%, n=99) was 66 years and the median duration of RNA positivity was 29 years. They had the shortest duration of RNA positivity at latest follow-up, with 46% positive for 30 years or longer and 71% positive for 25 years or longer.

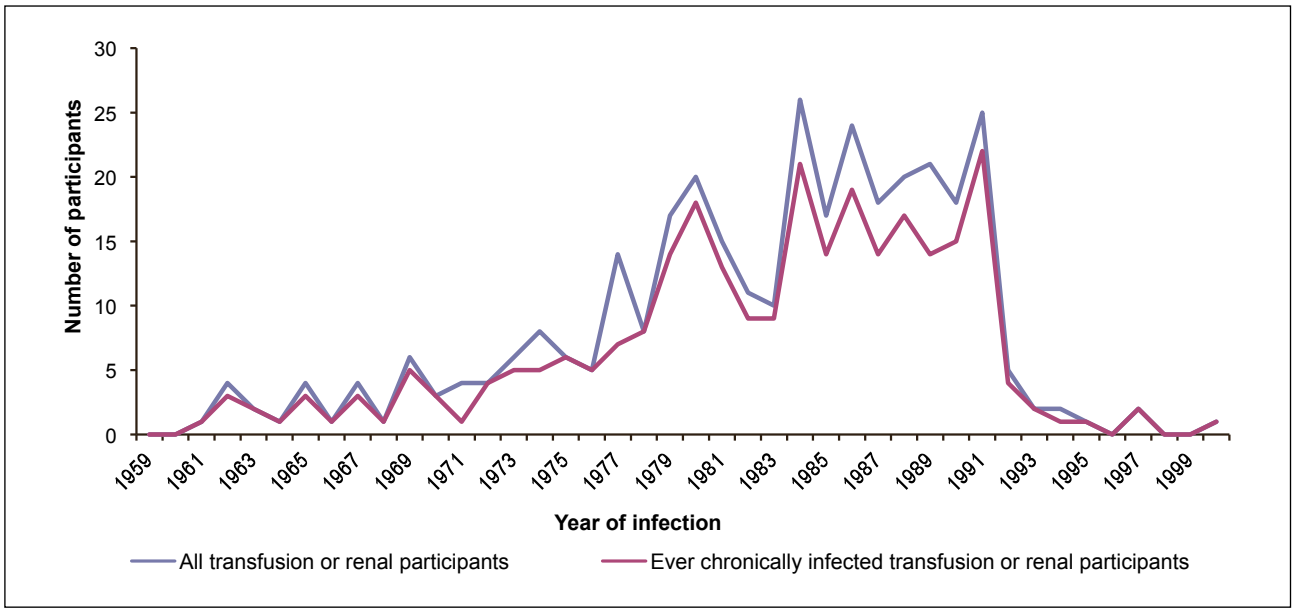


Figure 8. Number of transfusion or renal participants by year of HCV infection and RNA status

Table 20. Summary of demographic and virus characteristics for transfusion or renal database participants by RNA status

Transfusion or renal	All*		Ever chronically infected		Currently chronically infected		Alive & currently chronically infected		Chronically infected in the past		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%	Num	%	Num	%
All participants	**337**		**274**		**186**		**99**		**88**		**61**	
Sex (n=337)												
Females	198	58.8	153	55.8	101	54.3	60	60.6	52	59.1	44	72.1
Males	139	41.2	121	44.2	85	45.7	39	39.4	36	40.9	17	27.9
Age at infection (n=337)												
Median	**32**	**0-77**	**32**	**0-77**	**36**	**0-77**	**32**	**0-72**	**27.5**	**0.7**	**34**	**0-63**
<20	52	15.4	46	16.8	23	12.4	20	20.2	23	26.1	6	9.8
20-24	34	10.1	27	9.9	14	7.5	7	7.1	13	14.8	7	11.5
25-29	48	14.2	37	13.5	23	12.4	14	14.1	14	15.9	11	18.0
30-34	48	14.2	41	15.0	26	14.0	13	13.1	15	17.0	7	11.5
35-39	40	11.9	29	10.6	22	11.8	16	16.2	7	8.0	10	16.4
40+	115	34.1	94	34.3	78	41.9	29	29.3	16	18.2	20	32.8
Age at end of follow-up (n=337)												
Median	**63**	**16-91**	**63**	**16-91**	**65**	**21-91**	**66**	**21-90**	**56.5**	**16-83**	**62**	**16-91**
0-44	50	14.8	42	15.3	24	12.9	13	13.1	18	20.5	8	13.1
45-49	26	7.7	19	6.9	10	5.4	4	4.0	9	10.2	7	11.5
50-54	33	9.8	30	10.9	18	9.7	11	11.1	12	13.6	3	4.9
55-59	34	10.1	26	9.5	15	8.1	9	9.1	11	12.5	8	13.1
60-64	43	12.8	33	12.0	23	12.4	12	12.1	10	11.4	10	16.4
65-69	49	14.5	38	13.9	26	14.0	15	15.2	12	13.6	10	16.4
70+	102	30.3	86	31.4	70	37.6	35	35.4	16	18.2	15	24.6
Time since infection (n=337)												
Median	**26**	**1-51**	**26**	**1-51**	**25**	**1-49**	**29**	**7-49**	**28**	**14-51**	**24**	**7-42**
<20 years	81	24.0	61	22.3	53	28.5	9	9.1	8	9.1	19	31.1
20-29 years	147	43.6	119	43.4	76	40.9	44	44.4	43	48.9	28	45.9
30+ years	109	32.3	94	34.3	57	30.6	46	46.5	37	42.0	14	23.0
Duration RNA positivity (n=274)												
Median	**22**	**1-49**	**22**	**1-49**	**25**	**1-49**	**29**	**7-49**	**19.5**	**4-41**	**n/a**	
<20 years	97	35.4	97	35.4	53	28.5	9	9.1	44	50.0		
20-29 years	108	39.4	108	39.4	76	40.9	44	44.4	32	36.4		
30+ years	69	25.2	69	25.2	57	30.6	46	46.5	12	13.6		
Highest alcohol intake (n=303)												
Non drinker	96	31.7	79	31.5	61	36.5	32	34.8	18	21.4	16	31.4
Within recommended limits	142	46.9	119	47.4	67	40.1	39	42.4	52	61.9	23	45.1
Moderately high	26	8.6	20	8.0	11	6.6	7	7.6	9	10.7	6	11.8
High	39	12.9	33	13.1	28	16.8	14	15.2	5	6.0	6	11.8
HCV genotype (n=262)												
Genotype 1	154	58.8	154	58.8	121	66.9	71	71.7	33	40.7	n/a	
Genotype 2	26	9.9	26	9.9	13	7.2	7	7.1	13	16.0		
Genotype 3	81	30.9	81	30.9	46	25.4	21	21.2	35	43.2		
Genotype 4	1	0.4	1	0.4	1	0.6						
Genotype 5												
Body mass index (n=132)												
Normal or underweight	49	37.1	45	40.2	31	47.7	27	52.9	14	29.8	4	20.0
Overweight	48	36.4	40	35.7	20	30.8	14	27.5	20	42.6	8	40.0
Obese	35	26.5	27	24.1	14	21.5	10	19.6	13	27.7	8	40.0

*2 transfusion or renal database participants had no RNA results in their medical records. They are included in the data for the "All" category, but not in the breakdown by RNA status

n/a: not applicable

4.5.3 Participants infected through contaminated blood clotting factors (n=165)

Participants infected through clotting factors were predominantly male (93%, n=154) (table 21). Using the assumptions outlined in Methods section 3.3, most were infected as children in the mid-1970s to early 1980s (figure 9). The median age at infection was 13 years for the group as a whole and 14 years for those who were chronically infected. By latest follow-up, the median age for clotting factor participants who remained chronically infected and alive (17%, n=28) was 50 years and the median duration of RNA positivity was 38 years. Eighty six percent had been RNA positive for 30 years or longer (table 21). Forty two percent (n=69) of all clotting factor participants were co-infected with HIV and 32% (n=22) were alive at latest follow-up. Of these 22 participants, 9 remain currently chronically infected with HCV, 12 have cleared the virus through treatment and one was never chronically infected.

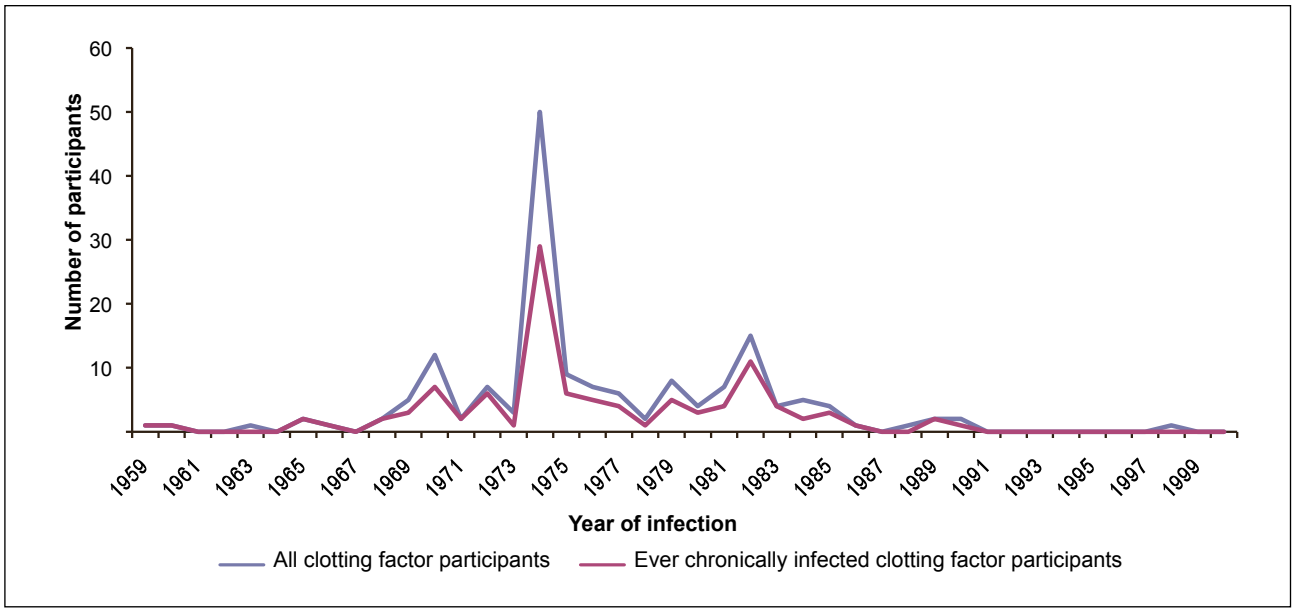


Figure 9. Number of clotting factor participants by year of HCV infection and RNA status

Table 21. Summary of demographic and virus characteristics for clotting factor database participants by RNA status

Clotting factors	All*		Ever chronically infected		Currently chronically infected		Alive & currently chronically infected		Chronically infected in the past		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%	Num	%	Num	%
All participants	**165**		**107**		**61**		**28**		**46**		**21**	
Sex (n=165)												
Females	11	6.7	7	6.5	3	4.9	1	3.6	4	8.7	2	9.5
Males	154	93.3	100	93.5	58	95.1	27	96.4	42	91.3	19	90.5
Age at infection (n=165)												
Median	**13**	**0-59**	**14**	**0-53**	**16**	**0-53**	**13.5**	**1-42**	**12**	**0-33**	**12**	**0-38**
<20	111	67.3	73	68.2	37	60.7	21	75.0	36	78.3	14	66.7
20-24	18	10.9	13	12.1	10	16.4	3	10.7	3	6.5	2	9.5
25-29	11	6.7	7	6.5	4	6.6	1	3.6	3	6.5	2	9.5
30-34	11	6.7	8	7.5	4	6.6	2	7.1	4	8.7	1	4.8
35-39	5	3.0	1	0.9	1	1.6					2	9.5
40+	9	5.5	5	4.7	5	8.2	1	3.6				
Age at end of follow-up (n=165)												
Median	**44**	**12-81**	**46**	**18-81**	**49**	**18-81**	**50**	**30-81**	**45.5**	**30-66**	**43**	**26-71**
0-44	83	50.3	45	42.1	25	41.0	10	35.7	20	43.5	11	52.4
45-49	18	10.9	14	13.1	6	9.8	3	10.7	8	17.4	2	9.5
50-54	21	12.7	17	15.9	10	16.4	6	21.4	7	15.2	2	9.5
55-59	17	10.3	15	14.0	8	13.1	3	10.7	7	15.2	1	4.8
60-64	14	8.5	8	7.5	6	9.8	3	10.7	2	4.3	3	14.3
65-69	6	3.6	4	3.7	2	3.3	1	3.6	2	4.3	1	4.8
70+	6	3.6	4	3.7	4	6.6	2	7.1			1	4.8
Time since infection (n=165)												
Median	**30**	**8-50**	**33**	**14-50**	**33**	**14-50**	**38**	**23-43**	**35.5**	**20-48**	**32**	**15-43**
<20 years	24	14.5	5	4.7	5	8.2					2	9.5
20-29 years	54	32.7	28	26.2	16	26.2	4	14.3	12	26.1	6	28.6
30+ years	87	52.7	74	69.2	40	65.6	24	85.7	34	73.9	13	61.9
Duration RNA positivity (n=107)												
Median	**30**	**4-50**	**30**	**4-50**	**33**	**14-50**	**38**	**23-43**	**27**	**4-45**	**n/a**	
<20 years	14	13.1	14	13.1	5	8.2			9	19.6		
20-29 years	37	34.6	37	34.6	16	26.2	4	14.3	21	45.7		
30+ years	56	52.3	56	52.3	40	65.6	24	85.7	16	34.8		
Highest alcohol intake (n=123)												
Non drinker	23	18.7	17	18.3	9	17.6	4	15.4	8	19.0	2	11.1
Within recommended limits	56	45.5	43	46.2	22	43.1	14	53.8	21	50.0	8	44.4
Moderately high	24	19.5	18	19.4	8	15.7	5	19.2	10	23.8	5	27.8
High	20	16.3	15	16.1	12	23.5	3	11.5	3	7.1	3	16.7
HCV genotype (n=92)												
Genotype 1	60	65.2	60	65.2	37	71.2	19	70.4	23	57.5	n/a	
Genotype 2	9	9.8	9	9.8	3	5.8	1	3.7	6	15.0		
Genotype 3	20	21.7	20	21.7	10	19.2	6	22.2	10	25.0		
Genotype 4	2	2.2	2	2.2	2	3.8	1	3.7				
Genotype 5	1	1.1	1	1.1	0	0.0	0	0.0	1	2.5		
Body mass index (n=40)												
Normal or underweight	11	27.5	10	27.8	8	40.0	7	43.8	2	12.5	1	25.0
Overweight	14	35.0	14	38.9	7	35.0	6	37.5	7	43.8		
Obese	15	37.5	12	33.3	5	25.0	3	18.8	7	43.8	3	75.0

*37 clotting factor database participants had no RNA results in their medical records. They are included in the data for the "All" category, but not in the breakdown by RNA status. All 37 are deceased and 31 were HIV positive.
n/a: not applicable

4.6 Outcomes

Summary table 1 shows that liver-related disease was rare in those who did not develop chronic HCV infection, therefore the focus of this results section is those participants who developed chronic infection.

4.6.1 Clinical signs of serious liver disease

Twenty nine percent (n=233) of chronically infected participants had one or more clinical signs of serious liver disease (as listed in table 22) recorded in their charts by latest follow-up. The most common conditions or signs recorded were cirrhosis, varices, portal hypertension and ascites.

Table 22. Number and percentage of participants with clinical signs of serious liver disease by RNA status*

Clinical signs of liver disease	All participants		Ever chronically infected		Currently chronically infected		Alive & currently chronically infected		Chronically infected in past		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%	Num	%	Num	%
One or more signs of serious liver disease	**246**	**18.6**	**233**	**28.7**	**186**	**33.1**	**91**	**23.3**	**47**	**18.7**	**6**	**1.3**
Cirrhosis	188	14.2	181	22.3	144	25.6	65	16.7	37	14.7	2	0.4
Varices	84	6.4	82	10.1	70	12.5	31	7.9	12	4.8	0	0
Portal Hypertension	77	5.8	76	9.3	65	11.6	30	7.7	11	4.4	0	0
Ascites	71	5.4	67	8.2	62	11.0	18	4.6	5	2.0	3	0.7
Splenomegaly	68	5.2	67	8.2	54	9.6	32	8.2	13	5.2	1	0.2
Liver Tumour/HCC	46	3.5	44	5.4	43	7.7	9	2.3	1	0.4	0	0
Hepatomegaly	36	2.7	33	4.1	27	4.8	9	2.3	6	2.4	3	0.7
Encephalopathy	27	2.0	25	3.1	24	4.3	7	1.8	1	0.4	1	0.2
Bleeding Varices	14	1.1	13	1.6	13	2.3	4	1	0	0	0	0
Decompensated Liver Disease	14	1.1	13	1.6	12	2.1	3	0.8	1	0.4	0	0
Hepatosplenomegaly	6	0.5	6	0.7	4	0.7	1	0.3	2	0.8	0	0
Hypersplenism	5	0.4	5	0.6	4	0.7	2	0.5	1	0.4	0	0
Hepatic Synthetic Dysfunction	1	0.1	1	0.1	1	0.2	0	0	0	0	0	0
Hepatopulmonary Syndrome	1	0.1	1	0.1	1	0.2	0	0	0	0	0	0
Portal Gastropathy	1	0.1	1	0.1	0	0	0	0	1	0.4	0	0
Hepato Renal Syndrome	1	0.1	1	0.1	1	0.2	1	0.3	0	0	0	0

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

The factors independently associated with having one or more clinical signs of serious liver disease on logistic regression analysis were high alcohol intake, longer duration of RNA positivity, male sex, older age at end of follow-up and genotype 3 (rather than genotype 1) HCV infection (table 23 – logistic regression model a). Participants with high alcohol consumption had more than five times higher odds of having signs of liver disease compared to those without. However, the number of chronically infected participants with high alcohol intake was low (n=73, 9.5%) and due to its sensitivity, alcohol consumption data may be inaccurately reported.

Table 23. Factors associated with having one or more clinical signs of serious liver disease in ever chronically infected participants – logistic regression model a (n=736)

Factors associated with clinical signs of serious liver disease	Odds ratio	p-value	95% confidence interval
Highest recorded alcohol consumption			
Non drinker/within recommended limits/moderately high	1		
High (>40 units per week or alcohol abuse in chart)	5.2	**<0.001**	2.96 - 9.09
Duration of RNA positivity			
<20 years	1		
20+ years	3.1	**<0.001**	1.80 - 5.48
Sex			
Female	1		
Male	2.3	**<0.001**	1.51 - 3.51
Age at end of latest follow-up (years)			
0-49 years	1		
50-64 years	1.8	**0.037**	0.34 - 2.09
65+ years	1.9	**0.024**	1.02 - 2.80
Genotype			
Genotype 1	1		
Genotype 2	0.8	0.716	0.34 - 2.09
Genotype 3	1.7	**0.04**	1.02 - 2.80

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

The effects of source of infection and sex cannot be assessed in the same logistic regression model as sex is too closely linked to source of infection in the database population. Genotype and older age at end of follow-up are not independently associated with clinical signs of serious disease when source of infection is included in the logistic regression model instead of sex. Blood transfusion/renal participants are significantly more likely to have one or more signs of liver disease compared to anti-D participants (table 24 – logistic regression model b).

Table 24. Factors associated with having one or more clinical signs of serious liver disease in ever chronically infected participants – *logistic regression model b (n=762)*

Factors associated with clinical signs of serious liver disease	Odds ratio	p-value	95% confidence interval
Highest recorded alcohol consumption			
Non drinker/within recommended limits/moderately high	1		
High (>40 units per week or alcohol abuse in chart)	5.2	**<0.001**	3.04 - 8.85
Duration of RNA positivity			
<20 years	1		
20+ years	3	**<0.001**	1.83 - 4.96
Source of infection			
Anti-D	1		
Transfusion or renal	2.3	**<0.001**	1.57 - 3.32
Clotting factors	1.6	0.064	0.97 - 2.70

Figures 10 and 11 show the prevalence of clinical signs of serious liver disease by duration of RNA positivity and alcohol intake, by sex and source of infection separately.

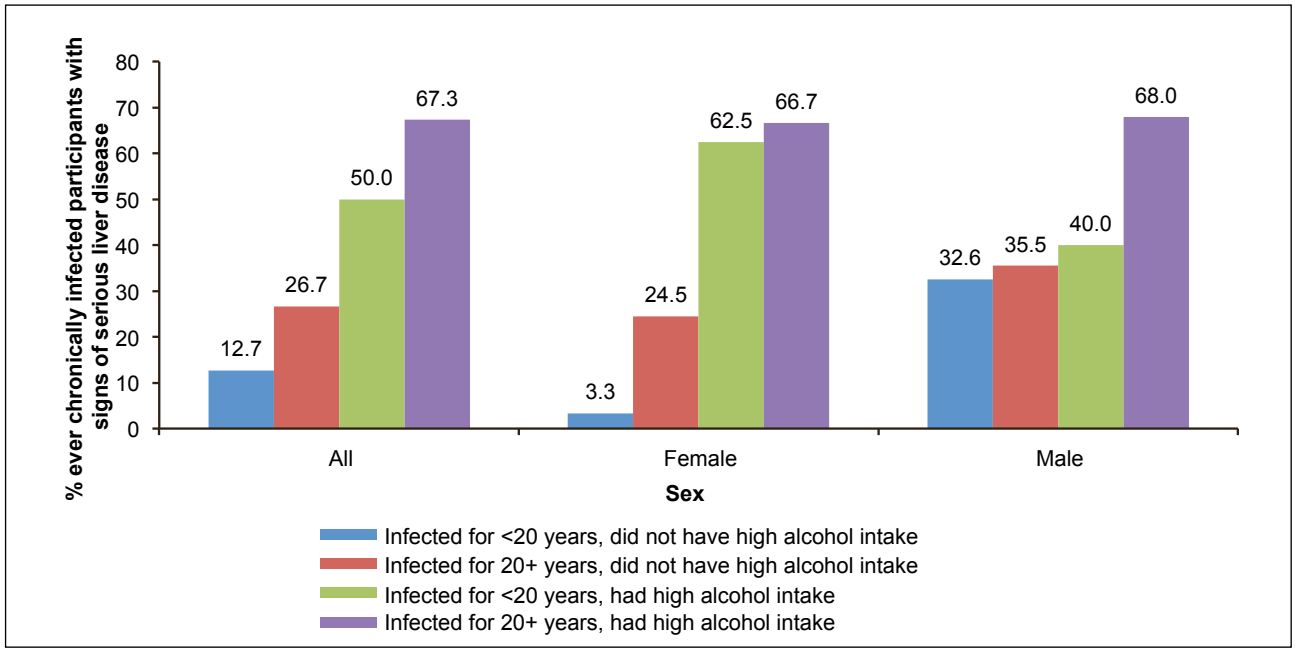


Figure 10. Percentage of ever chronically infected participants with one or more clinical signs of serious liver disease, by sex, duration of RNA positivity and alcohol consumption

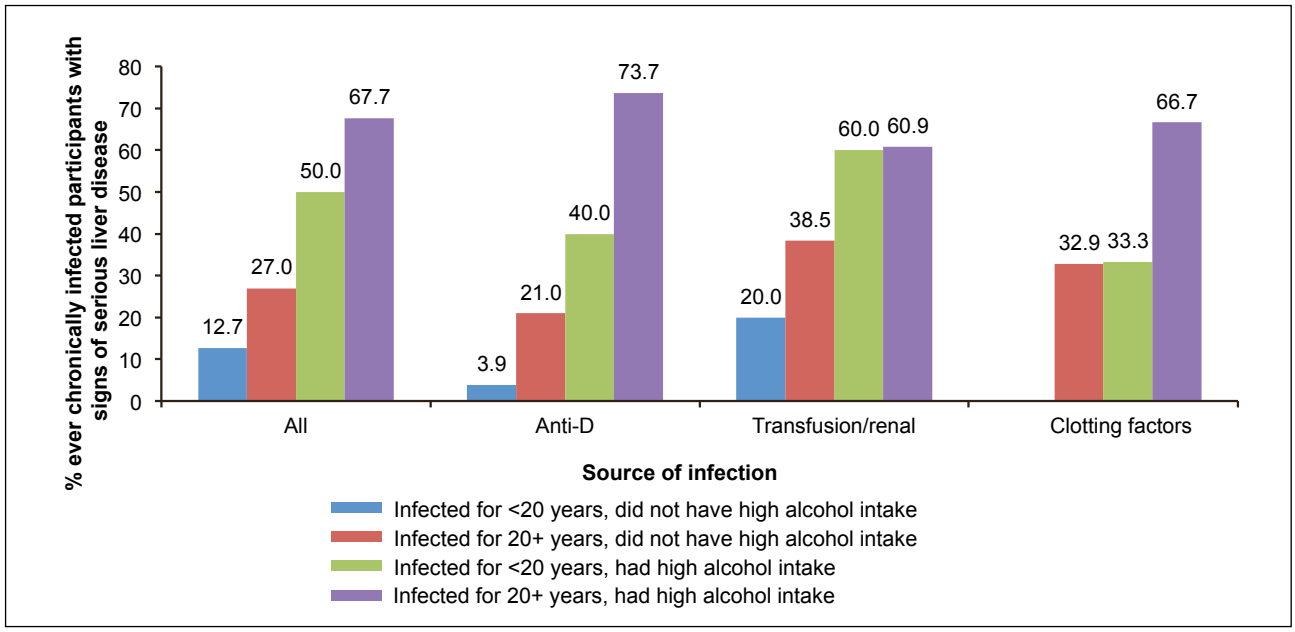


Figure 11. Percentage of ever chronically infected participants with one or more clinical signs of serious liver disease, by source of infection, duration of RNA positivity and alcohol consumption

4.6.2 Cirrhosis

Cirrhosis varied significantly by RNA status, with ever chronically infected participants significantly more likely to have developed cirrhosis compared to those who never became chronically infected (n=181, 22.3% compared to n=2, 0.4%, p<0.001). Those who were chronically infected on last RNA test had significantly higher prevalence of cirrhosis than those with past chronic infection (n=144, 25.6% compared to n=37, 14.7%, p=0.001) (table 25, figure 12).

Of the 37 participants with cirrhosis who have cleared the virus, 30 had developed cirrhosis prior to viral clearance (see Methods section 3.4 regarding the method of assigning dates of diagnosis). The median time between viral clearance and developing cirrhosis for the remaining seven was nine years (range: 2-13 years). Three of these participants had high alcohol intake, three had high fibrosis scores on pre-treatment biopsies and the remaining patient had not had a biopsy in the six years prior to viral clearance.

For ever chronically infected database participants, the median duration of RNA positivity at the estimated date of cirrhosis (see Methods section 3.4 and 3.5 for methods used) was 26 years (mean: 25.1 years) and the median age at cirrhosis was 55 years (mean: 55.4 years). On univariate analysis of ever chronically infected participants, the prevalence of cirrhosis was significantly higher in blood transfusion/renal participants compared to those infected through either anti-D or clotting factors. It was also higher in participants who had high alcohol intake recorded in their medical notes (table 25). Where alcohol data were recorded, 22% of ever 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 compared to 6% of ever chronically infected participants without cirrhosis.

Table 25. Cirrhosis in ever chronically infected database participants *(with univariate chi-square test for differences in prevalence of cirrhosis across different categories of host and virus variables)*

Ever chronically infected database participants	Number with cirrhosis	% with cirrhosis	Median age at cirrhosis diagnosis (years)	Median duration RNA positivity at cirrhosis (years)	p-value
All	181	22.3	55	26	
Sex					0.070
Females	122	20.6	59	27	
Males	59	26.6	51	24	
Source of infection					**0.001**
Anti-D all	77	18.0	56	30	
Anti-D 77-79	72	19.3	57	30	
Anti-D 91-94	3	8.1	42	12	
Transfusion or renal	82	29.9	57	22	
Clotting factors	21	19.6	45	30	
Highest recorded alcohol intake					**<0.001**
Non drinker	43	24.3	59	27	
Within recommended limits	77	16.9	56	27	
Moderately high	12	20.0	55	30	
High	38	52.1	54	22	
BMI					0.348
Normal or underweight	24	18.3	56	28	
Overweight	35	23.2	59	30	
Obese	30	25.9	55	26	
Age at end of latest follow-up (years)					0.059
0-49 years	24	15.2	39	23	
50-64 years	88	23.9	53	26	
65+ years	69	24.1	65	27	
RNA status at latest follow-up					**0.001**
Past chronic infection, cleared virus	37	14.7	55	30	
Currently chronically infected	144	25.6	56	32	
HCV genotype					0.848
Genotype 1	130	21.7	56	29	
Genotype 2	8	21.6	53	22	
Genotype 3	34	23.9	52	20	

High alcohol intake (OR 5.0, p<0.001), being 50 years or older at the end of latest follow-up (OR 2.4, p=0.002), being infected for 20 years or longer (OR 2.1, p=0.005) and male sex (OR 1.7, p=0.012), were all independently associated with higher prevalence of cirrhosis in ever chronically infected participants on multivariate logistic regression analysis. When source of infection was substituted for sex in the model, participants infected through blood transfusions or treatment for renal disease were significantly more likely to have developed cirrhosis compared to those infected through anti-D.

Cox multivariate regression analysis was used to look at factors associated with the higher cirrhosis rates. Participants who remained chronically infected (hazard ratio 1.8, p=0.003), those with high alcohol consumption (hazard ratio 3.0, p<0.001), those infected through blood transfusions or treatment for renal disease (hazard ratio 2.4, p<0.001) and those with genotype 3 HCV infection (compared to genotype 1)

(hazard ratio 1.8, p=0.008) had higher rates of cirrhosis. Although males had higher rates of cirrhosis than females, the difference was not statistically significant after adjusting for RNA status, alcohol consumption and genotype.

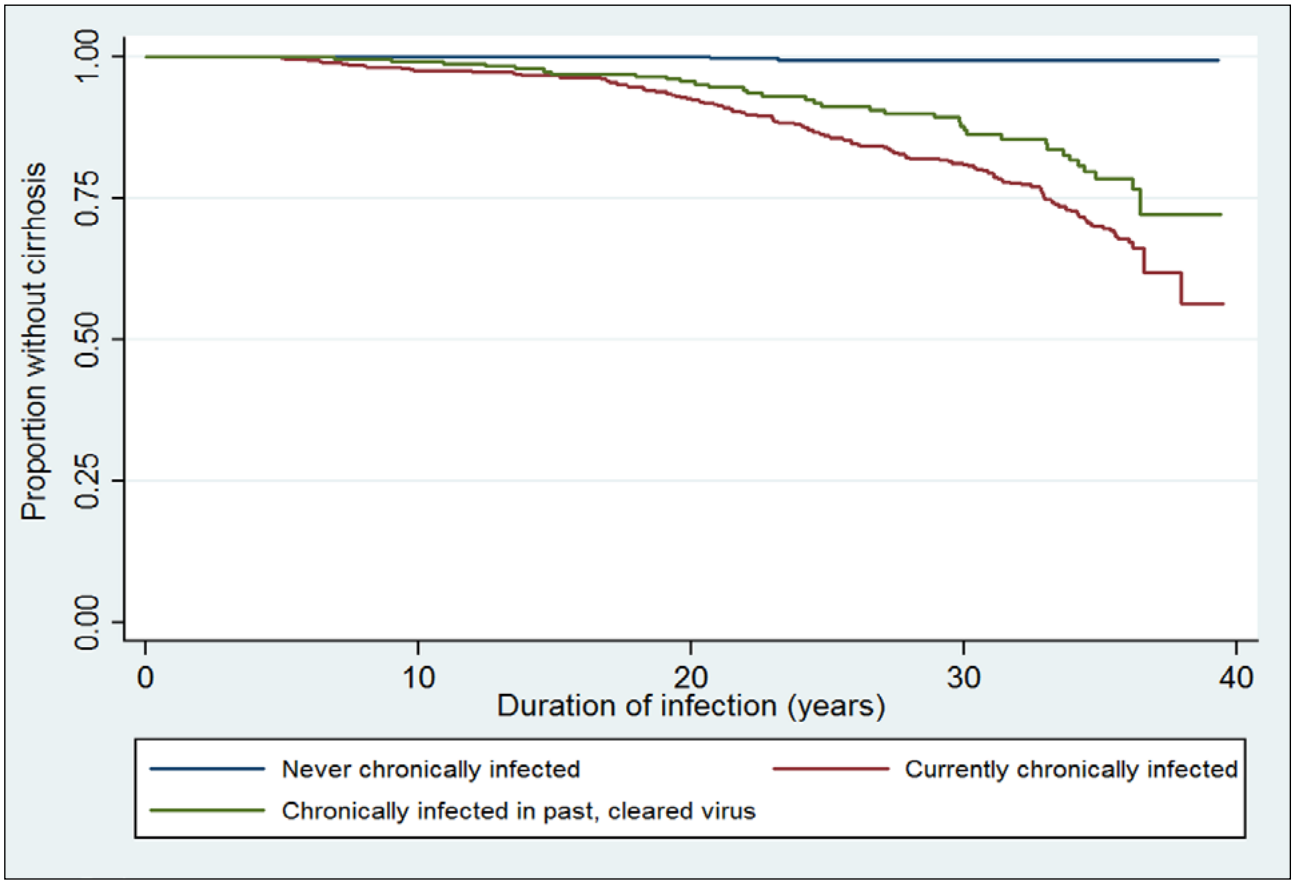


Figure 12. Proportion of participants who have not developed cirrhosis over the follow-up period by RNA status – Kaplan Meier estimates

4.6.3 Hepatocellular carcinoma (HCC)/liver cancer

By latest follow-up, 44 (5%) ever chronically infected participants and two participants with no RNA results had developed HCC. There were no cases of HCC in those who never developed chronic infection.

Thirty seven of the 46 participants (80.4%) with HCC were known to be deceased. The cause of death was directly liver-related for twenty eight, not directly liver-related for six and the death certificate was missing for the remaining three participants. The median time from date of diagnosis of cirrhosis to date of diagnosis of HCC was three years (see Methods section 3.4 regarding the method of assigning dates of diagnosis). Cirrhosis was not specifically mentioned in the medical records of five of the participants with HCC. However, two of these had ascites and one had varices. See section 4.12 below on liver transplants.

For ever chronically infected database participants, the median duration of RNA positivity at date of diagnosis of HCC was 29.5 years (mean: 27.7 years) and the median age at HCC was 62.5 years (mean: 61 years) (see Methods sections 3.4 and 3.5 regarding methods used). On univariate analysis of ever chronically infected participants, the prevalence of HCC was significantly higher in blood transfusion/ renal and clotting factor participants compared to those infected through anti-D. It was also significantly higher in males compared to females, and in participants who had high alcohol intake recorded in their medical notes (table 26). Where alcohol data were recorded, 24% of ever chronically infected participants with HCC had consumed over 40 units of alcohol per week or had alcohol abuse or alcoholic liver disease recorded in their charts at some stage compared to 9% of ever chronically infected participants without HCC.

***Table 26. Hepatocellular carcinoma (HCC) in ever chronically infected database participants**, (with univariate chi-square test for differences in prevalence of HCC across different categories of host and virus variables)*

Ever chronically infected database participants	Number with HCC	% with HCC	Median age at HCC diagnosis (years)	Median duration RNA positivity at HCC (years)	p-value
All	44	5.4	62.5	29.5	
Sex					**<0.001**
Females	18	3.1	67.5	29.5	
Males	26	11.7	57	29.5	
Source of infection					**<0.001**
Anti-D all	7	1.6	66	32	
Anti-D 77-79	7	1.9	66	32	
Anti-D 91-94	0	0.0			
Transfusion or renal	27	9.9	68	25	
Clotting factors	10	9.4	53.5	31	
Highest recorded alcohol intake					**0.005**
Non drinker	11	6.2	68	32	
Within recommended limits	17	3.7	60	29	
Moderately high	3	5.0	53	29	
High	10	13.7	59	29	
BMI					0.36
Normal or underweight	4	3.1	60.5	25.5	
Overweight	10	6.6	67	30	
Obese	5	4.3	53	32	
Age at end of latest follow-up (years)					0.339
0-49	7	4.4	45	27	
50-64	17	4.6	55	30	
65+	20	7.0	71	29.5	
RNA status at latest follow-up					**<0.001**
Past chronic infection, cleared virus	1	0.4	~	~	
Currently chronically infected	43	7.7	63	30	
HCV genotype					0.089*
Genotype 1	27	4.5	62	32	
Genotype 2	2	5.4	52	29.5	
Genotype 3	13	9.2	63	22	

* When comparing genotype 3 to genotype 1, there is a significant difference in prevalence of HCC p=0.028
~Data on median age and median duration of RNA positivity not presented as only one participant who was chronically infected in the past developed HCC

Aside from current chronic infection (OR 27.9, p=0.001), male sex (OR 4.4, p<0.001) and genotype 3 rather than genotype 1 infection (OR 2.4, p=0.031), were independently associated with HCC prevalence in chronically infected participants on multivariate logistic regression analysis. When source of infection was substituted for sex in the model, participants infected through blood transfusions/ treatment for renal disease and those infected through clotting factors were significantly more likely to have developed HCC compared to those infected through anti-D.

On Cox multivariate regression analysis participants who remained chronically infected (hazard ratio 28.5, p=0.001) (figure 13), those with high alcohol intake (hazard ratio 2.4, p=0.026), males (hazard ratio 4.1, p<0.001) and those with genotype 3 HCV infection (compared to genotype 1) (hazard ratio 3.9, p<0.001) had higher rates of HCC. When source of infection was substituted for sex in the model, transfusion/ renal and clotting factor participants had higher rates of HCC than anti-D participants and alcohol was no longer associated with rate of HCC.

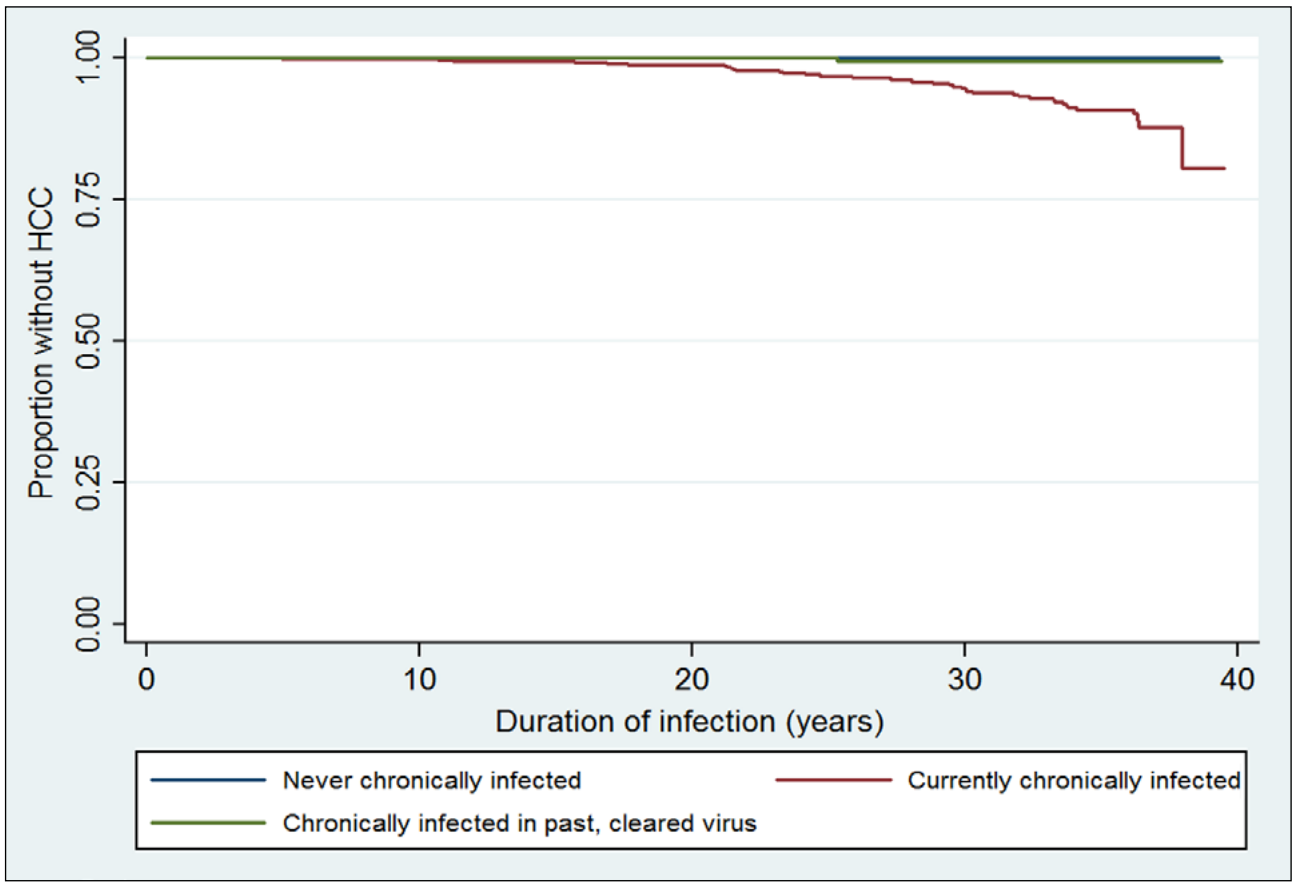


Figure 13. Proportion of participants who have not developed HCC over the follow-up period by RNA status – Kaplan Meier estimates

4.7 Liver-related diagnostic procedures: Liver biopsies, fibroscans, ultrasounds, CT scans and MRI scans

Most liver biopsies were carried out in the mid to late 1990s, with much smaller numbers being done in more recent years, therefore latest biopsy results alone may not be a good indicator of current disease status (figure 14). Disease progression is now more likely to be monitored using less invasive diagnostic procedures such as fibroscans, ultrasounds, CT scans, MRI scans and blood tests of liver function.

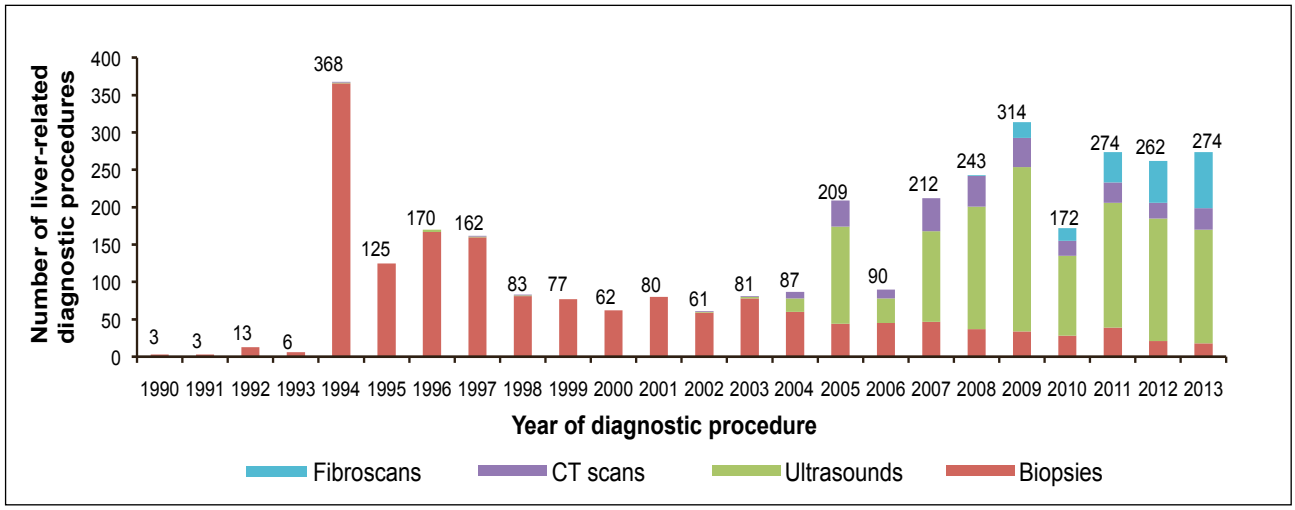


Figure 14. Number of liver-related diagnostic procedures by year and type of procedure for ever chronically infected participants

Note: multiple diagnostic procedures were carried out for some patients. Data on ultrasound, CT scans, MRI scans and fibroscans is more reliable since 2009, as the method and detail of recording these data has improved significantly since then.

4.7.1 Liver biopsies

Overall, 1785 biopsies have been carried out on 805 database participants. Ninety seven percent (n=1725) had an inflammation grade and 90% (n=1601) had a fibrosis score recorded. Eighty one percent (n=659) of chronically infected participants had at least one biopsy with a documented fibrosis score and 83% had at least one biopsy with a documented inflammation grade. The likelihood of having a biopsy varied by source of infection, with only 42% (n=45) of chronically infected clotting factor participants having biopsy results in their charts compared to 97% (n=414) of chronically infected anti-D participants and 82% (n=224) of those infected through blood transfusions or treatment for renal disease. Since 2009, 106 biopsies have been carried out on 102 participants, with 20% (n=77) of those who remained chronically infected and alive having a recent liver biopsy.

4.7.2 Results of liver biopsies

Inflammation

Twenty nine percent (n=195) of ever chronically infected participants had moderate or severe inflammation on last biopsy. Inflammation grade on biopsy varied by source of infection with 34% of chronically infected transfusion/renal participants having moderate or severe inflammation on their last biopsy compared to 27% of anti-D participants and 23% of participants infected through clotting factors.

Fibrosis

Fibrosis was scored using different scoring systems in different units. Overall 79% of biopsies were scored using a 0-6 scoring system, and a 0-4 system was used for the remaining 21%. Biopsy results scored from 0 to 6 were converted to the 0 to 4 scores (see Methods section 3.10) 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.

Twenty two percent (n=147) of chronically infected participants had a high fibrosis score on their most recent biopsy (where fibrosis score was recorded, n=659). Fibrosis varied by source of infection, with 33% (n=68) of chronically infected blood transfusion or renal participants having a high fibrosis score on most recent biopsy compared to 27% (n=12) of clotting factor participants and 16% (n=66) of anti-D participants (figure 15).

Aside from chronic infection, risk factors independently associated with having a high fibrosis score on latest biopsy on logistic regression analysis were: ever having high levels of alcohol consumption (OR 3.2, p=0.001), longer duration of RNA positivity at last biopsy (30+ years compared to <20 years) (OR 2.5, p=0.005), older age at last biopsy (55+ compared to less than 55 years) (OR 2.3, p<0.001), male sex (OR 2.2, p=0.001) and genotype 3 infection (compared to genotype 1 infection) (OR 1.9, p=0.037). When source of infection was substituted for sex in the model, participants infected through blood transfusions/ treatment for renal disease and those infected through clotting factors were significantly more likely to have developed cirrhosis compared to those infected through anti-D and genotype was no longer significantly associated with high fibrosis scores on latest biopsy.

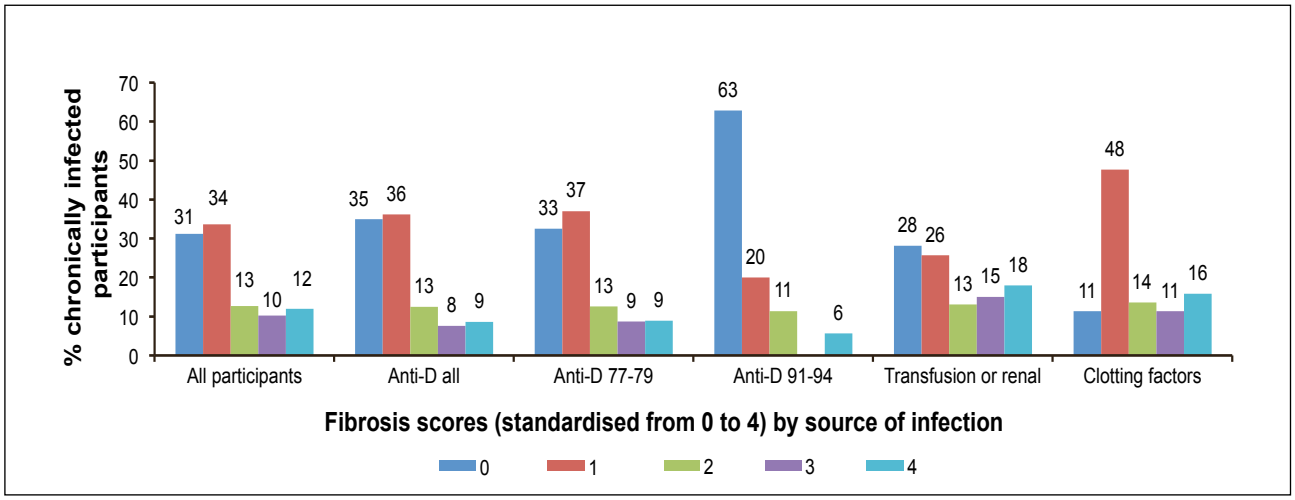


Figure 15. Fibrosis score* on last biopsy for chronically infected participants by source of infection (n=659)

*All 0-6 scores standardised to 0-4 (see Methods section 3.10 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 44 (41%) and the last biopsy was several years ago for many.

Changes in biopsy results post-treatment

Ninety six chronically infected participants who had pre-treatment biopsy results also had biopsy results at least six months after treatment. The changes in fibrosis scores (all standardised to 0 to 4 system) by anti-viral treatment response are shown in figure 16. Fibrosis scores improved for 59% (n=13) of those who achieved a sustained virological response (SVR) on treatment compared to 33% (n=24) of those who did not. Scores worsened for 5% (n=1) of those who achieved an SVR and 27% (n=20) of those who did not.

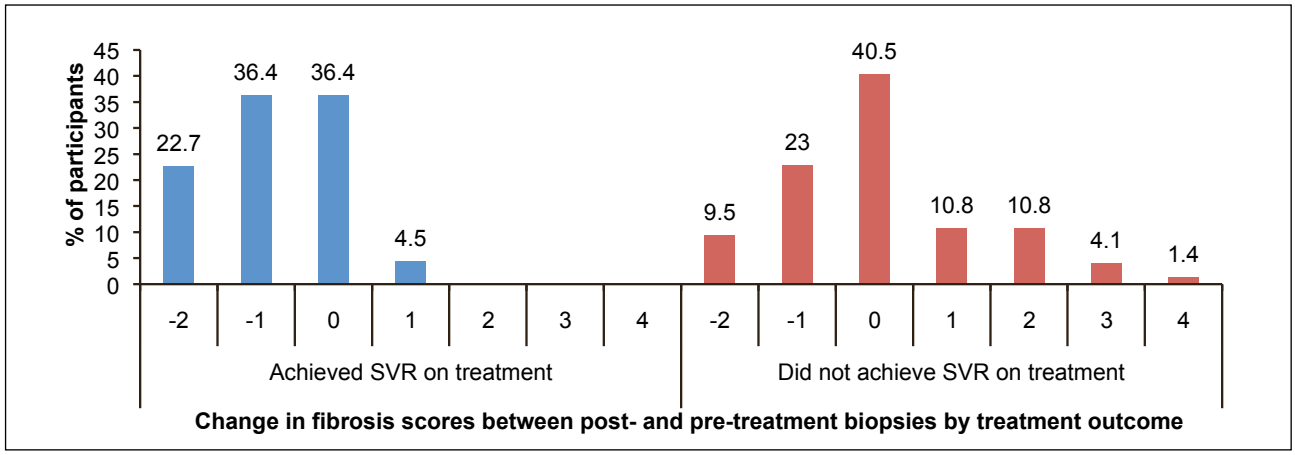


Figure 16. Changes in fibrosis scores (0-4) after treatment, by SVR status for participants who had pre- and post-treatment biopsy results (n=96)

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

4.7.3 Fibroscan results

Fibroscans are increasingly being used to monitor disease progression in the database cohort. Thirty two percent (n=126) of the database participants who remained alive and chronically HCV infected at the end of latest follow-up had a fibroscan test since 2009. Twenty nine percent of these (n=36) had fibroscan results in the cirrhotic or pre-cirrhotic range (table 27) (see Methods section 3.11).

Table 27. Latest fibroscan results for living chronically infected participants by source of infection (n=126)

Fibroscan results (kPa)	All participants		Anti-D all		Transfusion or renal		Clotting factors	
	Num	%	Num	%	Num	%	Num	%
0-7.0	65	51.6	54	57.4	8	40.0	3	25.0
7.1-8.6	18	14.3	9	9.6	5	25.0	4	33.3
8.7-9.4	7	5.6	7	7.4		0.0		0.0
9.5-14.4	23	18.3	16	17.0	6	30.0	1	8.3
14.5+	13	10.3	8	8.5	1	5.0	4	33.3
	126	**100.1**	**94**	**99.9**	**20**	**100**	**12**	**99.9**

4.8 Liver function tests, platelets and alpha-fetoprotein (AFP)

Low albumin levels, low platelet counts, elevated AFP levels and elevated ALT and bilirubin levels are all associated with cirrhosis and HCC in chronically infected participants. However a significant proportion of patients with these conditions may present with normal liver function test results (table 28).

Test data for chronically infected participants were very complete for albumin (99%), AFP (93%), ALT (98%) and bilirubin (99%). Platelet data were less complete, with results available for 75% of ever chronically infected participants.

Table 28. Liver function tests, platelets and AFP, by RNA status

Liver function test results	Ever chronically infected all		Ever chronically infected with cirrhosis		Ever chronically infected with HCC		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%
Albumin								
Normal	599	74.6	79	44.9	13	30.2	408	90.7
Low: <2 times lower normal limit	194	24.2	93	52.8	27	62.8	41	9.1
Low: ≥2 times lower normal limit	10	1.2	4	2.3	3	7.0	1	0.2
Platelets								
Normal	466	76.9	44	35.8	7	33.3	256	97.0
Low: <2 times lower normal limit	107	17.7	51	41.5	4	19.0	5	1.9
Low: ≥2 times lower normal limit	33	5.4	28	22.8	10	47.6	3	1.1
AFP								
Normal	587	77.2	80	47.3	8	18.6	352	93.6
Elevated: <2 times upper normal limit	80	10.5	25	14.8	6	14.0	18	4.8
Elevated: ≥2 times upper normal limit	93	12.2	64	37.9	29	67.4	6	1.6
ALT								
Normal	287	36.1	36	20.3	8	18.2	372	83.8
Elevated: <2.5 times upper normal limit	316	39.7	61	34.5	14	31.8	62	14.0
Elevated: ≥2.5 times upper normal limit	192	24.2	80	45.2	22	50.0	10	2.3
Bilirubin								
Normal	650	80.5	94	55.6	17	39.5	416	91.2
Elevated: <2 times upper normal limit	95	11.8	30	17.8	10	23.3	34	7.5
Elevated: ≥2 times upper normal limit	62	7.7	45	26.6	16	37.2	6	1.3

4.9 Deceased participants

Two hundred and sixty participants had died by latest follow-up. This includes forty eight additional deceased participants compared to the previous round of follow-up in 2009. On Cox multivariate regression analysis, all-cause mortality (i.e. deaths from any cause) varied significantly by RNA status: 31% (n=172) of those whose latest status was recorded as chronic infection were deceased by latest follow-up compared to 5% (n=13) of participants who were chronically infected in the past and had since cleared the virus (mostly through treatment) (hazard ratio 9.4, p<0.001) (figure 17). Other factors independently associated with higher all-cause mortality rates were male sex (hazard ratio 2.2, p<0.001), high alcohol intake (hazard ratio 1.9, p=0.003) and genotype 3 compared to genotype 1 infection (hazard ratio 2.5, p<0.001). When source of infection was substituted for sex in the model, blood transfusion/renal participants and clotting factor participants had significantly higher mortality rates than anti-D participants.

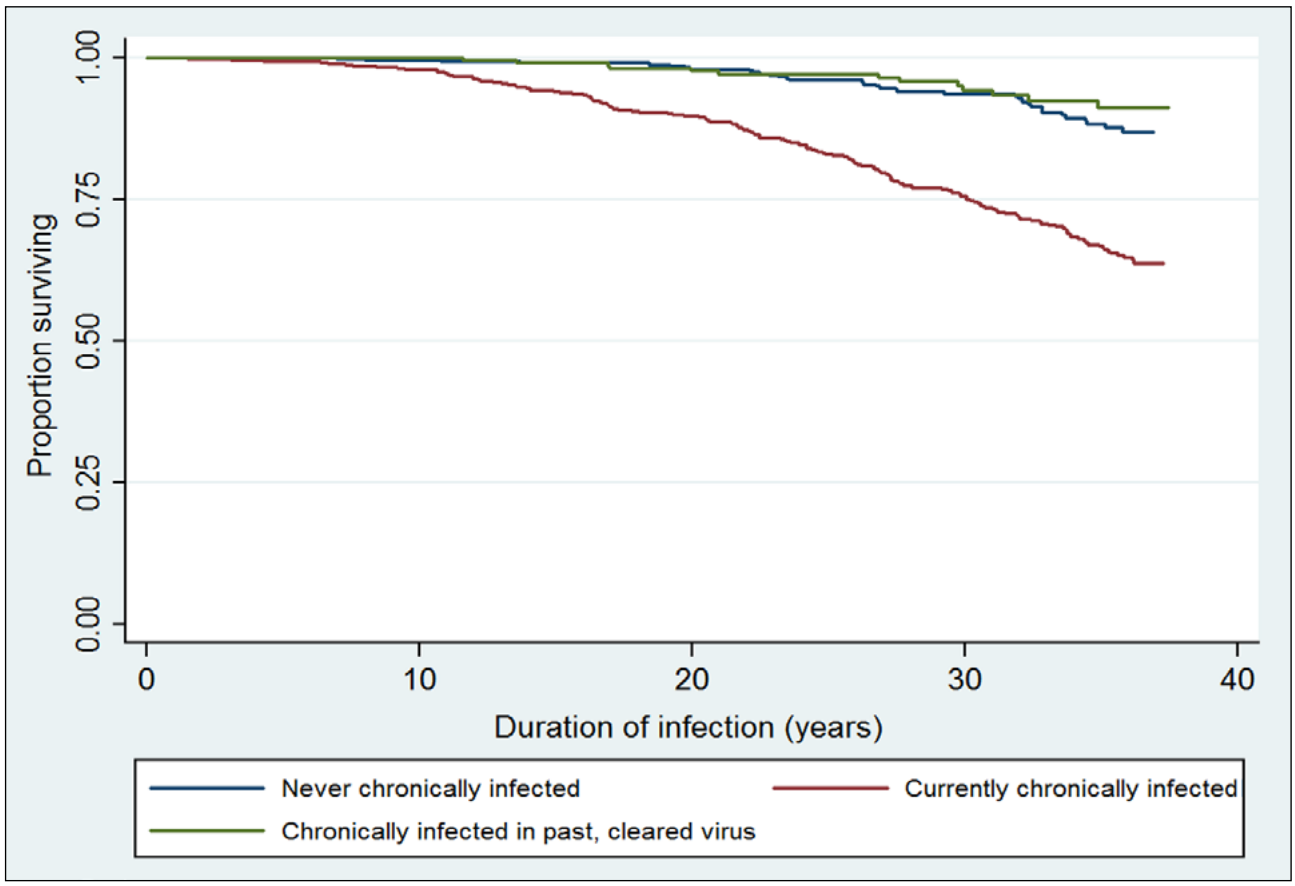


Figure 17. Proportion of participants who have not died (all-causes) over the follow-up period by RNA status – Kaplan Meier estimates

Where death certificates were available (n=237), death was directly caused by liver disease for 73 participants (table 29) (see Methods section 3.8 regarding coding of deaths). The causes of death for these 73 were:

- chronic viral hepatitis C (n=33)
- liver cell carcinoma (n=23)
- liver failure (n=6)
- cirrhosis of the liver (n=5)
- unspecified liver cancer (n=1)
- intrahepatic bile duct carcinoma (n=1)
- liver transplant failure and rejection (n=1)
- B-cell lymphoma (n=1)
- chronic viral hepatitis B (n=1)
- toxoplasma hepatitis (n=1)

HCV infection was one of the causes of death listed on the first part of the death certificate for sixty one 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. Of the 73 participants who died from liver-related causes, 60 were chronically HCV infected at the time of their death, 3 had been chronically infected in the past, but had cleared the virus, two were never chronically infected and eight had no RNA results in their charts. Table 29 shows further details on the 63 who were ever chronically infected.

Table 29. Death from liver-related disease in ever chronically infected database participants *(with univariate chi-square test for differences in prevalence of liver-related death across different categories of host and virus variables)*

Ever chronically infected database participants	Number who died directly from liver-related disease	% of each cohort who died directly from liver-related disease	Median age at death (years)	Median duration RNA positivity at death (years)	p-value
All	63	7.9	62	27	
Sex					**0.001**
Females	35	6.0	63	29	
Males	28	12.9	54.5	22.5	
Source of infection					**<0.001**
Anti-D all	18	4.3	61.5	31.5	
Anti-D 77-79	18	4.9	61.5	31.5	
Anti-D 91-94	0	0			
Transfusion or renal	31	11.6	65	21	
Clotting factors	13	12.4	49	27	
Highest recorded alcohol intake					**<0.001**
Non drinker	13	7.6	65	22	
Within recommended limits	18	4.0	60	30	
Moderately high	4	7.0	61	32.5	
High	21	29.6	59	26	
BMI					0.316
Normal or underweight	5	3.9	68	32	
Overweight	8	5.3	69	32.5	
Obese	2	1.7	51	36	
Age at end of latest follow-up (years)					0.765
0-49	13	8.6	43	25	
50-64	26	7.1	57	29.5	
65+	24	8.5	71.5	26.5	
RNA status at latest follow-up					**<0.001**
Past chronic infection, cleared virus	3	1.2	~	~	
Currently chronically infected	60	10.9	61.5	27	
HCV genotype					0.08
Genotype 1	46	7.8	62.5	30	
Genotype 2	6	16.2	68.5	23.5	
Genotype 3	7	5.1	55	23	

~Data on median age and median duration of RNA positivity not presented as only three participants who were chronically infected in the past died from liver-related causes

On Cox multivariate regression analysis, liver-related mortality was significantly higher in participants who were currently chronically infected with HCV (n=60, 10.9%) compared to those who had been chronically infected in the past and had since cleared the virus (mostly through treatment) (n=3, 1.2%) (hazard ratio 7.9, p=0.001) (figure 18). High alcohol intake (hazard ratio 5.7, p<0.001) and male sex (hazard ratio 2.1, p=0.009) were also independently associated with higher liver-related mortality rates. Information on alcohol consumption was available for 84% of those whose death was caused by liver disease. Thirty nine percent (n=24) had indicators of high levels of alcohol consumption in their medical charts. When source of infection was substituted for sex in the model those infected through blood transfusions (hazard ratio 3.4, p<0.001) or clotting factors (hazard ratio 2.3, p=0.044) were more likely to have died from liver-related causes than anti-D participants.

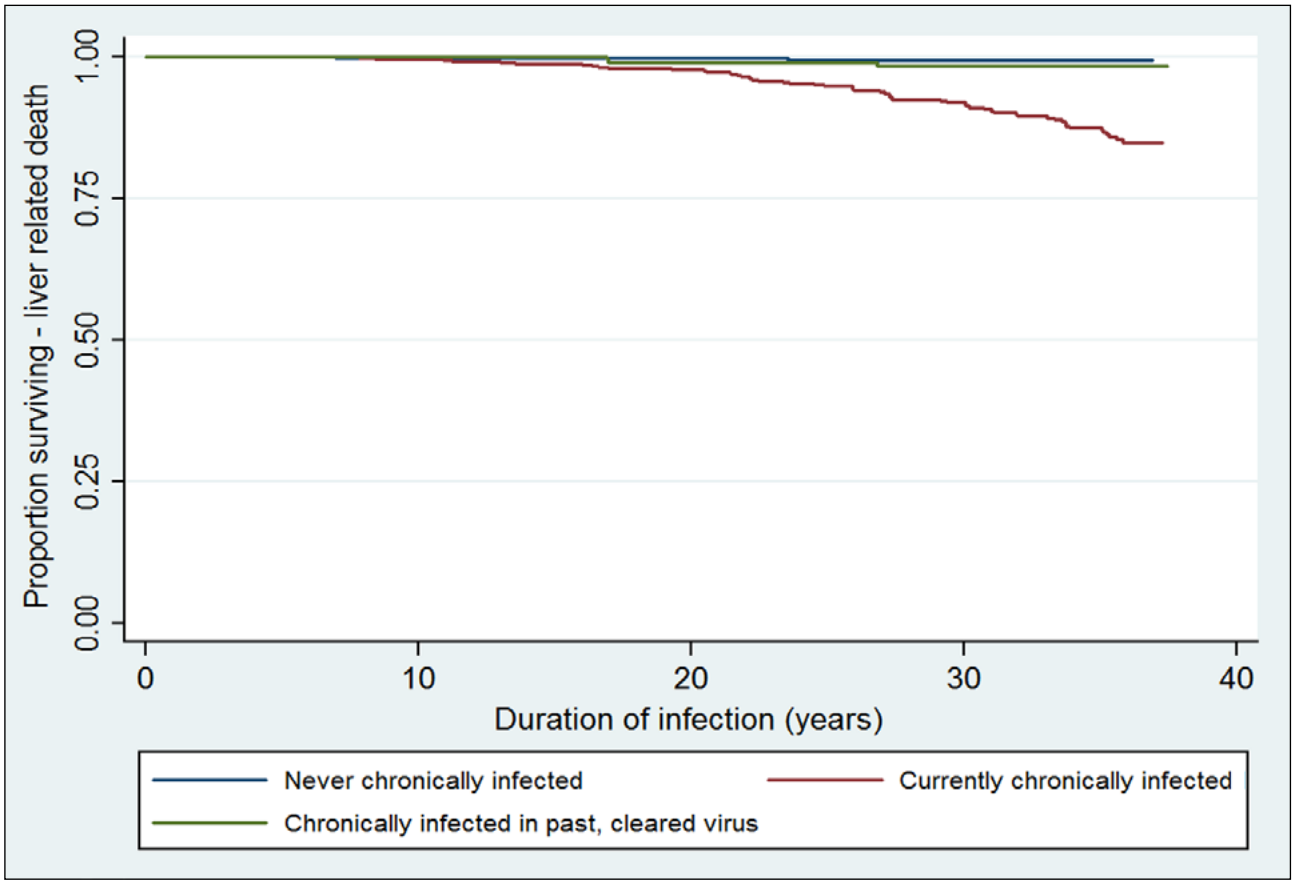


Figure 18. Proportion of participants who have not died from liver-related causes over the follow-up period by RNA status – Kaplan Meier estimates

4.10 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 duration of RNA positivity for database participants who became chronically infected is now 31 years (currently RNA positive: 34 years, RNA positive in past: 22 years). This is the fifth round of data collection and increases can be seen in the prevalence of liver-related health outcomes since baseline data were collected (figure 19). However, in interpreting the findings on fibrosis scores, it is important to note that few liver biopsies have been carried out in recent years.

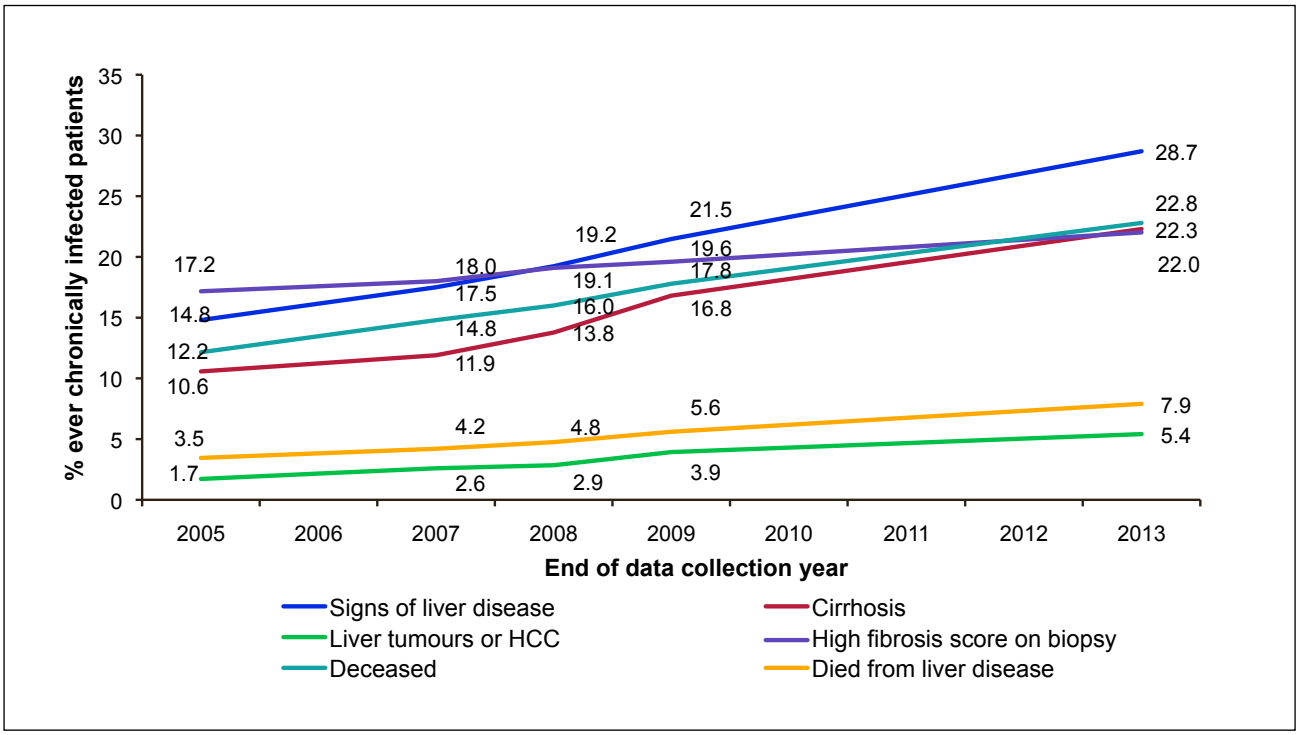


Figure 19. Changes in the prevalence of all cause mortality and liver-related outcomes for chronically infected participants since baseline data were collected.

Note: Few liver biopsies have been carried out in recent years

4.11 Anti-viral treatment for hepatitis C

Forty eight percent (n=390) of chronically infected participants had 526 courses of anti-viral treatment by latest follow-up. A treatment outcome was available for 504. Participants stopping treatment early are included when calculating sustained virological response (SVR). The SVR rate has improved in recent years, firstly with the introduction of combination therapy with pegylated interferon (peg-IFN) and ribavirin (RBV) and subsequently with the addition of telaprevir (TVR) or boceprevir (BOC) (figure 20). Tolerance of anti-viral treatment has remained an issue, with 15% (n=34) of treatment courses with peg-IFN and RBV, and 9% (n=2) of treatment courses with triple therapies stopped early due to side effects.

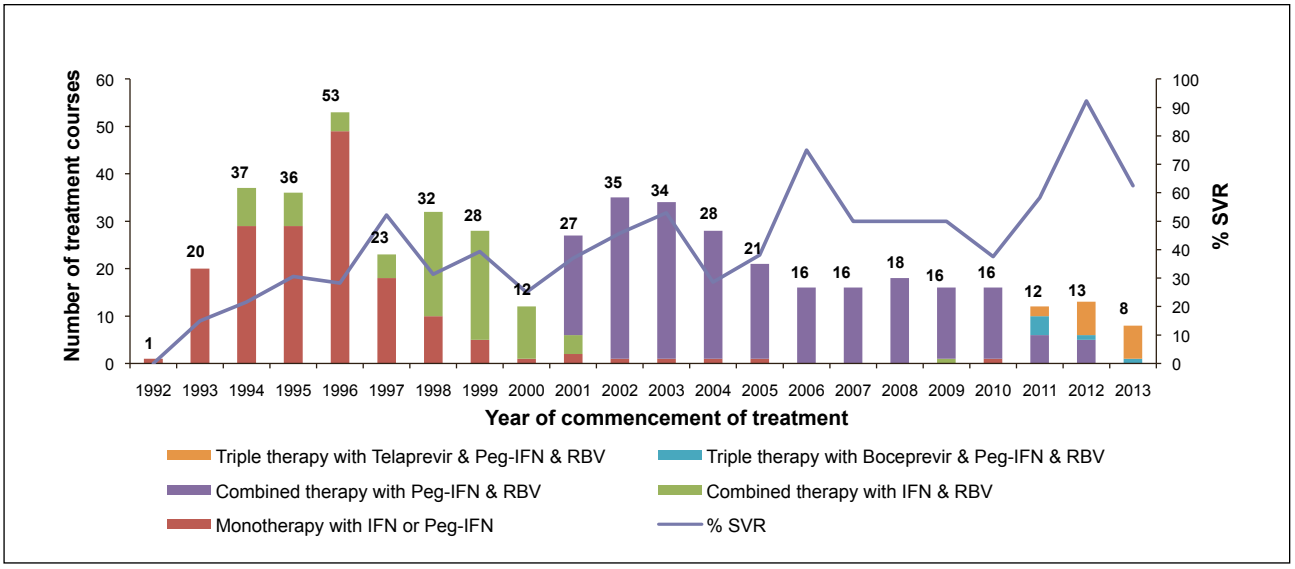


Figure 20.Number of treatment courses by type of treatment and percentage SVR, 1992-2013

Note: Outcome is awaited for 22 participants (not included when calculating SVR). One treatment course with ribavirin alone and one treatment course with faldaprevir and ribavirin also omitted.

4.11.1 Treatment response: last treatment, any drug regimen

The participants who were more likely to have been treated were those who were younger, those infected in the 1991-1994 anti-D outbreak, or through blood transfusions or clotting factors, those with higher fibrosis scores and participants with genotype 2 or 3 infections (table 30). On logistic regression analysis, younger participants, those with genotypes 2 or 3, those who were not cirrhotic prior to treatment and those who did not have high levels of alcohol intake were more likely to have had an SVR overall. Sex and source of infection were not significantly associated with SVR when these other factors were taken into account.

Table 30. Number and percentage of chronically infected participants treated with any drug regimen, and percentage SVR, by demographic and virus characteristics

Characteristic	Number of participants treated - any drug regimen	% treated - any drug regimen	Number with treatment outcome	% SVR on last treatment - any drug regimen
All	390	48.0	368	54.6
Sex				
Female	273	46.2	258	52.7
Male	117	52.7	110	59.1
Source of infection				
Anti-D all	184	43.0	175	52.6
Anti-D 77-79	140	37.4	131	42
Anti-D 91-94	34	91.9	34	91.2
Blood transfusion/renal	144	52.6	137	52.6
Blood clotting factors	60	56.1	55	65.5
Ever had a high fibrosis score on biopsy				
No	224	46.7	212	61.3
Yes	120	67.0	110	37.3
Genotype				
1	249	41.6	229	42.8
2	27	73.0	27	66.7
3	103	72.5	101	75.2
Age at latest follow-up				
0 to 49 years	91	57.6	84	71.4
50 to 64 years	196	53.1	185	54.1
65+ years	103	36.0	99	41.4

Note: Treatment outcome awaited for 22 participants, omitted when calculating SVR. Genotype not available for 9 participants who were treated. Two participants with genotype 5 who were treated were omitted from the genotype breakdown in this table. Fibrosis scores not available for 46 of the participants who were treated

4.11.2 Treatment response: pegylated interferon and ribavirin

SVR rates for treatment naïve participants on peg-IFN and RBV, by genotype and duration of treatment, are shown in figure 21. Seventy five percent (n=21) of genotype 2 or 3 participants on combination therapy for 24 weeks or more achieved an SVR compared to 59% (n=34) of genotype 1 participants treated for 48 or more weeks (standard of care for genotype 1).

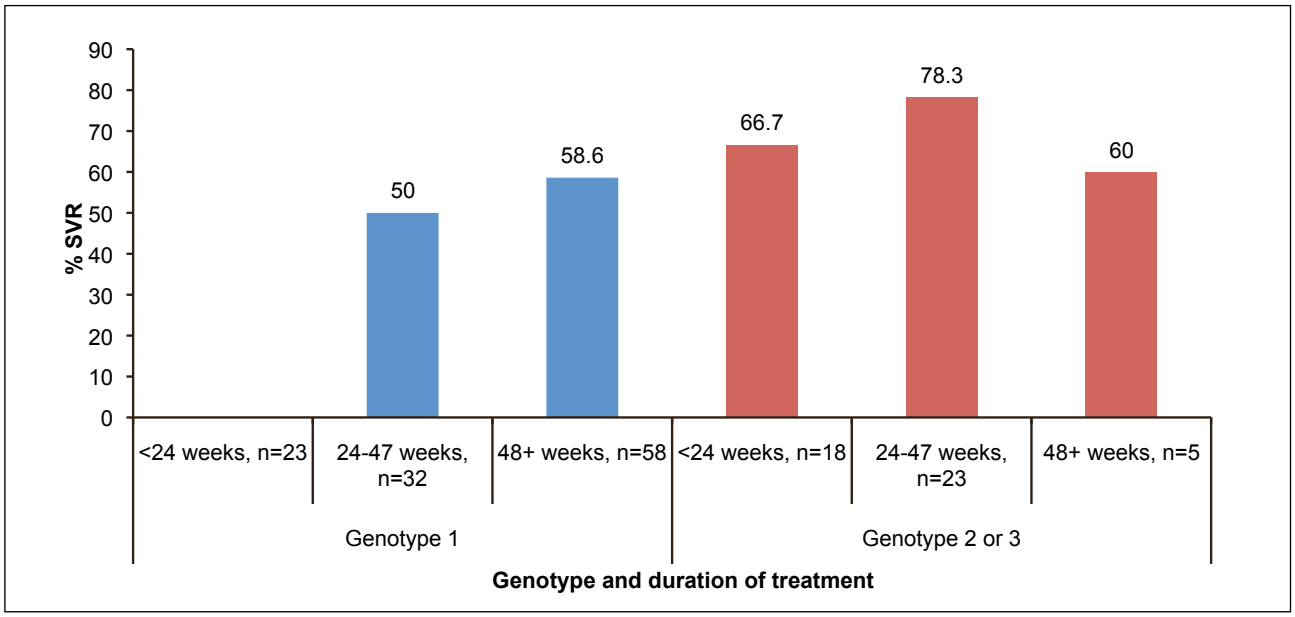


Figure 21. Percentage SVR for treatment-naïve participants treated with combination therapy with Peg-IFN and RBV (n=159), by genotype and duration of therapy

Sixty one participants were re-treated with peg-IFN and RBV having failed to achieve SVR on previous treatment courses with other drug regimens. Their response rate on first re-treatment was 34.4%. However, response rates were good for genotype 1 participants whose first re-treatment was for 48 or more weeks (50%) and for genotype 2 or 3 participants whose first re-treatment was for 24 or more weeks (73%). Response rates by genotype and duration of treatment are shown in figure 22.

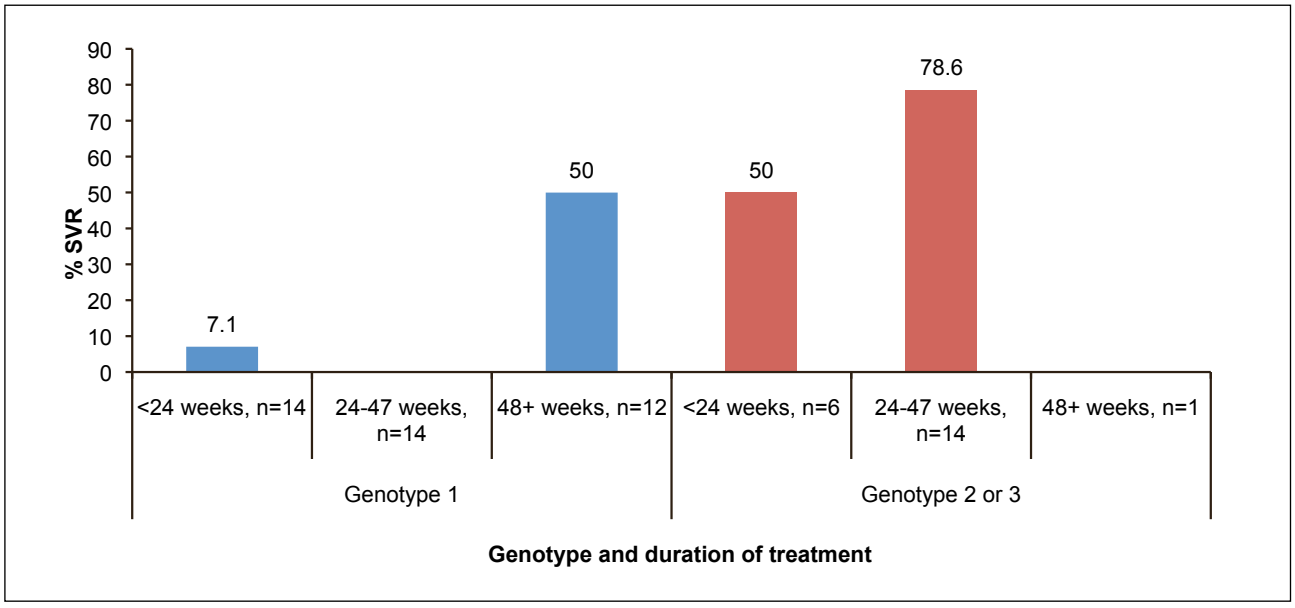


Figure 22. Percentage SVR for participants who previously failed to achieve SVR on other drug regimens and were re-treated with combination therapy with Peg-IFN and RBV (n=61), by genotype and duration of therapy

4.11.3 Treatment response: triple therapies

Twenty eight genotype 1 participants were treated with TVR in combination with Peg-IFN and RBV. Treatment response was available for sixteen at the end of latest follow-up. The overall SVR rate was 81% (n=13) and all participants treated for 24 weeks or longer achieved an SVR (n=11, 100% SVR) (figure 23). The 28 participants treated with this regime included two who were co-infected with HIV. .

Nine genotype 1 participants were treated with BOC in combination with Peg-IFN and RBV. Treatment response was available for five at the end of latest follow-up. The overall SVR rate was 80% (n=4) and all participants treated for 24 weeks or longer achieved an SVR (n=4, 100% SVR) figure 23.

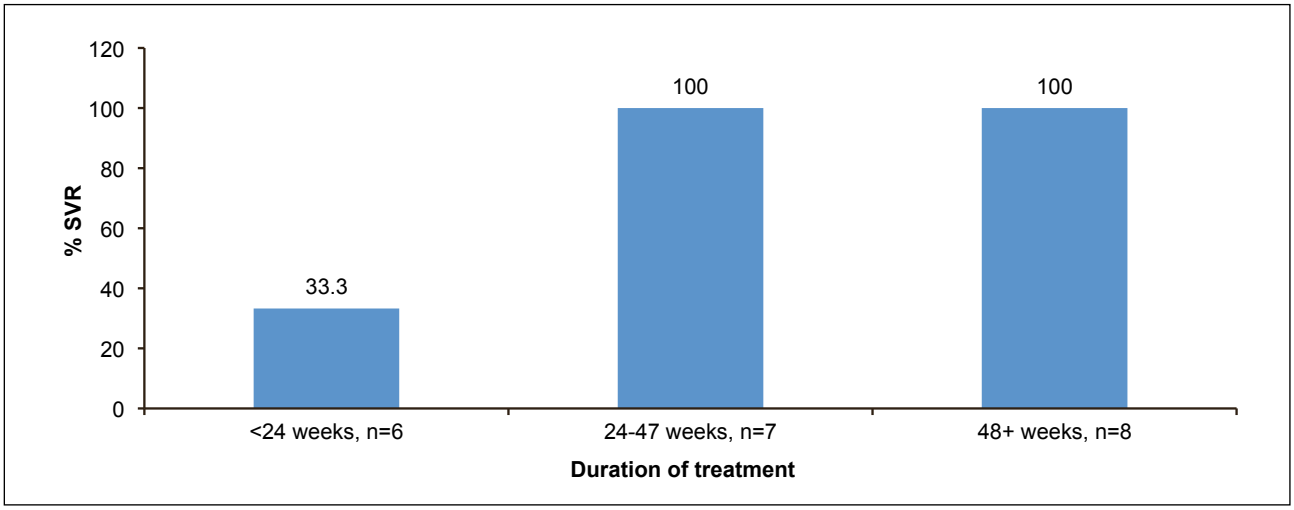


Figure 23. Percentage SVR for participants treated with BOC or TVR, in combination with Peg-IFN and RBV (n=21) by duration of treatment

4.12 Liver transplants

Twenty two database participants had received twenty five liver transplants by the end of 2013. Fifteen received transplants in 2007 or earlier, three were transplanted in 2008 and one was transplanted each year from 2009 to 2012. The median age at transplant was 53.5 years (range: 29-66 years) and the median duration of HCV infection at transplant was 29 years (range: 1-39 years). All transplant recipients were RNA positive when transplanted and all of those tested post-transplant (n=17) remained RNA positive. Six transplant recipients (27%) had evidence of high alcohol consumption at some stage.

Post-transplant biopsy or other staging results were available for twelve participants. Within five years of transplant, two developed HCC, five developed cirrhosis, one had moderate or advanced fibrosis, two had mild fibrosis and one had no fibrosis. One further participant developed cirrhosis and HCC many years after transplant.

Eleven of the liver transplant patients have since died. Five died from liver-related causes, five died from non-liver-related causes and no death certificate was available for the remaining patient. The median time between transplant and death for these patients was 29 months.

4.13 Medical conditions (relevant conditions only)

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 we think 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 31 shows common medical conditions that differ significantly by HCV RNA status, and other medical conditions of interest (i.e. mentioned in literature as associated with HCV, or raised by patient groups). The table indicates where there is a statistically significant ($p<0.05$) difference 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. It should also be noted that the numbers are small for some of these conditions.

Depression was significantly more likely to be recorded in the medical charts of chronically infected participants (n=273, 34%) compared to those who never became chronically infected (n=101, 22%). 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 71% (n=194) of chronically infected participants with depression.

On logistic regression analysis, fibromyalgia and osteoporosis were significantly more likely to be recorded for older chronically infected females.

Table 31. Medical conditions recorded in charts of participants *– conditions that differed significantly by RNA status, 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
	Num	%	Num	%	p-value	p-value	p-value
Depression	273	33.6	101	22.1	**<0.001**	**<0.001**	0.061
Fibromyalgia	107	13.2	46	10	0.101	**0.006**	0.312
Diabetes mellitus	78	9.6	25	5.5	**0.009**	**0.039**	0.476
Dermatitis and eczema	71	8.7	22	4.8	**0.01**	**0.049**	0.051
Osteoporosis	71	8.7	16	3.5	**<0.001**	**<0.001**	0.357
Anxiety	47	5.8	15	3.3	**0.046**	**0.021**	0.782
Malignant skin cancer	34	4.2	5	1.1	**0.002**	**0.003**	0.615
Thrombocytopenia or other purpura	18	2.2	2	0.4	**0.015**	**0.025**	0.357
Parkinson's Disease	8	1	3	0.7	0.543	0.56	0.683
Ovarian cancer (females only)	6	1	0			**0.038**	
Non-Hodgkin's Lymphoma	4	0.3	0		0.133	0.232	0.562

* Data for some conditions, mentioned in literature as associated with HCV, or raised by patient groups, are included even if the condition was not commonly reported and no statistically significant difference was seen between ever and never chronically infected participants.

Chapter 5. Focus on three individual patient groups

The database population consists of three groups which differ by their source of infection. This chapter provides more detail on each of these groups and compares them by characteristics and outcomes. The summary tables 1-12 at the beginning of the report provide details of RNA status and outcomes by group.

5.1 Summary and comparison of outcomes in the three groups

Database participants who ever became chronically infected with HCV through blood transfusions or treatment for renal disease had the highest prevalence of serious liver disease in spite of having the shortest median duration of RNA positivity at the end of latest follow-up. Thirty six percent (n=99) of transfusion/renal participants had clinical signs of serious liver disease, including 30% (n=82) with cirrhosis, after a median duration of HCV RNA positivity by latest follow-up of 22 years (table 9). The prevalence of serious liver disease was also high in participants who were ever chronically infected through clotting factors, with 37% (n=39) having clinical signs of serious liver disease and 20% (n=21) diagnosed with cirrhosis after a median duration of RNA positivity of 30 years (table 11). Chronically infected anti-D participants had better liver-related outcomes overall, with 22% (n=94) having clinical signs of serious liver disease, including 18% (n=77) with cirrhosis, after a median duration of RNA positivity of 35 years (table 3).

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 for ever chronically infected participants, compared to 28 years for anti-D participants and 14 years for participants infected through clotting factors. Sex 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 sex and hence by source of infection, with 13% of chronically infected transfusion/renal participants and 16% of chronically infected clotting factor participants consuming high levels of alcohol at some stage, compared to 6% of anti-D participants (tables 19, 20, 21).

5.2 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 of 28 years was younger than that for the transfusion/renal group but significantly older than that for those infected through clotting factors. However, the prevalence of clinical signs of serious liver disease has increased significantly (from 14% to 23%) in the four years since last follow-up in those infected between 1977 and 1979.

Anti-D participants infected between 1977 and 1979 have had the lowest uptake of antiviral treatment (n=140, 37.4%) (table 30). However treatment uptake has increased significantly in the past four years as only 29% were treated by the end of 2009. The overall SVR was 42% (n=55) in participants infected during the 1977-79 anti-D outbreak. Treatment uptake in participants infected during the second anti-D outbreak (1991-1994) has been extremely high (n=34, 92%). The percentage achieving SVR has also been very high (91%), even in comparison with other genotype 3 database participants (67%, n=45).

Demographic characteristics, liver-related outcomes and treatment data for participants infected during each anti-D outbreak period are shown in table 32.

Table 32. Summary of demographic characteristics, liver-related outcomes and antiviral treatment data by anti-D outbreak in chronically infected participants.

Characteristic	1977-1979 Anti-D outbreak		1991-1994 Anti-D outbreak	
	Num	%	Num	%
Hepatitis C genotype	**Genotype 1**		**Genotype 3**	
Chronically infected with hepatitis C	**374**		**37**	
Median age at infection (years)	28		30	
Median age at end of follow-up (years)	63		50	
Median years since infection at end of follow-up	36		20	
Mean duration RNA positivity (years)	36		6	
Alcohol intake				
Alcohol data available (highest reported)	***366***		***36***	
≤14 units per week	328	89.6	30	83.3
15 to 40 units per week	19	5.2	1	2.8
>40 units per week or alcohol abuse in chart	19	5.2	5	13.9
Outcomes				
Signs of liver disease	87	23.3	5	13.5
Cirrhosis	72	19.3	3	8.1
HCC	7	1.9	0	0.0
High fibrosis score on biopsy	83	22.2	2	5.4
Deceased	53	14.2	1	2.7
Liver-related disease directly caused death	18	4.9	0	0.0
Hepatitis C treatment				
Treated	140	37.4	34	91.9
Treated and treatment response available	131	35.0	34	91.9
SVR on peg-IFN & RBV - treatment naïve participants	31 (of 65)	47.7	5 (of 8)	62.5
SVR on peg-IFN & RBV with TVR or BOC	10 (of 13)	76.9		
Overall SVR on last treatment with any drug regimen	55 (of 131)	42.0	31 (of 34)	91.2

5.3 Participants infected through blood transfusions or treatment for renal disease

Database participants infected through blood transfusions or treatment for renal disease had a high rate of HCV chronicity at diagnosis. RNA results were missing for two, but where results were available, 82% (n=274) were chronically infected and 18% (n=61) had cleared the HCV virus by this time (table 10).

The group of participants infected through blood transfusions or treatment for renal disease was 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 facilitate the examination of the host and virus characteristics associated with clinical signs of serious liver disease. Logistic regression was used to model the factors that were independently and significantly associated with serious liver disease in this population (table 33).

High alcohol intake, longer duration of infection, older age at the end of latest follow-up, male sex and HCV genotype 3 were all found to be independently associated with clinical signs of serious liver disease in chronically infected blood transfusion/renal patients (table 33). The effect of genotype 3 is borderline significant as the lower confidence interval is very close to 1.

Table 33. Factors associated with serious liver disease in chronically infected participants infected through blood transfusions/treatment for renal disease - logistic regression model (n=239)

Factors associated with signs of serious liver disease	Odds ratio	p-value	95% confidence interval
Highest recorded alcohol consumption			
Non drinker/within recommended limits/moderately high	1		
High (>40 units per week or alcohol abuse in chart)	3	**0.009**	1.31 - 6.66
Duration of RNA positivity			
<20 years	1		
20+ years	3.2	**0.001**	1.63 - 6.25
Age at end of latest follow-up (years)			
0-49 years	1		
50+ years	2.4	**0.022**	1.13 - 4.96
Sex			
Female	1		
Male	2.1	**0.017**	1.14 - 3.85
Genotype			
Genotype 1	1		
Genotype 2	0.8	0.632	0.27 - 2.19
Genotype 3	1.9	**0.039**	1.03 - 3.65

5.4 Participants infected through contaminated blood clotting factors

Of the 165 database participants infected through blood clotting factors, 65% (n=107) were chronically infected with HCV at diagnosis and 22% (n=37) had no RNA results in their charts (figure 24). These patients had all died prior to RNA testing. It is likely that they were chronically infected with HCV when they died. The remaining 13% (n=21) 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 (table 12).

Thirty five percent (n=37) of the chronically infected participants, 84% (n=31) of those with no HCV RNA results and one participant who never tested RNA positive were co-infected with HIV (figure 24). It was difficult to ascertain the true effects of HIV co-infection on HCV disease progression as 68% (n=47) of the co-infected participants have died.

However, 38% (n=26) of those who were HIV positive had clinical signs of serious liver disease by latest follow-up compared to 24% (n=18) of those who were HIV negative (figure 24), even though they had a shorter median duration of follow-up (25 years compared to 31 years). High alcohol intake was also found to be associated with serious liver disease in HIV negative participants. Among HIV negative participants, fifty six percent (n=5) with high alcohol consumption were classified as having serious liver disease by latest follow-up compared to 20% (n=11) 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% (n=4) of those with high alcohol consumption classified as having serious disease compared to 44% (n=14) of those without. However, as alcohol data were not available for all, these data comprise small numbers of participants and may not be representative.

Overall, 74 clotting factor participants had died by latest follow-up (table 11). Forty seven were HIV positive and twenty seven were HIV negative. Death certificates were available for 43 of the HIV positive and 26 of the HIV negative participants who had died. The underlying cause of death was HIV infection for

twelve of those who were HIV positive. A further eight had causes of death relating to immunodeficiency and two died from infections, but the term HIV was not specifically mentioned on any of their death certificates. The proportion of deaths that were directly liver-related differed between HIV positive (23%, n=10) and HIV negative participants (39%, n=10), but this difference was not statistically significant and was mainly due to a significant proportion of HIV positive participants dying of HIV-related causes prior to the development of effective antiretroviral treatments. Seventeen percent of deaths in clotting factor participants were due to haemorrhages.

Sixty (56%) participants chronically infected through blood clotting factors had received anti-viral treatment for HCV by latest follow-up (table 30). The percentage treated did not vary significantly by HIV status (54% HIV positive, 57% HIV negative). Treatment outcome was available for 55 and the percentage who achieved SVR on any drug regimen did not differ significantly by HIV status (61% HIV positive, 68% HIV negative achieved SVR).

Twenty nine treatment naïve participants were initially treated using peg-IFN and RBV combination therapy. Outcome was available for twenty eight (15 HIV negative and 13 HIV positive) and SVR was achieved by 54% of HIV positive participants and 53% of HIV negative participants. The combined (HIV positive and negative) response rates on initial treatment with peg-IFN and RBV were 36% (n=5) for genotype 1 participants and 69% (n=9) for genotype 2/3 participants. These SVR rates were similar to those achieved by participants infected through other means (45% SVR for genotype 1 and 73% for genotype 2/3).

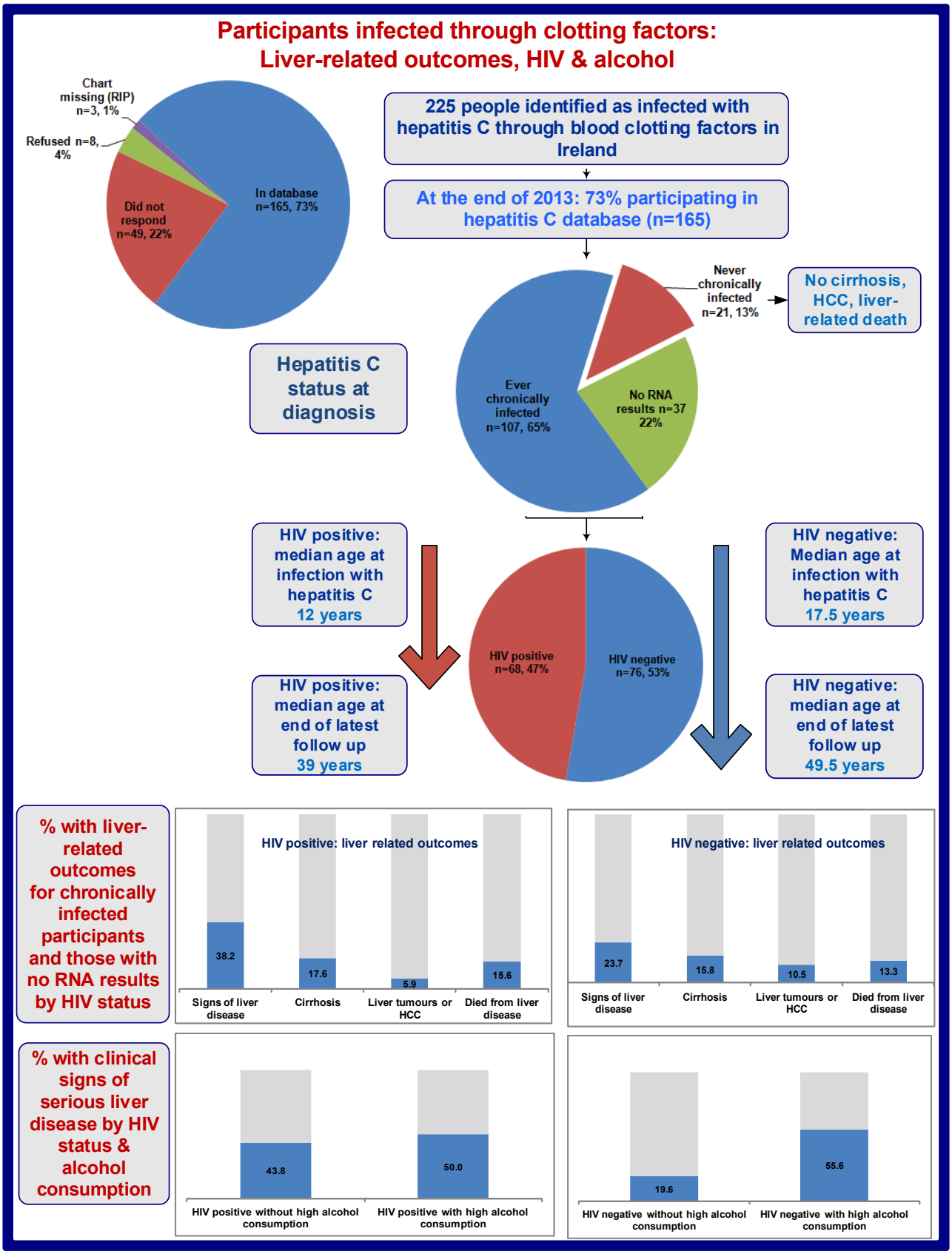


Figure 24. Summary of hepatitis C infection and disease progression in participants infected through clotting factor, by HIV status

Chapter 6. Conclusion

This report shows the current or last known health status of 1,320 people infected with HCV through the administration of blood or blood products in Ireland. The database has a high participation rate of 77% and allows us to follow the effects of HCV on their health as the population ages and the duration of infection increases. More than half the database population are now in their fourth decade since they acquired HCV infection. It is clear that those who did not develop chronic HCV infection do not show signs of liver-related disease. Among those who developed chronic infection, the majority have not been shown to have signs of liver-related disease. However, a significant number have developed serious liver disease such as cirrhosis and liver cancer, some of whom have died. There has also been a clear progression in the prevalence of adverse health outcomes overall since the last round of data collection four years ago. Of the total database population, 390 people were alive and still HCV infected at the end of the current data collection period.

The factors found to be associated with liver disease progression in the database participants with chronic infection have been well described in the literature: male sex, longer duration of infection, older age and high alcohol intake.[1,6,10] There is clear evidence from published international sources that heavy alcohol use accelerates fibrosis progression and increases the risk of cirrhosis, HCC and end stage liver disease.[32,33,34] The most important factor in disease progression in the database population was alcohol. Participants with high alcohol consumption had five times higher odds of having signs of serious liver disease including cirrhosis compared to those without. However, information on alcohol consumption was not available for all participants and for many others it had not been recorded in recent years. It would be helpful to have up to date information on alcohol intake for all participants.

As in previous reports on the database, genotype 3 has again been found to be independently associated with having severe liver disease in this population. Although the analysis has adjusted for factors such as duration of infection, alcohol intake, sex, and age, there may be residual confounding in the relationship between genotype and outcome - for example, due to inaccuracies in reporting of alcohol intake and low data availability for BMI. Therefore, this finding is difficult to interpret. Results published in the international literature have been conflicting in relation to the impact of HCV genotypes on fibrosis progression, and development of cirrhosis and HCC.[35,36,37]

BMI was not shown to be a key factor in disease progression in the database population. However, data are available for only half of chronically infected participants and may not be representative of the whole group. We continue to encourage better recording of BMI data in the hepatology units.

Fibroscans (measures of liver stiffness) are increasingly being used instead of liver biopsies to monitor liver disease progression, particularly in combination with blood biomarkers.[13] We hope to report further results on these non-invasive diagnostic methods in the next review of the database population.

The rapidly shifting therapeutic landscape for HCV infection, with the arrival of new highly effective drug regimens, of shorter duration and fewer side effects, offers a more optimistic future for those who still have chronic infection. In Ireland, an early access programme started at the end of 2014 to facilitate rapid access to these new treatments for those with greatest clinical need. A National Hepatitis C Treatment Programme is being established in the HSE in 2015 to govern the ongoing access to hepatitis C treatment on a phased basis. We hope to reflect the impact of these new treatments in the next review of the database population in several years' time.

The ongoing support of participants, support groups and health professionals is essential to the success of this database work. Eligible people who are not yet participants in the database may join at any time by contacting their hepatology unit. The database project team invites participants, health professionals and researchers to contact us with suggestions for further development or improvement of the database, and requests for information from the database.

References

1. Poynard T, Yeun M-F, Ratziu V, Lai CL. Viral Hepatitis C. Lancet 2003;362:2095-8.
2. Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium, J Viral Hepat 1999;6;35-47.
3. Hoofnagle JH. Course and outcome of hepatitis C. Hepatology 2002;36:S21-S29.
4. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41-52.
5. NIH consensus statement on management of hepatitis C:2002 June 10-12;19(3):1-46.
6. Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). Liver Int 2009;29(s1):89-99.
7. Kenny-Walsh E, for the Irish Hepatology Research Group. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. N Engl J Med 1999;340:1228-33.
8. Wiese M, Berr F, Lafrenz M, Porst H, Oesen U, for the East German Hepatitis C Study Group. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in Germany: a 20-year multicenter study.Hepatology 2000;32:91-6.
9. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61:S58-68.
10. Rustgi VK. The epidemiology of hepatitis C infection in the United States. J Gastroenterol 2007;42:513-21.
11. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut 2006;55(9):1350-9.
12. National Institute for Clinical Excellence. NHS. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of chronic hepatitis C. Technology appraisal 75. London: NICE; 2004.
13. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2015. J Hepatol 2015, http://dx.doi.org/10.1016/ j.jhep.2015.03.025
14. McGee H, Hickey A, Smith M, Byrne M. Review of health services available for persons who contracted hepatitis C through the administration within the state of blood and blood products. Dublin: Consultative Council on Hepatitis C, Department of Health and Children; 2000.
15. Health Protection Surveillance Centre. National Hepatitis C Database. Baseline Report. October 2007. Available at: http://www.hpsc.ie/A-Z/Hepatitis/HepatitisC/HepatitisCDatabase/BaselineandFollow-upReports/
16. Health Protection Surveillance Centre. National Hepatitis C Database. Follow-Up Report 2009. Available at: http://www.hpsc.ie/A-Z/Hepatitis/HepatitisC/HepatitisCDatabase/BaselineandFollow-upReports/
17. Health Protection Surveillance Centre. National Hepatitis C Database. 2010 Report. Available at: http://www.hpsc.ie/A-Z/Hepatitis/HepatitisC/HepatitisCDatabase/BaselineandFollow-upReports/
18. Health Protection Surveillance Centre. National Hepatitis C Database. 2012 Report. Available at: http://www.hpsc.ie/A-Z/Hepatitis/HepatitisC/HepatitisCDatabase/BaselineandFollow-upReports/
19. Takaki A, Wiese M, Maertens G, Depla E, Seifert U, Liebetrau A, et al. Cellular immune responses persist and humoral responses decrease two decades after recovery from a single-source outbreak of hepatitis C. Nature Medicine 2000;6:578-82.
20. Nikolaeva LI, Blokhina NP, Tsurikova NN, Voronkova NV, Miminoshvili MI, Braginsky DM, et al. Virus-specific antibody titres in different phases of hepatitis C virus infection. J Viral Hepat 2002;9:429-37.
21. Wawrzynowicz-Syczewska M, Kubicka J, Lewandowski Z, Boron-Kaczmarska A, Radkowski M. Natural history of acute symptomatic hepatitis type C. Infection 2004;32:138-43.
22. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: A systematic review of longitudinal studies. J Viral Hepat 2006;13(1):34-41.
23. Jauncey M, Micallef JM, Gilmour S, Amin J, White PA, Rawlinson W, et al. Clearance of hepatitis C virus after newly acquired infection in injection drug users. JID 2004;190:1270-4.
24. Department of Health and Children. Strategic Task Force on Alcohol. Second report. Sept 2004. Dublin: Health Promotion Unit, Department of Health and Children.
25. Department of Health. Steering Group Report on a National Substance Misuse Strategy. February 2012. Dublin: Department of Health.
26. Knodell RG, Ishak KG, Black WC, Chent TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981;1(5):431-5.
27. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22(6):696-9.
28. Desmet V, Gerber M, Hoofnagle J, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19(6):1513-1520.
29. Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol 1991;13:372-4.
30. de Lédinghen V, Vergniol J. Transient elastography (FibroScan). Gastroenterol Clin Biol 2008;32(6 Suppl 1):58-67
31. Finlay TA. Report of the Tribunal of Inquiry into the Blood Transfusion Service Board. Dublin: Government Publications; 1997.

32. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in participants with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR and DOSVIRC groups. Lancet 1997;349:825-32.

33. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, etal. The natural history of hepatitis C virus infection. Host, viral and environmental factors. JAMA 2000;284:450-6.

34. Hutchinson SJ, Bird SM, Goldberg DJ. Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. Clin Gastroenterol Hepatol 2005;3:1150-9.

35. Zeuzem S. Forewarned is forearmed. J Hepatol 2009;51:626-7.

36. Bochud P-Y, Cai T, Overbeck K, Bochud M, Dufour J-F, Mullhaupt B, et al. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. J Hepatol 2009;51:655-66.

37.Harris HE, Eldridge KP, Harbour S, Alexander G, Teo C-G, Ramsay ME, et al. Does the clinical outcome of hepatitis C infection vary with the infecting hepatitis C virus type? J Virol Hepat 2007;14:213-220.

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 (as per guideline that was current at the time of setting up the database)
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 (at the time of setting up the database) 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.[24]

(Note: Low-risk drinking guidelines have since been revised and are now defined as 11 standard drinks for women and 17 standard drinks for men, per week.[25])

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.

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.

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).

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.

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.

Signs of liver disease
In this report, the term "signs of liver disease" refers to clinical signs of serious liver disease and includes the following: cirrhosis, HCC, varices, portal hypertension, ascites, decompensated liver disease, encephalopathy, splenomegaly, hepatomegaly, hepatosplenomegaly, hypersplenism, hepatopulmonary syndrome, hepatic synthetic dysfunction, hepatorenal syndrome and portal gastropathy.

Splenomegaly
Enlarged spleen.

Sustained virological response
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

AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase (a liver enzyme)
Anti-HCV	Antibody to hepatitis C virus
BOC	Boceprevir
EIA	Enzyme immunoassay, a screening test for hepatitis C
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
PCR	Polymerase chain reaction
RBV	Ribavirin
RIBA	Recombinant immunoblot assay, a more specific hepatitis C test
RNA	Ribonucleic acid
SVR	Sustained virological response
TVR	Telaprevir
WHO	World Health Organization

Appendix A

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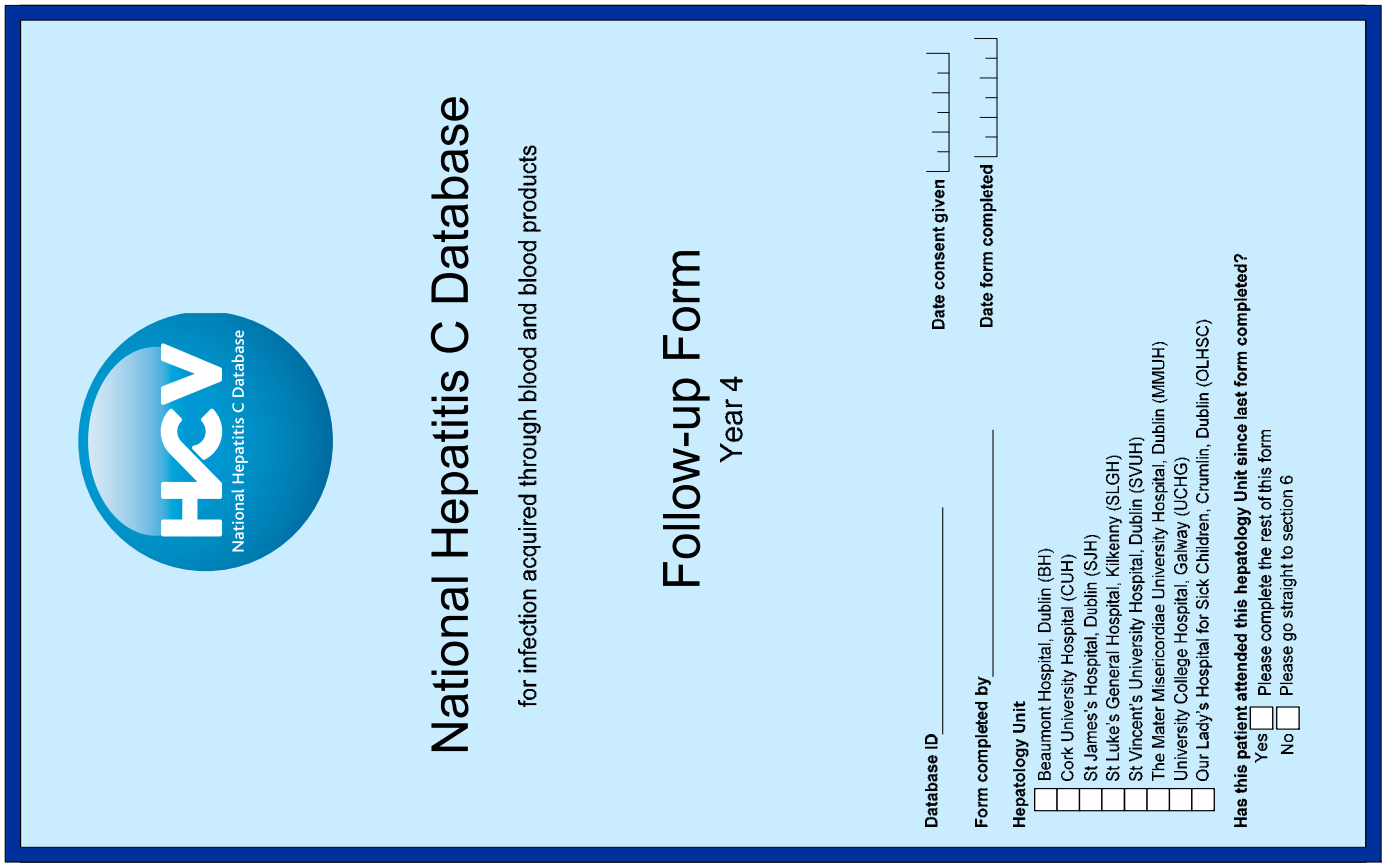
Dr Stephen Stewart, Mater Misericordiae University Hospital

Dr Lelia Thornton, Health Protection Surveillance Centre

Appendix C Data collection form for fourth round of follow-up



National Hepatitis C Database

for infection acquired through blood and blood products

Follow-up Form

Year 4

Database ID _____ Date consent given

Form completed by _____ Date form completed

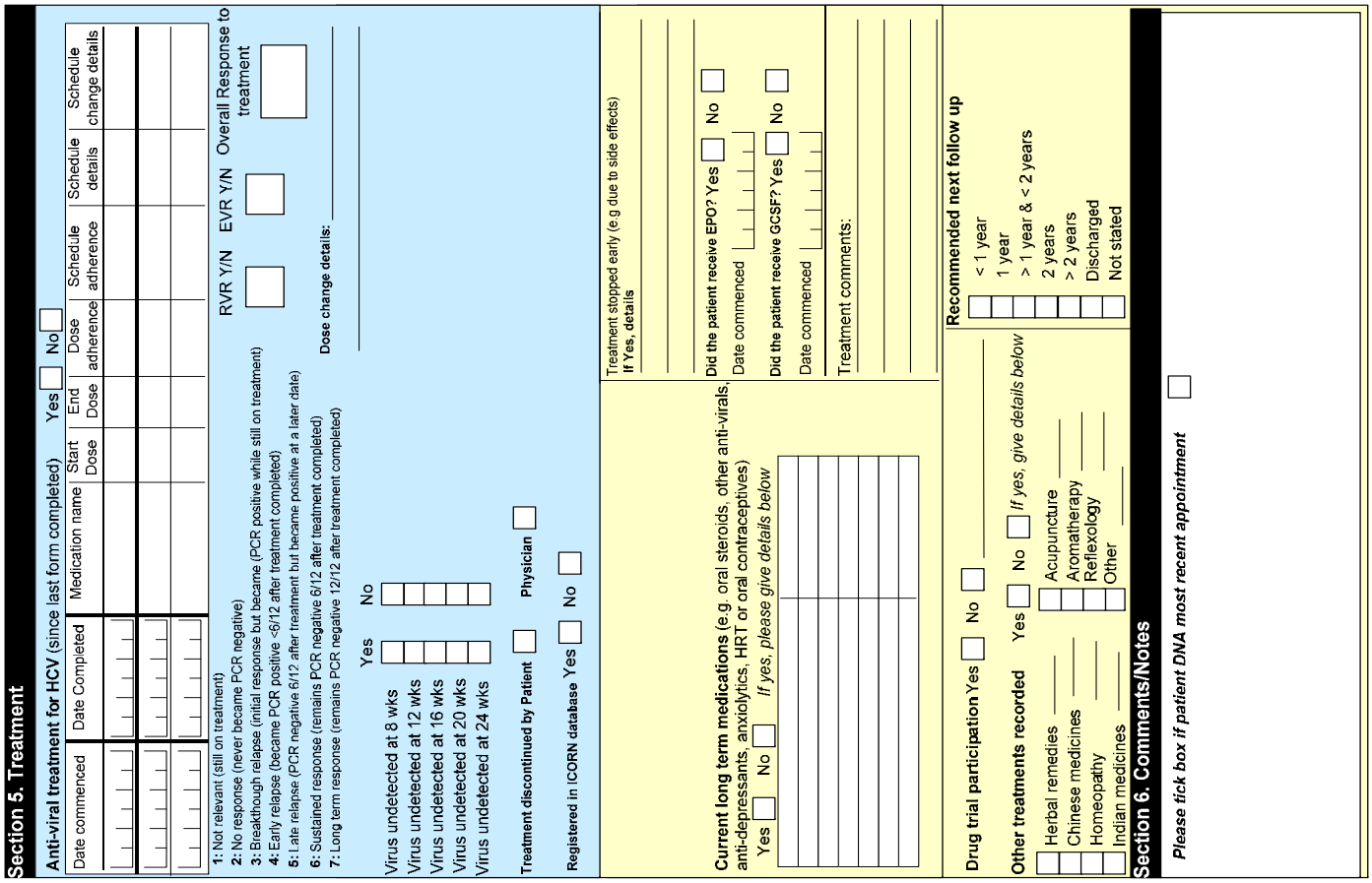
Hepatology Unit

- 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)

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

Anti-viral treatment for HCV (since last form completed) Yes ☐ No ☐

Date commenced	Date Completed	Medication name	Start Dose	End Dose	Dose adherence	Schedule adherence	Schedule details	Schedule change details

1: Not relevant (still on treatment)
2: No response (never became PCR negative)
3: Breakthough relapse (initial response but became (PCR positive while still on treatment)
4: Early relapse (became PCR positive <6/12 after treatment completed)
5: Late relapse (PCR negative 6/12 after treatment but became positive at a later date)
6: Sustained response (remains PCR negative 6/12 after treatment completed)
7: Long term response (remains PCR negative 12/12 after treatment completed)

RVR Y/N EVR Y/N Overall Response to treatment

Dose change details: _____

	Yes	No
Virus undetected at 8 wks	☐	☐
Virus undetected at 12 wks	☐	☐
Virus undetected at 16 wks	☐	☐
Virus undetected at 20 wks	☐	☐
Virus undetected at 24 wks	☐	☐

Treatment discontinued by Patient ☐ **Physician** ☐

Registered in ICORN database Yes ☐ No ☐

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*

Treatment stopped early (e.g due to side effects)
If Yes, details

Did the patient receive EPO? Yes ☐ No ☐
Date commenced

Did the patient receive GCSF? Yes ☐ No ☐
Date commenced

Treatment comments:

Drug trial participation Yes ☐ No ☐ _____

Other treatments recorded Yes ☐ No ☐ *If yes, give details below*

- Herbal remedies _____
- Chinese medicines _____
- Homeopathy _____
- Indian medicines _____
- Acupuncture _____
- Aromatherapy _____
- Reflexology _____
- Other _____

Recommended next follow up

- < 1 year
- 1 year
- > 1 year & < 2 years
- 2 years
- > 2 years
- Discharged
- Not stated

Section 6. Comments/Notes

Please tick box if patient DNA most recent appointment ☐

Database ID _____ Date last form completed ___/___/___

Section 1. Patient Details

Patient initials ___ **DOB** (dd/mm/yy) ___/___/___ **Height** _____ **Weight** _____

BMI _____ **Sex** **Male** ☐ **Female** ☐ **County of residence** _____

Alcohol intake at last visit (*units/week*)

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

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

Patient's death recorded since last form completed? Yes ☐ No ☐

If yes: date of death (dd/mm/yy): ___/___/___ **Cause of death** _____

Other significant viral infection(s) (diagnosed since last form completed)? Yes ☐ No ☐

If yes, please specify _____

Other known liver disease (diagnosed since last form completed)? Yes ☐ No ☐

If yes, please specify _____

Other significant medical conditions (diagnosed since last form completed)? Yes ☐ No ☐

If yes, please specify _____

Section 2. Clinical Status

Signs of HCV related liver disease (diagnosed since last form completed)

Yes ☐ No ☐

	Severity	Date diagnosed
☐ Ascites		
☐ Varices		
☐ Bleeding Varices		
☐ Steatosis		
☐ Cirrhosis		
☐ Liver tumour/HCC		
☐ Encephalopathy		
☐ Other (please specify)		

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

Date of most recent visit for HCV related care (dd/mm/yy) ___/___/___ Number of outpatient visits _____

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

Liver related(US/CT/MRI)results (date) ___/___/___

Procedures undergone since last form completed

Procedure	No. of times	Procedure site	Liver related Yes/No
☐ Diagnostic gastroscopy			
☐ Banding gastroscopy			
☐ Injection gastroscopy			
☐ TIPPS			
☐ Ultrasound			
☐ CT			
☐ MRI			
☐ Hepatic angiography			

Other, specify procedure and number of times _____

Fibroscan result (most recent)

Date (dd/mm/yy) ___/___/___ Success Rate % _____

Fibroscan result (Kpa) _____ IQR _____

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

_____

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

_____

Database ID _____ Date last form completed ___/___/___

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

Liver function tests (LFTs) (most recent)

Date (dd/mm/yy) ___/___/___

Gamma GT	Urea	Creatinine	
ALT	HB	INR	PTR
AST	Neutrophils	WCC	
Bilirubin	TST	Platelets	
Albumin	T3	Neutrophils	
Random Glucose	T4	LDL	
Fasting Glucose	AFP	HDL	
HbA1C	Alk Phos	Triglycerides	

IL-28B **(dd/mm/yy)** ___/___/___ Result _____

Hepatitis B test results (most recent)

Date (dd/mm/yy) ___/___/___

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

Glucose Tolerance test result

OGTT 30 mins _____ OGTT 120 mins _____

OGTT 60 mins _____ OGTT 150 mins _____

OGTT 90 mins _____ OGTT 180 mins _____

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.
___/___/___	___	___	___	___	___	___	☐	☐	☐

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.
___/___/___	___	___	___	___	☐	☐	☐

HCV antibody tests

	Date of test (*dd/mm/yy*)	Pos.	Neg.	Weak
EIA (earliest recorded)	___/___/___	☐	☐	☐

HCV PCR (ALL since last form completed)

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

HCV genotype/sequence information:

Genotype/subtype _____

Sequence information ☐ 1977 ☐ 1991

HOMA Score

Date (dd/mm/yy) ___/___/___

Result _____

HLA type

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

Autoantibodies (*most recent*)

Date (dd/mm/yy) ___/___/___

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

CHILD Pugh **A** ☐ **B** ☐ **C** ☐

Date (dd/mm/yy) ___/___/___

MELD score _____

Date (dd/mm/yy) ___/___/___

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[26]	Modified HAI or Modified Knodell or Ishak[27] or Desmet[28]	Scheuer[29]
0	No fibrosis	No fibrosis	None
1	Fibrosis portal expansion	Fibrosis expansion of some portal areas, with or without short fibrous septa	Enlarged, fibrotic portal tracts
2		Fibrosis expansion of most portal areas, with or without short fibrous septa	Periportal or portal-portal septa with intact architecture
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
4	Cirrhosis	Fibrosis expansion of portal areas, with marked bridging (portal to portal as well as portal to central)	Probable or definite cirrhosis
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

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

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.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 Hepatitis C National Office
Ms Michele Tait, Hepatitis C National Co-ordinator, Mill Lane, Palmerstown, Dublin 20 Tel 01 6201750 / 01 6201712

HSE Dublin North East
Mr Larry Bathe, Health Service Executive, Primary Care Unit, Railway Street, Navan, Co Meath Tel: 046 9076451

HSE South Dublin, Kildare & Wicklow
Ms Michelle Hayes, Health Service Executive, Mill Lane, Palmerstown, Dublin 20 Tel 01 6201840

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

HSE Mid-West
Ms Ellen Rush, Tyone Health Centre, Tyone, Nenagh, Co Tipperary. Tel: 067 46449

HSE-North West
Mr Colin McCann, 1st Floor, County Clinic, St Conal's Hospital, Letterkenny, Co Donegal. Tel 074 9104698

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

HSE South East
Ms Anne Bambrick, Primary Care Unit, Health Service Executive, Lacken, Dublin Road, Kilkenny, Co Kilkenny. Tel: 056 7784296

HSE South
Mr Donal Murphy, Primary Care Unit, HSE South, Floor 3, Block 15, St. Finbarr's Hospital, Douglas Rd, Cork Tel 021-4923833

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/

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

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