

National Hepatitis C Database

for infection acquired through blood
and blood products



2012 Report



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive





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Foreword

On behalf of the National Hepatitis C Database Steering Committee, I am very happy to introduce the 2012 report from the National Hepatitis C Database. This is the fourth report to be produced from the database and is based on information up to the end of 2009 and describes the main findings from this data.

The National Hepatitis C Database Steering Committee oversees the management and development of the database and a debt of gratitude is owed to Dr Lelia Thornton and her team in the HSE Health Protection Surveillance Centre for their dedication and continuing commitment to this project. It is hoped that the database will continue to provide an excellent resource to clinicians and researchers in terms of monitoring the disease progression and also to health service planners in terms of developing services for those infected with hepatitis C through blood and blood products. Through the Database Steering Committee, requests have been made by researchers and clinicians for access to the data which will greatly assist in helping understand more about the disease and its progression.

Ireland's cohort of patients who were infected through contaminated blood and blood products are a source of important information 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 we 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. We also know that the majority of participants in the database do not show evidence of having serious liver disease, which is very encouraging for patients. Factors which increase the rate of disease progression and disease severity include high alcohol consumption and a high BMI, both of which can be controlled through careful lifestyle changes.

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

Chairperson, National Hepatitis C Database Steering Committee

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Acknowledgements

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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

Dr Jeff Connell, National Virus Reference Laboratory

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Hepatitis C Liaison Officers

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HPSC National Hepatitis C Database Team

Dr Lelia Thornton, Specialist in Public Health Medicine (Project Co-ordinator)

Niamh Murphy, Surveillance Scientist

Margaret McIver, Surveillance Assistant

Paula Flanagan, Research Nurse

Hepatology Units

Beaumont Hospital, Dublin

Cork University Hospital

Mater Misericordiae University Hospital, Dublin

Our Lady's Children's Hospital, Crumlin, Dublin

St Luke's Hospital, Kilkenny

St James's Hospital, Dublin

St Vincent's University Hospital, Dublin

University College Hospital, Galway

Executive Summary

Hepatitis C virus (HCV) infection is a major cause of liver disease and death throughout the world. Between 55% and 85% of those infected develop chronic infection. It is estimated that up to 20% of those with chronic infection will develop cirrhosis of the liver over 20-25 years, with 3-4% of these developing hepatocellular carcinoma per year. Very effective treatments for HCV are now available which eradicate the virus in over 50% of cases depending on the genotype. The virus is transmitted by blood and now occurs primarily through injecting drug use. Transfusion-related HCV infection is rare now since the introduction of routine screening of blood in the early 1990s.

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. This report is based on the fourth round of data collection and includes data on database participants up to the end of 2009.

Main findings

Profile of participants

- There are 1316 database participants, a participation rate of 77%.
- The source of infection was anti-D immunoglobulin in 61%, blood transfusion or treatment for renal disease in 26% and blood clotting factors in 13%.
- The average age at last follow-up was 57 years.
- The average time interval from infection to last follow-up was 30 years.

Hepatitis C status

- 48% of participants were still chronically infected at the time of last testing.
- The spontaneous viral clearance rate in this population is between 19% and 36% (having taken account of those who died before RNA testing, and allowing for the possibility that some participants may have had false positive screening test results).
- Females were more likely to have cleared the virus spontaneously.
- The most common genotype is genotype 1 (76%), followed by genotype 3 (18%).

Alcohol consumption

- Alcohol consumption in excess of recommended levels was recorded for 15% of those chronically infected. This was higher in males and in younger people.

Outcomes

Cirrhosis

- Cirrhosis had developed in 137 participants (17%) who ever had chronic infection, at an average duration of infection of 24 years and an average age of 53 years. This was an increase of 26 cases since the last round of data collection.

- Alcohol consumption was the biggest determinant of risk of cirrhosis in those with chronic infection. Other factors associated with cirrhosis were duration of infection, male gender and genotype 3 infection.
- Participants infected through blood transfusions or treatment for renal disease were more likely to have cirrhosis than those in the anti-D cohort.
- There were no cases of cirrhosis in participants who did not become chronically infected.

Hepatocellular carcinoma (HCC)/liver cancer

- HCC had developed in 32 (4%) of those who ever had chronic infection, at an average duration of infection of 28 years and an average age of 63 years. The prevalence was significantly higher in males than in females. Participants infected through transfusions or treatment for renal disease or through blood clotting factors were more likely to have HCC than those in the anti-D cohort.
- This was an increase of 9 in the number of HCC cases since the last round of data collection.
- There were no cases of HCC in participants who did not become chronically infected.

Liver biopsies

- Note: Liver biopsies have been infrequently carried out in recent years so for some participants their last biopsy may have been many years ago.
- Moderate or severe inflammation on the last liver biopsy was recorded in 26% of ever chronically infected participants compared with 1% of those who did not develop chronic infection. This proportion was higher (34%) in those infected through blood transfusion or treatment for renal disease.
- A high fibrosis score on the last liver biopsy was recorded in 19% of ever chronically infected participants compared with 4% of those who never developed chronic infection. This proportion was higher (32%) in those infected through blood transfusion or treatment for renal disease.
- Factors associated with having a high fibrosis score were male gender, older age, genotype 3 infection and high alcohol consumption.

Deaths

- By latest follow-up, 212 participants (16%) had died, an additional 25 deaths since the previous round of data collection. The proportion who had died was higher in those who ever had chronic infection (18%) than in those who did not develop chronic infection (6%).
- Those who had been chronically infected but had cleared the virus (mostly through treatment) had a lower mortality rate at 4%.
- Death from liver disease occurred in 55 participants (4%), most of whom had developed chronic infection or had no RNA results in their charts (and had died before RNA testing began).
- High alcohol intake was a highly significant predictor of liver-related mortality. Liver-related mortality was also higher in males and those infected through blood transfusions or blood clotting factors.

Severe liver disease - summary measure

- Using a summary measure of "severe liver disease", 31% of participants with current chronic infection were classified as having severe liver disease, compared with 2% of those who were never chronically infected.
- The determinants of having severe liver disease were high alcohol intake, older age at last follow-up, male gender, longer duration of infection and HCV genotype 3.

- Participants infected through blood transfusions/treatment for renal disease and those infected through blood clotting factors were more likely to have severe liver disease compared with the anti-D cohort.
- The most important factor in disease progression was alcohol intake. Participants who had high alcohol intake had more than 5 times higher odds of having severe liver disease compared to those without.

Anti-viral treatment

- Forty two percent of chronically infected participants had received at least one course of anti-viral treatment.
- Twenty four percent of all treatment courses were stopped early due to side-effects.
- Younger participants, those infected in the 1991-1994 anti-D outbreak, or through blood transfusion or clotting factors, those with high fibrosis scores and those with genotype 2 or 3 infections were more likely to have been treated.
- Among those whose first treatment was with pegylated interferon and ribavirin, a sustained virological response was achieved for 73% of genotype 2 or 3 participants compared with 41% of genotype 1 participants.

Liver transplants

- Nineteen database participants had received a liver transplant. The average age at transplant was 53 years and the average duration of infection was 29 years.
- All those tested post-transplant remained RNA positive.
- Five of the liver transplant recipients have since died.

Focus on different patient groups

- Detailed descriptions of the 3 patient groups (anti-D, blood transfusion/renal and blood clotting factors), with information on their health outcomes and treatment, are provided in individual sections in Chapter 4.

Service usage

- Most participants had attended their hepatology unit in the previous 2 years (76%), this figure being higher (88%) for those with chronic infection.
- The specialist services other than hepatology that were most commonly used by chronically infected participants were haematology, endocrinology, rheumatology and psychiatry/psychology/counselling.

Conclusion

This report describes the current health of a large group of people who were infected with hepatitis C virus through the administration of blood or blood products many years ago. Almost half of this population still have chronic hepatitis C infection. Despite this, the majority do not have evidence of serious liver disease after an average of more than 30 years of infection. However, the findings of this latest round of data collection have demonstrated further progression of liver disease in a small number of participants

It is hoped that there may be more active recording of up to date information on alcohol consumption and BMI in the patient medical notes by the time of the next period of data collection. We hope to be able to

report on genetic and metabolic factors affecting disease progression in the next report from the database. The recent addition of protease inhibitors into the management of genotype 1 infection will be captured in the next round of data collection and reported in the next report.

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=1316)		Ever chronically infected * (n=815)		Currently chronically infected (n=605)		Chronically infected in past (n=210)		Never chronically infected † (n=451)		No RNA results (n=50)	
	Num	%	Num	%	Num	%	Num	%	Num	%	Num	%
Signs of liver disease	187	14.2	175	21.5	149	24.6	26	12.4	5	1.1	7	14.0
Cirrhosis	142	10.8	137	16.8	118	19.5	19	9.1	0	0.0	5	10.0
Liver tumours or HCC	34	2.6	32	3.9	31	5.1	1	0.5	0	0.0	2	4.0
High fibrosis score on biopsy ‡	167	12.7	160	19.6	125	20.7	35	16.7	4	0.9	3	6.0
Deceased	212	16.1	145	17.8	137	22.6	8	3.8	26	5.8	41	82.0
Died from liver disease §	55	4.2	45	5.6	43	7.2	2	1.0	2	0.4	8	17.4

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

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

‡ Ever had a fibrosis score of 3 or 4 on biopsy scored from 0 to 4 or a fibrosis score of 4, 5 or 6 on biopsy scored from 0 to 6. 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.

§ Liver-related disease directly caused death. Denominator for this is all participants minus the 13 participants whose cause of death was not available (n=1303)

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

Final status	All (n=1266)		Ever chronically infected* (n=815)	
	Num	%	Num	%
Currently chronically infected †	605	47.8	605	74.2
Treated and cleared virus	176	13.9	176	21.6
Cleared virus without treatment ‡	485	38.3	34	4.2
Had positive confirmatory antibody results §	225	17.8	34	4.2
Not confirmed positive	260	20.5		

* At least one positive hepatitis C RNA result

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

‡ Hepatitis C antibody positive, never treated

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

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

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

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

Outcomes	All * (n=808)		Ever chronically infected (n=432)		Currently chronically infected (n=335)		Chronically infected in past (n=97)		Never chronically infected (n=366)	
	Num	%	Num	%	Num	%	Num	%	Num	%
Signs of liver disease	64	7.9	60	13.9	51	15.2	9	9.3	3	0.8
Cirrhosis	50	6.2	49	11.3	42	12.5	7	7.2	0	0.0
Liver tumours or HCC	5	0.6	5	1.2	5	1.5	0	0.0	0	0.0
High fibrosis score on biopsy	76	9.4	73	16.9	62	18.5	11	11.3	2	0.6
Deceased	56	6.9	37	8.6	35	10.5	2	2.1	18	4.9
Died from liver disease †	13	1.6	11	2.6	11	3.3	0	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

† Denominator for this is all participants minus the three participants whose cause of death was not available (n=805)

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

Final status	All (n=798)		Ever chronically infected (n=432)	
	Num	%	Num	%
Currently chronically infected	335	42.0	335	77.6
Treated and cleared virus	76	9.5	76	17.6
Cleared virus without treatment	387	48.5	21	4.9
Had positive confirmatory antibody results	167	20.9	21	4.9
Not confirmed positive	220	27.6		

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

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

Outcomes	All * (n=679)		Ever chronically infected (n=378)		Currently chronically infected (n=320)		Chronically infected in past (n=58)		Never chronically infected (n=295)	
	Num	%	Num	%	Num	%	Num	%	Num	%
Signs of liver disease	57	8.4	53	14.0	47	14.7	6	10.3	3	1.0
Cirrhosis	45	6.6	44	11.6	39	12.2	5	8.6	0	0.0
Liver tumours or HCC	5	0.7	5	1.3	5	1.6	0	0.0	0	0.0
High fibrosis score on biopsy	73	10.8	70	18.5	61	19.1	9	15.5	2	0.7
Deceased	54	8.0	36	9.5	35	10.9	1	1.7	17	5.8
Died from liver disease †	13	1.9	11	2.9	11	3.5	0	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 the three participants whose cause of death was not available (n=676)

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

Final status	All (n=673)		Ever chronically infected (n=378)	
	Num	%	Num	%
Currently chronically infected	320	47.6	320	84.7
Treated and cleared virus	40	5.9	40	10.6
Cleared virus without treatment	313	46.5	18	4.8
Had positive confirmatory antibody results	154	22.9	18	4.8
Not confirmed positive	159	23.6		

Note: Participants with no RNA results in their charts were omitted from this table as there is no way of determining their RNA status (n=6).

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=38)		Currently chronically infected (n=5)		Chronically infected in past (n=33)		Never chronically infected (n=31)	
	Num	%	Num	%	Num	%	Num	%	Num	%
Signs of liver disease	5	6.9	5	13.2	3	60.0	2	6.1	0	0.0
Cirrhosis	3	4.1	3	7.9	2	40.0	1	3.0	0	0.0
Liver tumours or HCC	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
High fibrosis score on biopsy	2	2.7	2	5.3	1	20.0	1	3.0	0	0.0
Deceased	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Died from liver disease	0	0.0	0	0.0	0	0.0	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

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

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

Final status	All (n=69)		Ever chronically infected* (n=38)	
	Num	%	Num	%
Currently chronically infected	5	7.3	5	13.2
Treated and cleared virus	30	43.5	30	79.0
Cleared virus without treatment	34	49.3	3	7.9
Had positive confirmatory antibody results	7	10.1	3	7.9
Not confirmed positive	27	39.1		

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

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

Outcomes	All *(n=337)		Ever chronically infected (n=273)		Currently chronically infected (n=194)		Chronically infected in past (n=79)		Never chronically infected (n=61)	
	Num	%	Num	%	Num	%	Num	%	Num	%
Signs of liver disease	86	25.5	83	30.4	70	36.1	13	16.5	2	3.3
Cirrhosis	71	21.1	70	25.6	58	29.9	12	15.2	0	0.0
Liver tumours or HCC	21	6.2	21	7.7	20	10.3	1	1.3	0	0.0
High fibrosis score on biopsy	82	24.3	78	28.6	56	28.9	22	27.9	2	3.3
Deceased	85	25.2	75	27.5	72	37.1	3	3.8	7	11.5
Died from liver disease †	22	6.6	21	7.8	19	10.1	2	2.5	1	1.6

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

† Denominator for this is all participants minus the six participants whose cause of death was not available (n=331)

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

Final status	All (n=334)		Ever chronically infected (n=273)	
	Num	%	Num	%
Currently chronically infected	194	58.1	194	71.1
Treated and cleared virus	71	21.3	71	26.0
Cleared virus without treatment	69	20.7	8	2.9
Had positive confirmatory antibody results	34	10.2	8	2.9
Not confirmed positive	35	10.5		

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

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

Outcomes	All (n=165)		Ever chronically infected (n=107)		Currently chronically infected (n=73)		Chronically infected in past (n=34)		Never chronically infected (n=21)		No RNA results (n=37)	
	Num	%	Num	%	Num	%	Num	%	Num	%	Num	%
Signs of liver disease	36	21.8	31	29.0	27	37.0	4	11.8	0	0.0	5	13.5
Cirrhosis	20	12.1	17	15.9	17	23.3	0	0.0	0	0.0	3	8.1
Liver tumours or HCC	8	4.9	6	5.6	6	8.2	0	0.0	0	0.0	2	5.4
High fibrosis score on biopsy	9	5.5	9	8.4	7	9.6	2	5.9	0	0.0	0	0.0
Deceased	70	42.4	32	29.9	29	39.7	3	8.8	1	4.8	37	100.0
Died from liver disease *	19	11.8	12	11.3	12	16.4	0	0.0	0	0.0	7	20.6

* Denominator for this is all participants minus the four participants whose cause of death was not available (n=161)

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

Final status	All (n=128)		Ever chronically infected (n=107)	
	Num	%	Num	%
Currently chronically infected	73	57.0	73	68.2
Treated and cleared virus	29	22.7	29	27.1
Cleared virus without treatment	26	20.3	5	4.7
Had positive confirmatory antibody results	22	17.2	5	4.7
Not confirmed positive	4	3.1		

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

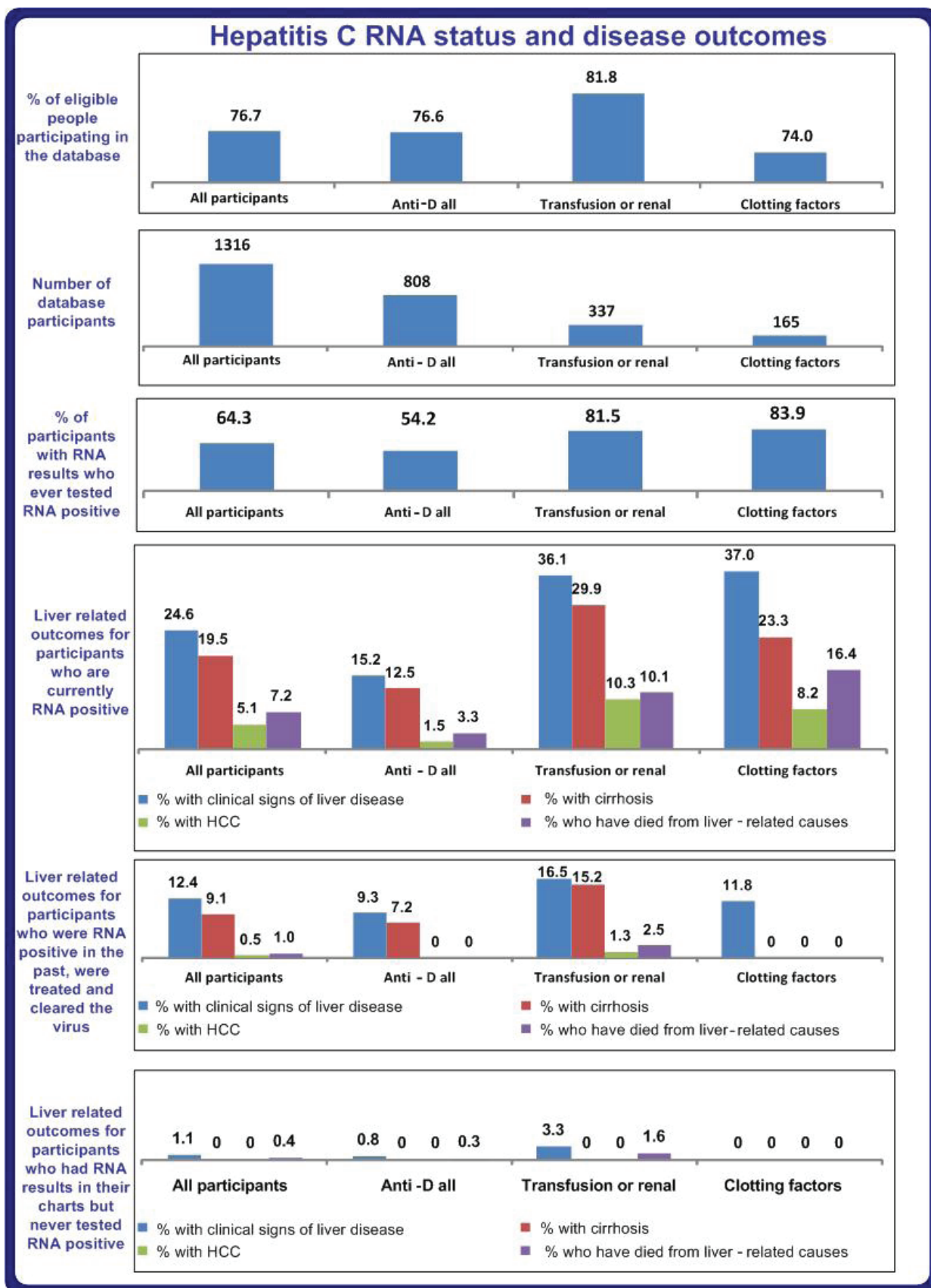


Figure 1. Summary of RNA status, and disease progression by RNA status, for all participants and by source of infection

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

Chapter 1 Hepatitis C Virus Infection

Chronic hepatitis C infection is a major cause of chronic liver disease and death throughout the world.¹ Approximately 3% of the world's population is infected with hepatitis C virus (HCV).² Hepatitis C infection is caused by an RNA virus that was first identified in 1989.³ Six distinct but related genotypes and multiple subtypes have been identified. In Western Europe genotypes 1a and 1b are most common, followed by genotypes 2 and 3.⁴

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

Acute HCV infection, in general, is relatively mild with only 20-30% of infected persons developing symptoms or clinically evident acute infection.² In most persons who become infected with HCV, viremia persists. Chronic HCV infection is marked by persistence of HCV RNA for at least 6 months after onset of infection. Spontaneous resolution after 6 or 12 months of infection is unusual.³ Between 55% and 85% of those infected develop chronic infection⁶, the lower end of the range being accounted for mainly by women, particularly young women.^{7,8}

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

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

Very effective treatments for hepatitis C are now available. The standard of care for the past decade has been a combination of pegylated interferon and ribavirin for 24 to 48 weeks, depending on the genotype. This has resulted in a successful response to treatment in more than 75% of patients with genotypes 2 and 3 HCV infection, and 40-50% of those with genotype 1.^{10,11} In recent years, directly acting antiviral agents have been developed. Two of these are the protease inhibitors telaprevir and boceprevir which, when used in combination with pegylated interferon and ribavirin in genotype 1 patients, have greatly improved sustained virological response rates in both treatment naïve patients and patients who have had previous virological failure on treatment.^{12, 13}

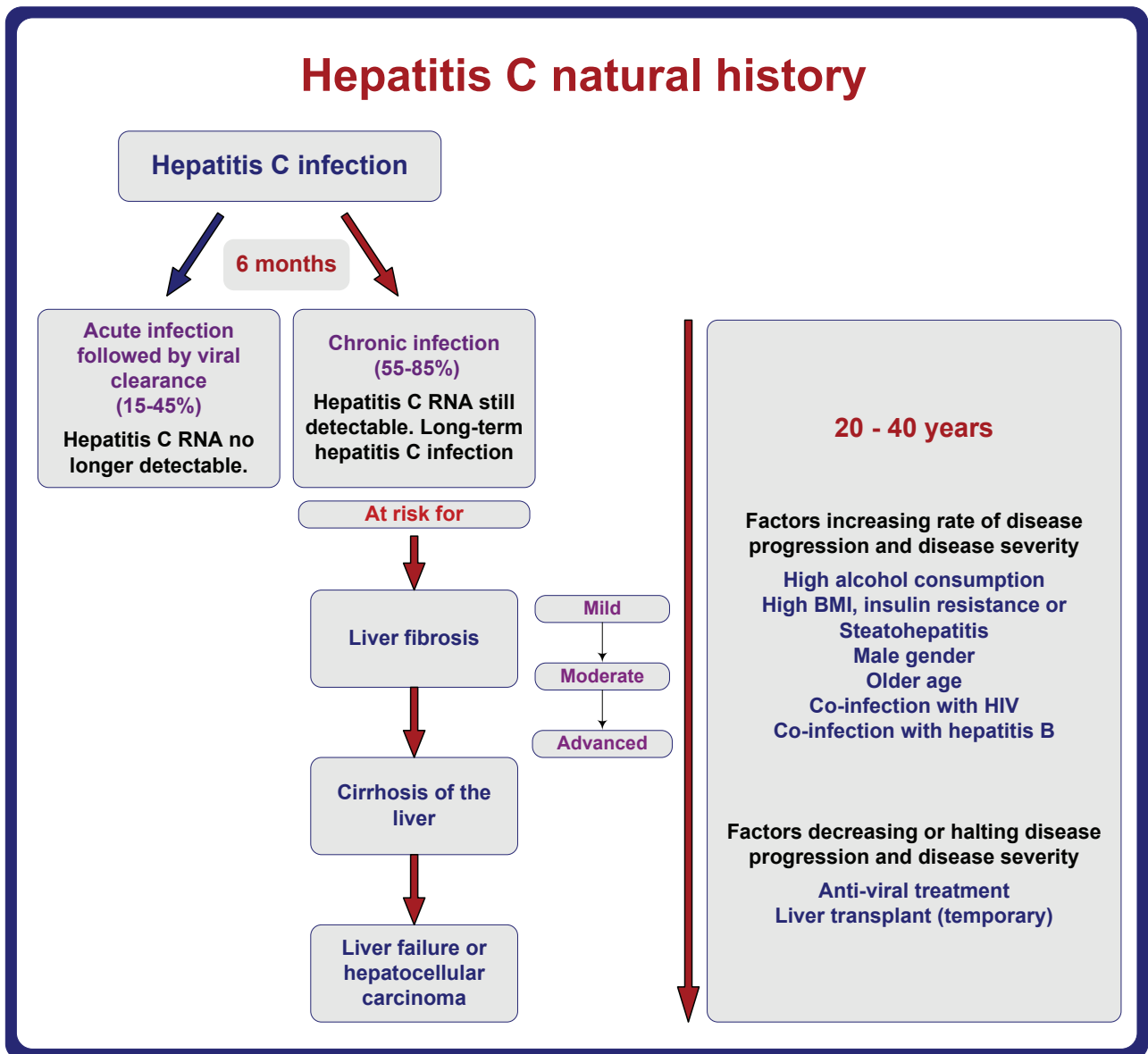


Figure 2. Summary of natural history of hepatitis C infection

Chapter 2 National Hepatitis C Database

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 persons 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 transfusion, 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).

The objectives of the database are:

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

Baseline data were collected in 2005 and 2006 and included all relevant data from the date of diagnosis on all consented participants. A baseline report¹⁵ describing these data was published in October 2007. Two follow-up reports have been published since baseline data collection, in 2009¹⁶ and 2010.¹⁷ This is the third follow-up report and includes information on all participants up to the end of 2009. All reports and patient newsletters are available through the hepatology units, patient support groups, hepatitis C liaison officers and on the database website (www.hcvdatabase.ie).

Database population

Any person (alive or dead) who contracted HCV infection through the administration of blood or blood products within the state is eligible to be included in the database. These include women infected through anti-D immunoglobulin, recipients of blood transfusion, people with haemophilia and other blood clotting disorders and people who received treatment for renal disease. Eligible patients were identified by the eight specialist hepatology units.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 are ELISA (enzyme linked immunosorbent assay)/EIA (enzyme immunoassay) positive or weak positive, recombinant immunoblot assay (RIBA)/INNO-LIA positive or indeterminate, or hepatitis C polymerase chain reaction (PCR)/RNA positive.

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

Source of data

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

Data security

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

Chapter 3 Follow-up Data Collection to end 2009

Data Collection

The fourth round of data collection began in September 2010 capturing data on patients up to 31st December 2009. Data are extracted from the participants' medical notes by a HPSC research nurse. Information collected includes clinical, demographic and lifestyle data which has been added to the participants' medical records between the date of last data collection (up to the end of 2008) and the date of follow-up data collection (up to 31st December 2009). Data were entered into the database by a surveillance assistant. Double entry was used to maximise accuracy. In order to continuously improve the information held on participants, additional data fields were included in the latest follow-up data collection form. These included more detailed results of haematology and biochemistry tests, fibroscans and other diagnostic tests. More details were also recorded on side effects of antiviral treatment.

Recruitment of new participants

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

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

Assumptions

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

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

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

Variables were created to indicate if participants had cirrhosis or liver cancer on biopsy or mentioned elsewhere in their medical charts or death certificates. Estimated dates of onset were generated for both conditions, but these were approximate. If multiple biopsies, ultrasounds or CT scans were done, the midpoint between the first positive

and last negative date was used. Where cirrhosis or liver cancer was first mentioned on death certificates, the midpoint between the date of death and last negative diagnostic test or last visit to the hepatology unit was used. Otherwise the earliest date mentioned in relation to a diagnosis of cirrhosis or liver cancer was taken.

Estimating duration of hepatitis C ribonucleic acid (RNA) positivity

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

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

Coding of death certificates

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

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

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

Death was considered to be directly caused by liver-related disease in the following situations:

If hepatocellular carcinoma or end-stage liver disease (varices, ascites, liver failure or hepatic encephalopathy) were listed as any of the causes of death in section I of the death certificate

Or if liver disease was not specified as end-stage (e.g. cirrhosis) but the sequence of causes of death on the certificate suggested death was due to liver disease,

Or if liver disease was coded as the underlying and only cause of death.

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

Long-term medications

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

Liver biopsies

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

- Knodell system: ¹⁸ fibrosis scored from 0-4
- Modified Knodell system, ^{19,20} also known as the Ishak or the modified HAI system: fibrosis scored from 0-6
- Scheuer system: ²¹ fibrosis scored from 0-4
- International Group of Hepatopathologists system: fibrosis scored from 0-4

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

Data analysis

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

Chapter 4 Main Findings

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). Thirteen people have been added to the database since the last round of data collection, bringing the total number of participants to 1,316. The new database participants include six new consents and seven people who are newly deceased or newly identified as deceased. Figure 3 details the response rate by source of infection.

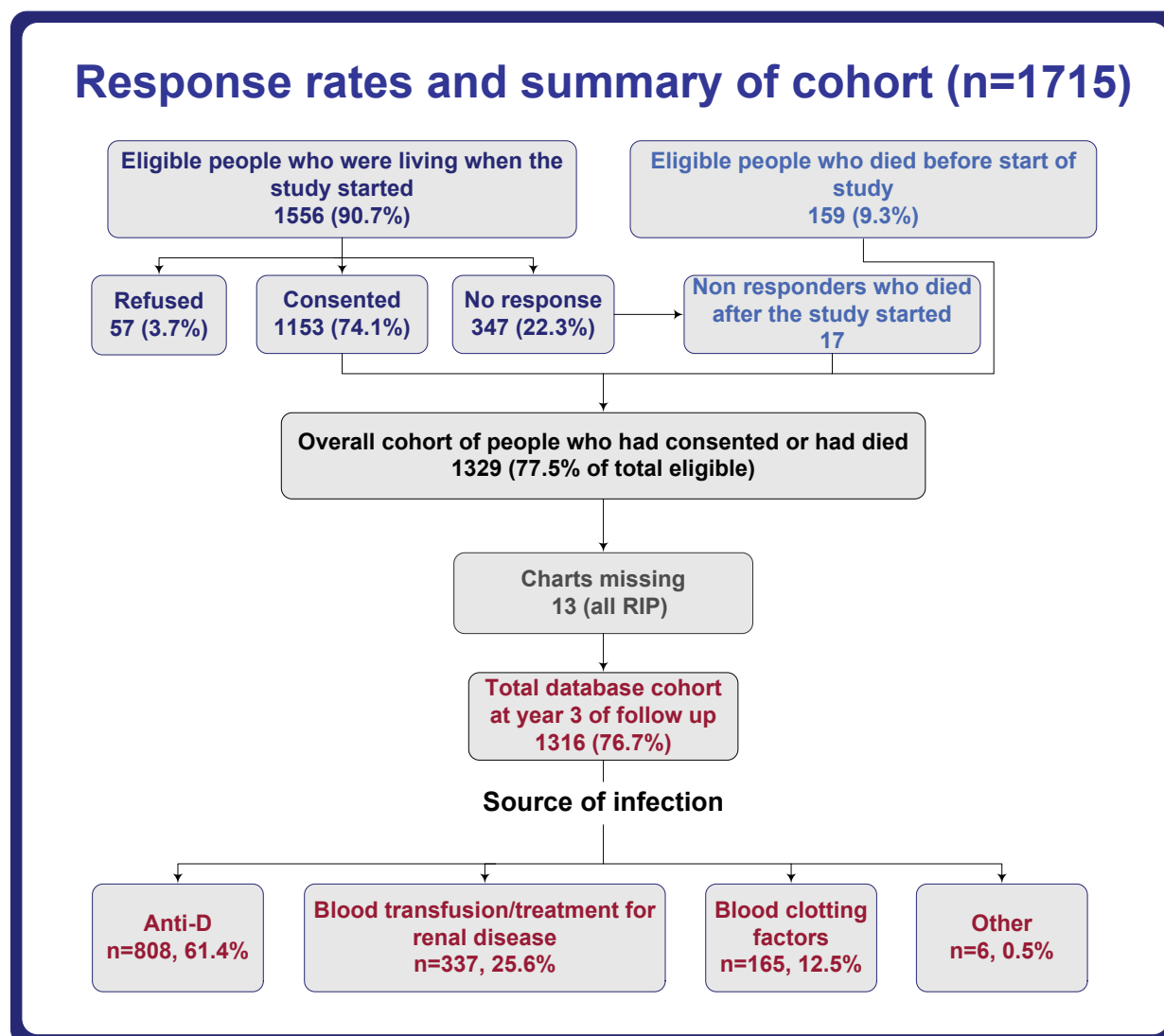


Figure 3. Participation rates and database cohort

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

The anti-D group includes 679 participants infected in the 1977-1979 outbreak, 73 participants infected in the 1991-1994 outbreak, 51 participants infected during non outbreak years and 5 participants infected in outbreak years, but who had a different HCV genotype to the outbreak genotype.

Although we do not have patient-based data on source of infection or gender for non-participants, the hepatology units provide us with summary data to enable us to assess how representative the database population is of the entire eligible population. Database participation varied with age and RNA status, with older people and those who became chronically infected more likely to participate. This difference was statistically significant and was also evident when deceased patients were excluded from the analysis.

Description of database population

RNA results

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

As the vast majority of participants were diagnosed some years after infection, ever testing RNA positive was found to be an excellent indicator of chronic long-term infection. Throughout this report, we treat participants who ever tested RNA positive as having been chronically infected with HCV and these participants are the primary focus when looking at clinical outcomes and disease progression to date.

We have no way of knowing the timing of viral clearance for participants who cleared the virus spontaneously prior to HCV testing (and thus had no positive RNA results). However, studies have found that spontaneous viral clearance usually occurs within a year of infection, so we assumed that these participants experienced acute infection only and were never chronically infected.^{22,23}

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 was 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.

Overall, 62% (n=815) of database participants had at least one positive RNA result in their charts (figure 4) and a further 15% (n=194) had positive confirmatory tests for HCV antibodies but no positive RNA results. The remaining 23% (n=307) tested either ELISA/EIA positive or weak positive, or RIBA/INNO-LIA indeterminate, and had no other positive HCV results. People with positive or weak positive ELISA/EIA tests or indeterminate RIBA/INNO-LIA tests were included in the database as many patients were tested many years after suspected infection, 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.^{24,25,26}

Twenty two percent (n=37) of participants infected through clotting factors had no RNA test results in their charts (figure 4). All were deceased and most had died in the early to mid 1990s. RNA tests were only commonly used from 1994 onwards in Ireland. These participants were found to be similar to participants known to be chronically infected in terms of liver-related outcomes and it is likely that a large proportion would have been RNA positive if they had been tested prior to their death.

Once participants with no RNA results were excluded, the overall spontaneous viral clearance rate, as determined by testing RNA negative at the time of first diagnosis, was 36%. This varied by gender and source of infection. Females (n=414, 41%) were significantly more likely to have cleared the virus by the time of their diagnosis than males (n=37, 14%). This gender imbalance remained but was significantly lessened when anti-D participants were excluded (23% for females compared to 14% for males).

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

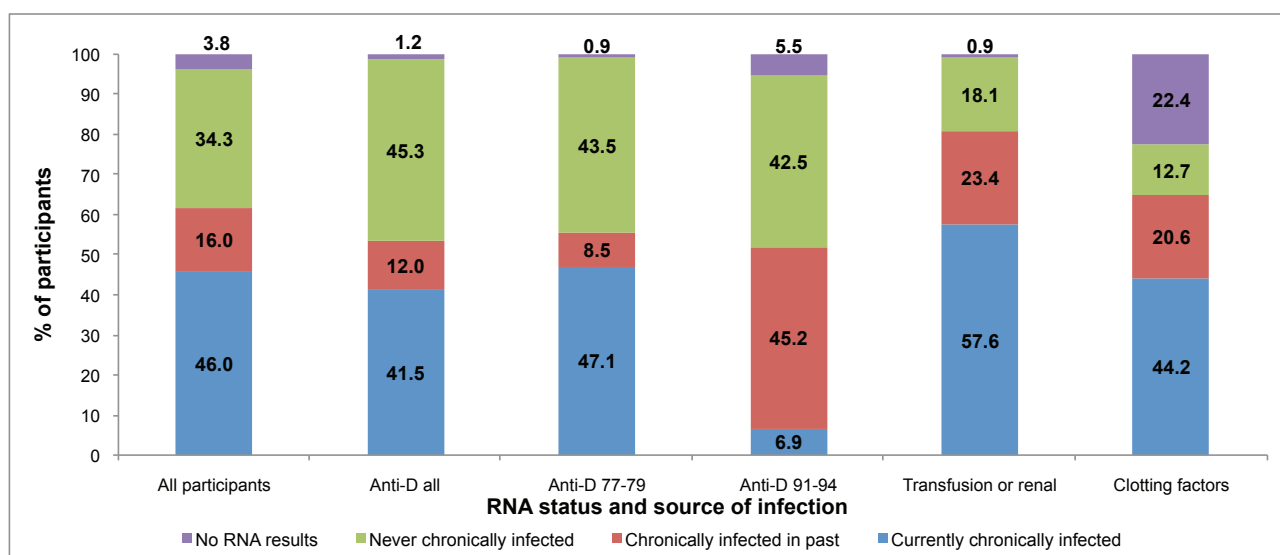


Figure 4. Hepatitis C RNA results for all participants and by source of infection.

End of latest follow-up

Data up to the end of 2009, 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, their last test result or their date of death, as this is the last date when information was recorded in their medical charts.

Seventy six percent of all living database participants had attended their hepatology unit in 2008 or 2009 and a further 3% had been followed up through other services within the same hospital in this time period. The frequency of attendance at the hepatology units varied with RNA status. Eighty eight percent of participants who had ever been chronically infected attended their unit in 2008 or 2009 and a further four percent were followed up through other services in the hospital. Participants who had never become chronically infected were less likely to have attended recently, with 57% attending in 2008 or 2009 and an additional 4% attending other services in the hospital. 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.

Database participants by source of infection

Participants infected through contaminated anti-D immunoglobulin

The anti-D group is entirely composed of females who were infected during their child-bearing years (median age at infection: 28 years) (figure 5, table 13). As a group, they would be expected to have been relatively healthy when infected.

Infection due to contaminated anti-D has been largely traced to batches of anti-D from two infected donors.²⁷ Batches from the first donor were contaminated with genotype 1 HCV and were distributed between 1977 and 1979. Eighty four percent (n=679) 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 five additional participants infected between 1991 and 1994 did not match the outbreak genotype. The estimated year of infection for the remaining fifty one participants was outside of these outbreak periods and sixty seven percent of these (n=34) did not have positive confirmatory results for HCV. The source of their infection is unclear.

By latest follow-up, the median age of anti-D participants who became chronically infected was 58 years and the median duration of RNA positivity was 32 years. Eighty percent had been RNA positive for 25 years or longer.

Participants infected through contaminated blood transfusions or treatment for renal disease

This group was the most heterogeneous in terms of age and gender (figure 5, table 13). They had the highest median age at infection (32), but this ranged from 0 to 77 years. Fifty six percent of chronically infected participants were

female and forty four percent were male, making this the only group with sizeable proportions of each gender. Using the assumptions outlined in chapter 3, most of the blood transfusion/renal participants were infected in the late 1970s and 1980s. They had the shortest duration of RNA positivity at latest follow-up, with 34% positive for 25 years or longer. At latest follow-up, the median age of transfusion/renal participants who became chronically infected was 61 years and the median duration of RNA positivity was 21 years.

Participants infected through contaminated blood clotting factors

Participants infected through clotting factors were predominantly male (93%) and 42% were co-infected with HIV (figure 5). Using the assumptions outlined in chapter 3, most were infected as children in the mid-1970s to early 1980s. The median age at infection was 13 years for the group as a whole and 14 years for those who were chronically infected (table 13). By latest follow-up, the median age for clotting factor participants who became chronically infected was 42 years and the median duration of RNA positivity was 28 years (table 13). Seventy percent were RNA positive for 25 years or longer.

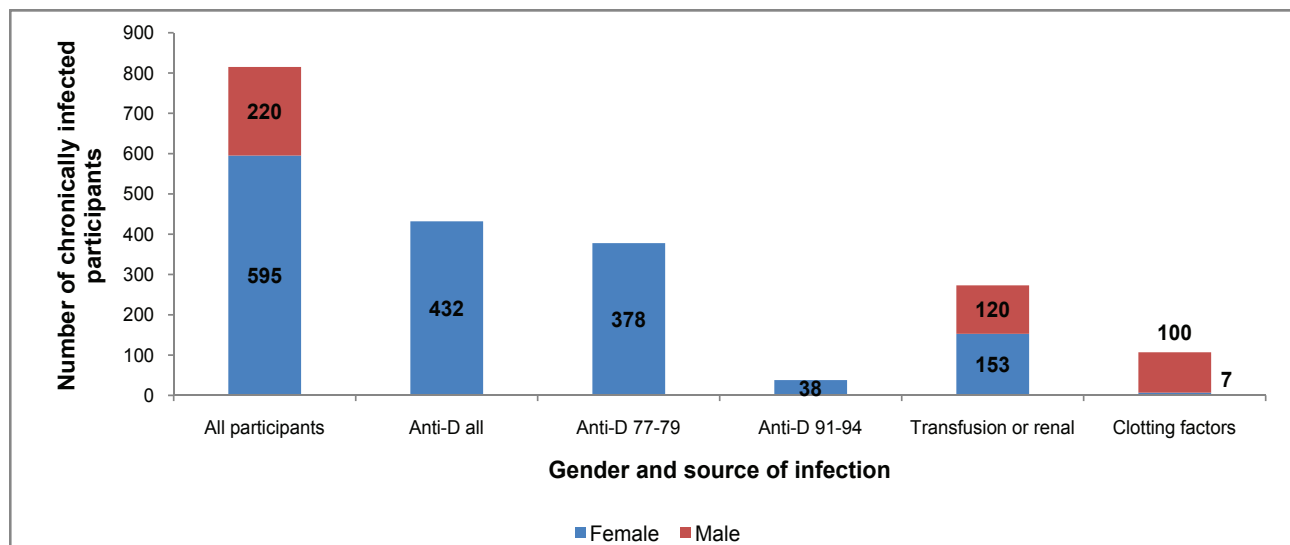


Figure 5. Number of chronically infected participants by gender and source of infection (n=815).

Note: The 'All' category includes 3 participants with "other" sources of infection.

The "Anti-D all" category includes participants infected in non-outbreak years and those with a non-outbreak genotype.

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

Source of infection and RNA status	Age at infection	Age at end of follow up	Duration of infection (years since infection at last follow-up or death)	Duration RNA positivity
	Median (range)	Median (range)	Median (range)	Median (range)
Anti-D	28 (16-44)	57 (26-76)	32 (4-45)	
Ever chronically infected	28 (17-44)	58 (31-76)	32 (9-42)	32 (1-42)
Currently chronically infected	28 (17-44)	59 (33-76)	32 (9-42)	32 (9-42)
Chronically infected in past	28 (18-39)	55 (31-71)	31 (10-33)	18 (1-32)
Never chronically infected	28 (16-43)	57 (26-75)	31 (4-45)	
Anti-D 1977-1979	28 (17-44)	58 (33-76)	32 (17-33)	
Ever chronically infected	28 (17-44)	59 (33-76)	32 (17-33)	32 (15-33)
Currently chronically infected	28 (17-44)	60 (33-76)	32 (17-33)	32 (17-33)
Chronically infected in past	26.5 (18-39)	58.5 (47-71)	32 (27-33)	25 (15-32)
Never chronically infected	28 (17-43)	58 (41-75)	31 (17-33)	
Anti-D 1991-1994	30 (18-39)	46 (26-56)	16 (4-18)	
Ever chronically infected	30 (19-39)	46 (31-56)	16 (10-18)	6 (1-18)
Currently chronically infected	26 (23-30)	43 (34-48)	18 (11-18)	18 (11-18)
Chronically infected in past	30 (19-39)	46 (31-56)	16 (10-18)	5 (1-15)
Never chronically infected	31 (18-39)	45 (26-56)	14 (4-18)	
Transfusion or renal	32 (0-77)	61 (16-91)	23 (1-48)	
Ever chronically infected	32 (0-77)	61 (16-91)	24 (1-48)	21 (1-46)
Currently chronically infected	35 (0-77)	63 (19-61)	23 (1-46)	23 (1-46)
Chronically infected in past	27 (0-66)	53 (16-83)	25 (13-48)	18 (4-39)
Never chronically infected	34 (0-63)	60 (16-91)	22 (7-38)	
Clotting factors	13 (0-59)	42 (12-81)	27 (8-50)	
Ever chronically infected	14 (0-53)	44 (18-81)	31 (14-50)	28 (4-50)
Currently chronically infected	15 (0-53)	46 (18-81)	31 (14-50)	31 (14-50)
Chronically infected in past	12.5 (0-33)	43 (30-66)	32 (17-40)	25 (4-40)
Never chronically infected	12 (0-38)	39 (19-71)	28 (11-38)	
All	28 (0-77)	57 (12-91)	30 (1-50)	
Ever chronically infected	28 (0-77)	57 (16-91)	31 (1-50)	30 (1-50)
Currently chronically infected	28 (0-77)	59 (18-91)	32 (1-50)	32 (1-50)
Chronically infected in past	27 (0-66)	53 (16-83)	28 (10-48)	19 (1-40)
Never chronically infected	28 (0-63)	57 (15-91)	30 (4-45)	

Genotype

The HCV genotype was available for nearly all of the database participants who became chronically infected (n=776, 95%). Genotype 1 predominated: 76% (n=593) were infected with genotype 1, 18% (n=143) were infected with genotype 3, 5% (n=36) were infected with genotype 2 and four participants were infected with genotypes 4 or 5 (figure 6).

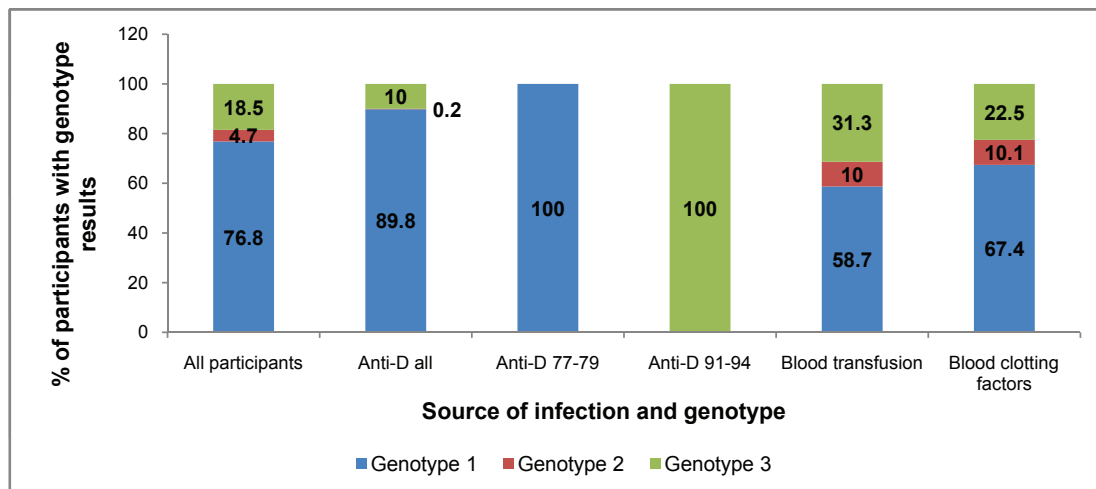


Figure 6. Distribution of hepatitis C genotypes by source of infection (n=772, genotypes 4 & 5 omitted, n=4)

Alcohol consumption

At the time of this study, 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.²⁸ (Note: Low-risk drinking guidelines have been revised and are now defined as 11 standard drinks for women and 17 standard drinks for men, per week.²⁹)

Participants consuming between these limits (21 for males, 14 for females) and 40 units per week were classified as having moderately high alcohol intake and those consuming over 40 units were classified as having high alcohol intake. Some data on units of alcohol were available for 93% of those who became chronically infected. However, it is unusual for alcohol consumption to have been recorded at every visit, and in many cases it was last recorded many years ago. Alcoholic liver disease or alcohol abuse was also mentioned in the charts of some participants. This additional information was combined with alcohol intake data when looking at the effects of alcohol on disease progression and these participants were considered to have had high alcohol intake at some stage. Alcohol intake in excess of the recommended limits was recorded in the medical charts of 15% of chronically infected participants for whom data were available (table 14).

Table 14. Highest recorded alcohol intake for all database participants and by RNA status (where data available, n=1193, 93%)*

Alcohol consumption	All		Ever chronically infected		Currently chronically infected		Chronically infected in past		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%	Num	%
Non drinker	296	24.8	183	24	143	25.4	40	20.1	107	25.9
Within recommended limits	739	61.9	461	60.6	329	58.5	132	66.3	270	65.4
Moderately high	76	6.4	54	7.1	37	6.6	17	8.5	21	5.1
High	82	6.9	63	8.3	53	9.4	10	5	15	3.6
Total	1193		761		562		199		413	

* No alcohol intake data for 123 database participants. RNA status not known for 19 participants with alcohol intake data. Data for these participants shown under the "All" category, but not by RNA status

Differences in alcohol consumption by gender and source of infection

Males and females differed in their reported exposure to alcohol with 32% (n=62) of chronically infected males exceeding the recommended limits for alcohol intake compared to 10% (n=55) of females (figure 7). Younger participants were also more likely to drink alcohol in excess of recommendations. Alcohol consumption differed by source of infection with participants infected through anti-D significantly less likely to consume alcohol in excess of recommendations compared to those infected through other means (figure 8). However, this is likely to be largely attributable to the differences in age and gender by source of infection.

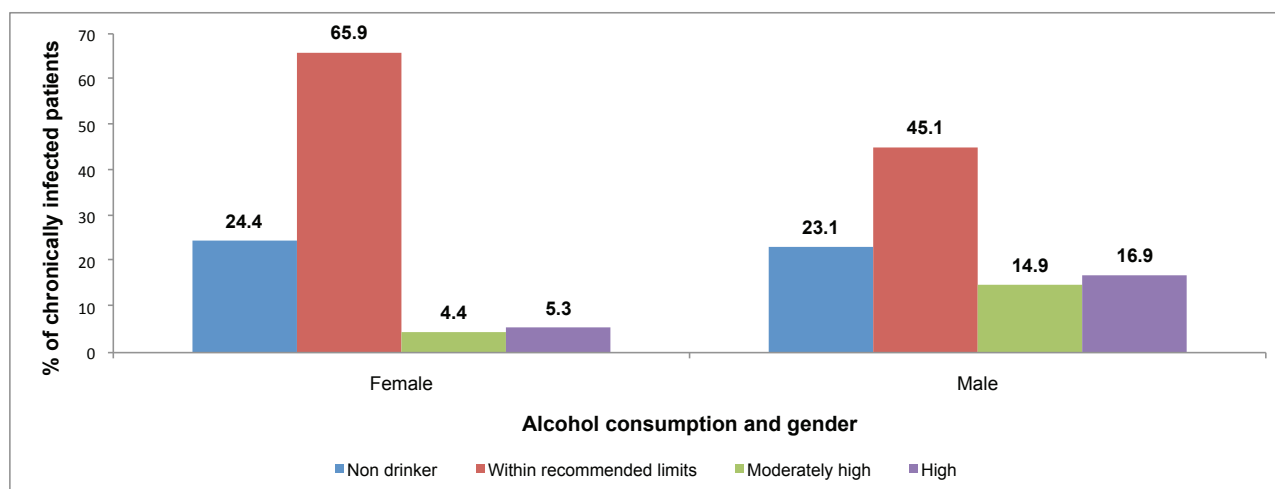


Figure 7. Distribution of highest reported alcohol consumption by gender for participants who became chronically infected (where data available, n=761, 93%)

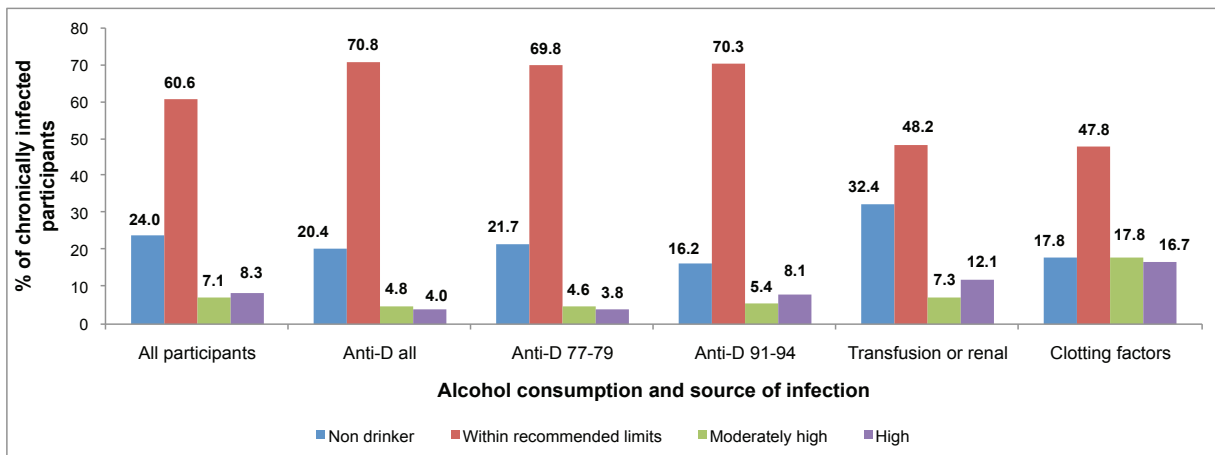


Figure 8. Distribution of highest reported alcohol consumption by source of infection for participants who became chronically infected (where data available, n=761, 93%).

Outcomes

Clinical signs of liver disease

One hundred and eighty seven (14.2%) participants had one or more clinical signs of liver disease recorded in their charts at latest follow-up. Eighty percent of these (n=149) were currently chronically infected, 14% (n=26) were chronically infected in the past, 4% (n=7) had no RNA results in their charts and 3% (n=5) never tested RNA positive. The most common conditions or signs recorded were cirrhosis, varices, portal hypertension and ascites. (See table 15 for a list of clinical signs included).

Table 15. Number and percentage of participants with clinical signs of liver disease by RNA status*

Clinical signs of liver disease	All		Ever chronically infected		Currently chronically infected		Chronically infected in past		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%	Num	%
Cirrhosis	142	10.8	137	16.8	118	19.5	19	9.1	0	0.0
Varices	68	5.2	66	8.1	60	9.9	6	2.9	0	0.0
Portal hypertension	58	4.4	57	7.0	49	8.1	8	3.8	0	0.0
Ascites	57	4.3	53	6.5	50	8.3	3	1.4	3	0.7
Hepatomegaly or splenomegaly or both	65	4.9	61	7.5	53	8.8	8	3.8	4	0.9
HCC	34	2.6	32	3.9	31	5.1	1	0.5	0	0.0
Encephalopathy	25	1.9	23	2.8	22	3.6	1	0.5	1	0.2
Decompensated liver disease	12	0.9	11	1.3	10	1.7	1	0.5	0	0.0
Hypersplenism	4	0.3	4	0.5	3	0.5	1	0.5	0	0.0
Hepatorenal syndrome	1	0.1	1	0.1	1	0.2	0	0.0	0	0.0
Portal gastropathy	1	0.1	1	0.1	1	0.2	0	0.0	0	0.0
Hepatosynthetic 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
One or more signs of liver disease	187	14.2	175	21.5	149	24.6	26	12.4	5	1.1

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

Cirrhosis

By latest follow-up, 17% (n=137) of ever chronically infected participants had developed cirrhosis (table 15). Eighty six were female (15% of ever RNA positive females) and fifty one were male (23% of ever RNA positive males) (table 16). Five deceased participants with no RNA results in their charts had also developed cirrhosis. For ever chronically infected database participants, the median duration of RNA positivity at the estimated date of cirrhosis (see chapter

3 re methods used) was 24 years and the median age at cirrhosis was 53 years. There were no cases of cirrhosis in those who never developed chronic HCV infection.

The number of participants with cirrhosis has increased by 26 since the last round of data collection. Sixteen were diagnosed with cirrhosis in 2009, four were new database participants who had died, all of whom were diagnosed with cirrhosis in 2008, and the remaining six had previous comments relating to potential cirrhosis which were since clarified.

Note: A diagnosis of cirrhosis was assigned if cirrhosis was mentioned in the patient's medical chart (whether ever diagnosed by biopsy, ultrasound scan, CT scan etc) or on death certificate. Based on biopsy results alone, 86 of 679 chronically infected participants (13%) ever had a diagnosis of cirrhosis.

After RNA status, alcohol consumption was the biggest determinant of risk of cirrhosis in the database cohort. Where alcohol data were recorded, 23% 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 5% of ever chronically infected participants without cirrhosis. Factors independently associated with cirrhosis were: current chronic infection compared to past chronic infection (or longer duration of infection) (figure 9), male gender, high alcohol intake and genotype 3 infection. The prevalence of cirrhosis also varied by source of infection, with participants infected through transfusions or treatment for renal disease significantly more likely to have developed cirrhosis compared to those infected through anti-D (table 16).

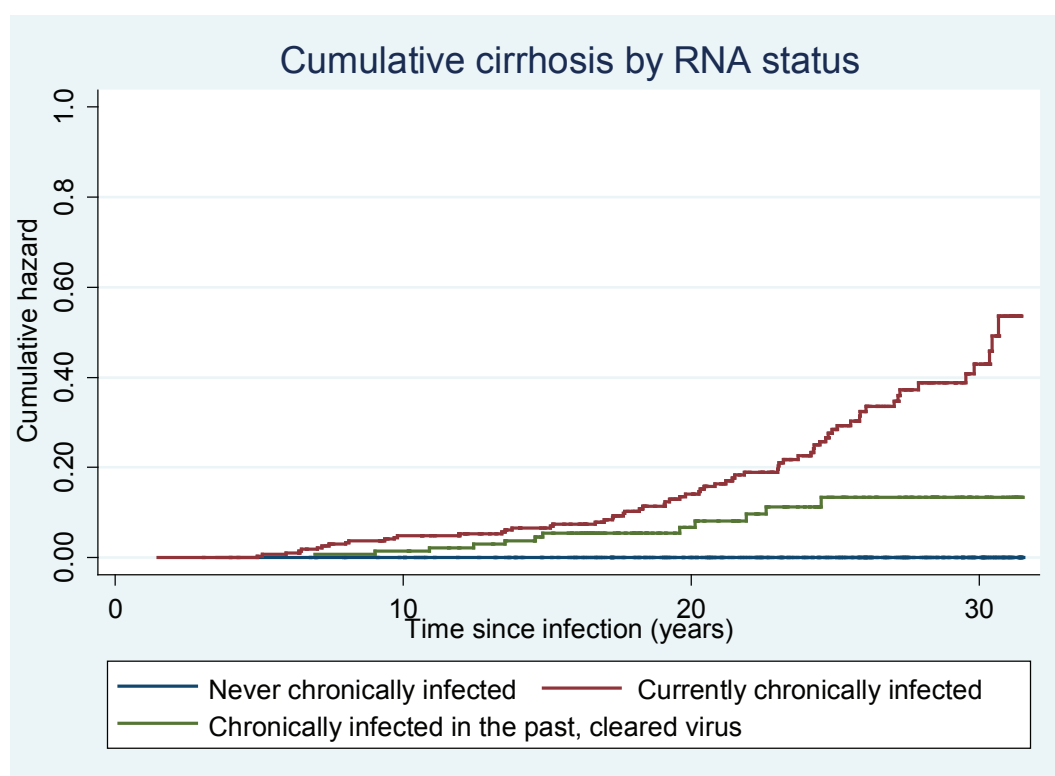


Figure 9. Comparison of rates of cirrhosis for participants who are currently chronically infected, were chronically infected in the past and have since cleared the virus, and those who were never chronically infected.

Table 16. Summary of cirrhosis by gender and source of infection for ever chronically infected participants

Source of infection	Number with cirrhosis	% with cirrhosis	% of those with cirrhosis with high alcohol consumption	Median age at cirrhosis in years (range)	Median duration RNA positivity at cirrhosis in years (range)
Gender					
Females	86	14.5	19.8	55 (24-81)	24 (6-46)
Males	51	23.2	29.8	51 (23-79)	22 (5-38)
Source of infection					
Anti-D	49	11.3	18.4	52 (38-70)	24 (7-33)
Transfusion or renal	70	25.6	21.4	55.5 (23-81)	20.5 (1-46)
Clotting factors	17	15.9	29.4	45 (31-61)	27 (13-38)

Hepatocellular carcinoma (HCC)/liver cancer

By latest follow-up, 32 (4%) ever chronically infected participants and two participants with no RNA results had developed HCC or liver cancer (figure 10). This is an additional nine participants compared to the previous round of follow-up data collection. All were diagnosed with HCC in 2009. There were no cases of HCC in those who never developed chronic infection.

The prevalence of HCC was significantly higher in chronically infected males (n=20, 9%) compared to chronically infected females (n=12, 2%). Chronically infected participants infected through blood transfusions/treatment for renal disease and those infected through contaminated clotting factors were also significantly more likely to have developed HCC compared to those infected through contaminated anti-D (table 17). Where alcohol data were available, eight (28%) of those with HCC had high alcohol intake at some stage.

Twenty seven (79%) of the participants with HCC were known to be deceased. The cause of death was directly liver-related for twenty two, not liver-related for three and the death certificate was missing for the remaining two participants. The median duration of infection at the time of HCC diagnosis was 27.5 years (range: 5-40 years) and the median age at diagnosis of HCC was 63 years (range: 43-82 years). (See chapter 3 re methods used).

The median time from estimated date of diagnosis of cirrhosis to estimated date of diagnosis of HCC was three years. Cirrhosis was not specifically mentioned in the charts or on the death certificates of five of the participants with HCC. However, two of these participants had ascites and one had varices. See section on liver transplants below.

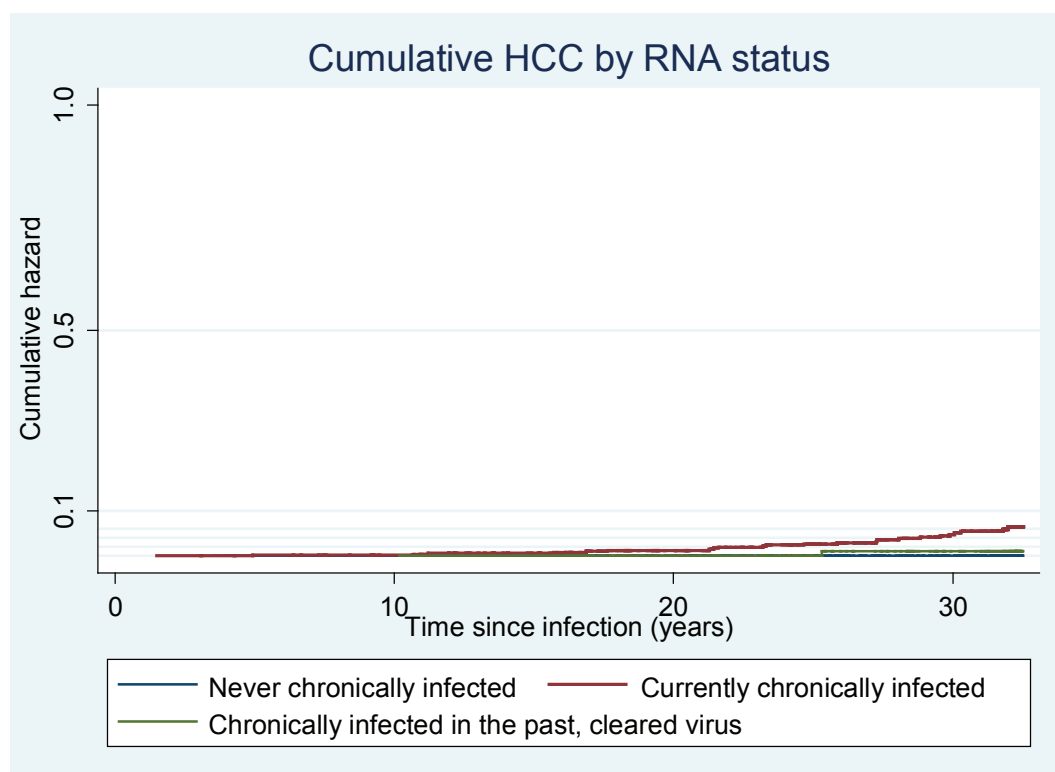


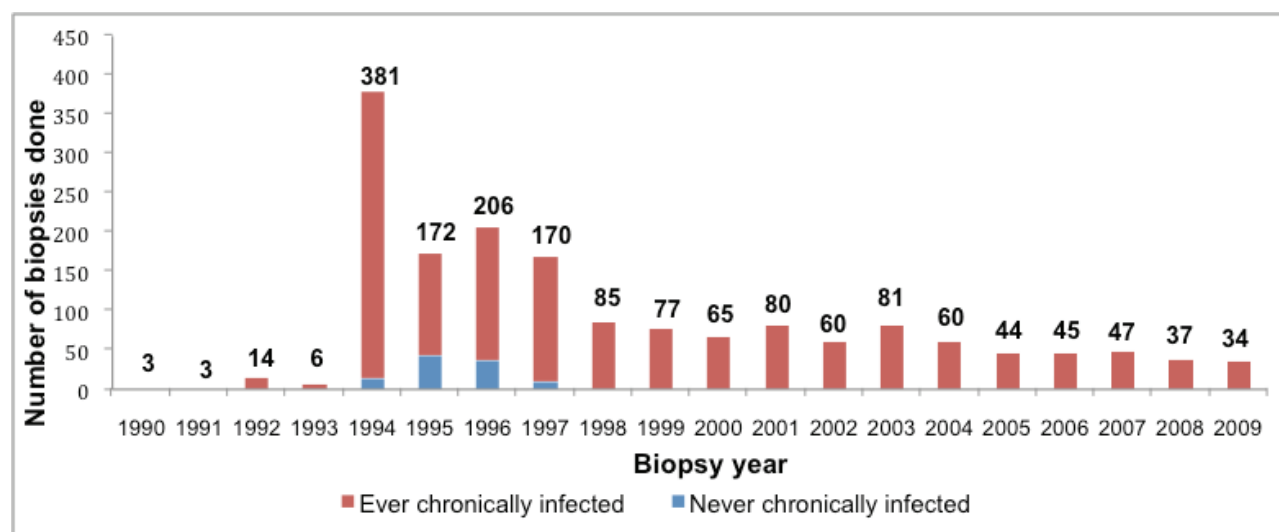
Figure 10. Comparison of rates of HCC for participants who are currently chronically infected, were chronically infected in the past and have since cleared the virus, and those who were never chronically infected.

Table 17. Summary of HCC by gender and source of infection for ever chronically infected participants.

Gender and source of infection	Number with HCC	% with HCC	Median age at HCC in years (range)	Median duration RNA positivity at HCC in years (range)
Gender				
Females	12	2.0	67 (47-74)	29.5 (21-40)
Males	20	9.1	61.5 (43-82)	24 (5-38)
Source of infection				
Anti-D	5	1.2	66 (47-68)	30 (27-32)
Transfusion or renal	21	7.7	70 (44-82)	25 (5-40)
Clotting factors	6	5.6	54.5 (43-63)	28.5 (22-38)

Liver biopsy results

Most of the liver biopsies were carried out in the mid to late 1990s, with much smaller numbers being done in more recent years (figure 11). Thirty seven participants had a biopsy in 2008 and thirty four had a biopsy in 2009. Overall, the likelihood of having a biopsy varied by RNA status with 83% (n=679) of chronically infected participants having a biopsy compared to 24% (n=110) of those with no positive RNA results. Participants infected through contaminated clotting factors were least likely to have had biopsies, with only 37% (n=40) of those ever testing RNA positive having biopsy results in their charts compared to 96% (n=415) of chronically infected anti-D participants and 81% (n=222) of those infected through blood transfusions or treatment for renal disease. Disease progression may be more likely to be monitored using ultrasounds, CT scans and other tests for participants infected through clotting factors and the available biopsy results in these participants are not likely to be a good indicator of disease status or progression.

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

Inflammation

Of the 1,679 liver biopsies carried out, inflammation grade was available for 99%. Twenty six percent (n=178) of ever chronically infected participants had moderate or severe inflammation on last biopsy compared to 1% (n=1) of participants who did not become chronically infected. 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 23% of anti-D participants and 23% of participants infected through clotting factors.

Fibrosis

Of the 1,679 liver biopsies carried out, fibrosis scores were available for 91%. Fibrosis was scored using different scoring systems in different hepatology units. Overall 78% of biopsies were scored using a 0-6 scoring system, and a 0-4 system was used for the remaining 22%. Biopsy results scored from 0 to 6 were converted to the 0 to 4 scores (see chapter 3 for details) for some analyses to allow all biopsy results to be analysed together.

We considered high fibrosis scores to be scores of 4-6 on biopsies scored from 0-6 and scores of 3-4 on biopsies scored from 0-4. Nineteen percent (n=127) of chronically infected participants had a high fibrosis score on their most recent biopsy (where fibrosis score was recorded, n=653) compared to 4% (n=4) of those who never tested RNA positive (where fibrosis score was recorded, n=104). Fibrosis also varied by source of infection. Thirty two percent (n=66) of chronically infected blood transfusion or renal participants had a high fibrosis score on most recent biopsy compared to 23% (n=9) of clotting factor participants and 13% (n=52) of anti-D participants (figure 12).

Aside from chronic infection, risk factors independently associated with ever having a high fibrosis score on biopsy were: male gender, older age at last biopsy (55+ compared to less than 55 years), genotype 3 infection (compared to genotype 1 infection) and ever having high levels of alcohol consumption.

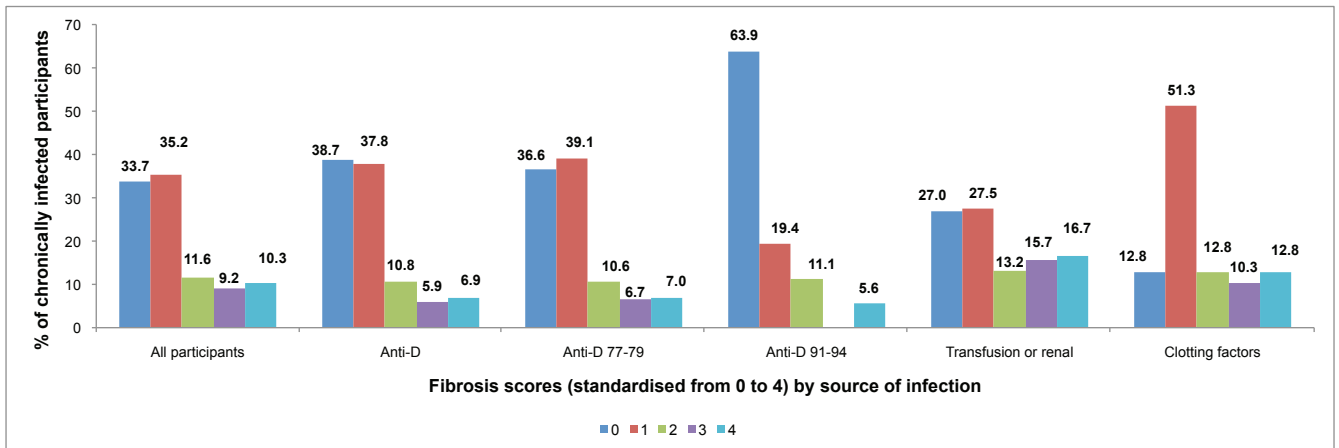


Figure 12. Fibrosis score* on last biopsy for chronically infected participants by source of infection (n=653).

*All 0-6 scores standardised to 0-4 (see chapter 3 for description) to allow all biopsies to be analysed together.

Note: results for clotting factor participants are not representative as data are only available for 39 and the last biopsy was several years ago for many patients.

Changes in biopsy results post treatment

Eighty seven 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 13. Fibrosis scores improved for 57% (n=12) of those who achieved sustained virological response (SVR) on treatment compared to 35% (n=23) of those who did not.

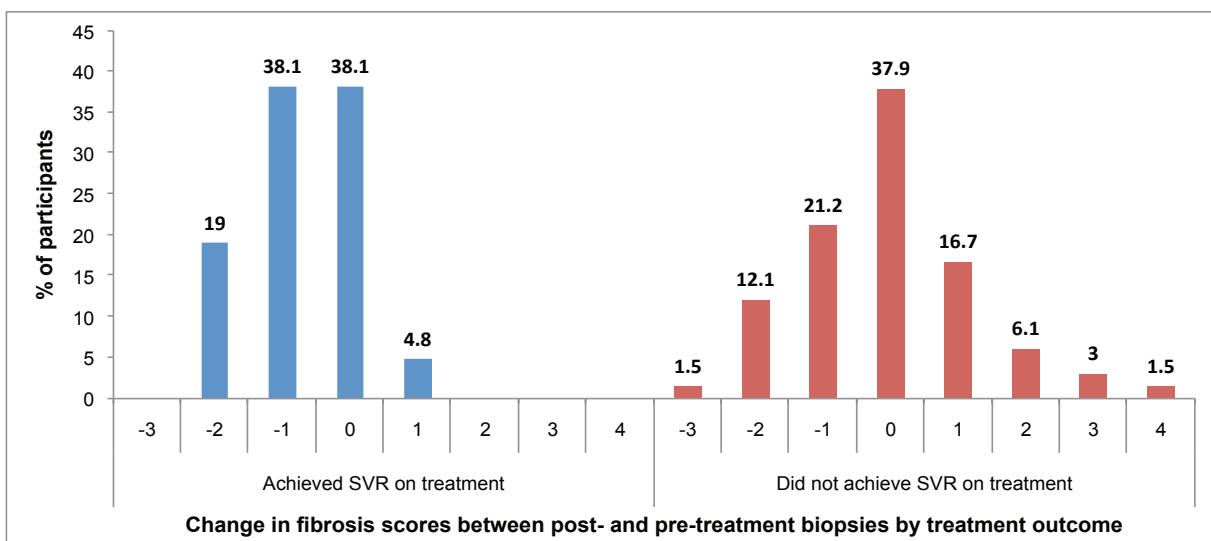


Figure 13. Changes in fibrosis scores (0-4) after treatment, by SVR status for participants who had pre- and post-treatment biopsy results (n=87).

*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.

Liver function tests – alanine aminotransferase (ALT)

Ninety five percent of database participants had at least one ALT result in their charts and 71% had two or more tests done. Levels were elevated on at least one test for 74% of currently chronically infected participants, 33% of participants who were chronically infected in the past and have since cleared the virus and 14% of those with no positive RNA results. Twenty five percent of currently chronically infected participants had ALT levels 2.5 or more times the upper normal limit on at least one test compared to 9% of those who were chronically infected in the past and 2% of those who never became chronically infected.

In addition to chronic infection, the independent risk factors for ever having elevated ALT levels, and for having ALT levels 2.5 or more times the upper normal limit on any test, were current chronic infection (compared to past chronic infection) and male gender. Participants infected through clotting factors had the highest ALT levels but this may be due to high proportion of males in this group. Table 18 shows the highest ALT results by RNA status, gender and source of infection.

Table 18. Highest alanine amino transferase results by RNA status, gender and source of infection

Alanine aminotransferase results	Ever chronically infected (%)	Currently chronically infected (%)	Chronically infected in past (%)	Never chronically infected (%)
Females				
Normal	39.6	29.1	71.7	87.4
Elevated: <2.5 times upper normal limit	41.1	47.5	21.4	10.4
Elevated: ≥2.5 times upper normal limit	19.3	23.3	6.9	2.2
Males				
Normal	28.9	18.1	55	73.5
Elevated: <2.5 times upper normal limit	45.1	50.7	31.7	23.5
Elevated: ≥2.5 times upper normal limit	26	31.3	13.3	2.9
Anti-D				
Normal	35.2	25.1	70.5	86.9
Elevated: <2.5 times upper normal limit	45.5	52.4	21.1	10.6
Elevated: ≥2.5 times upper normal limit	19.3	22.5	8.4	2.5
Transfusion or renal				
Normal	42.5	33.2	64.6	86.4
Elevated: <2.5 times upper normal limit	35.7	39.6	26.6	11.9
Elevated: ≥2.5 times upper normal limit	21.8	27.3	8.9	1.7
Clotting factors				
Normal	27.8	12.1	61.3	73.7
Elevated: <2.5 times upper normal limit	45.4	53	29	26.3
Elevated: ≥2.5 times upper normal limit	26.8	34.8	9.7	0

Deceased participants

Two hundred and twelve participants had died by latest follow-up. This represents twenty five additional deceased participants compared to the previous round of follow-up data collection. Seventeen died in 2009, three died in 2008, three died in earlier years but were newly identified as deceased, and date of death was not available for the remaining two. All cause mortality rates varied significantly by RNA status: 23% of currently chronically infected participants were deceased by latest follow-up compared to 4% of participants who were chronically infected in the past and had since cleared the virus (mostly through treatment) and 6% of participants who never became

chronically infected (figure 14). All cause mortality was also significantly higher in males or participants infected through blood transfusions or clotting factors and those who had high alcohol intake.

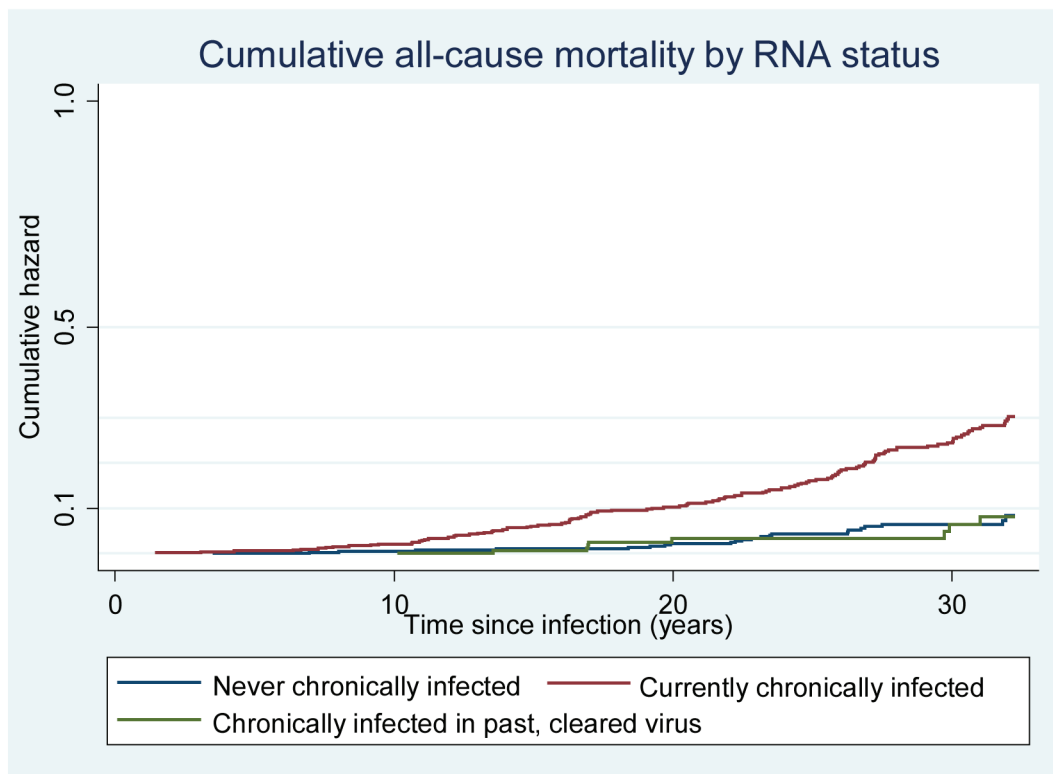


Figure 14. Comparison of liver-related mortality rates for participants who are currently chronically infected, were chronically infected in the past and have since cleared the virus, and those who were never chronically infected.

Where death certificates were available (n=199), death was directly caused by liver disease for 55 participants. The causes of death for these 55 were:

- liver cell carcinoma (n=20)
- cirrhosis of the liver (n=15)
- liver failure (n=10) (one caused by hepatitis B)
- chronic viral hepatitis C (n=4)
- hepatorenal failure (n=2)
- oesophageal varices (n=2)
- toxoplasma hepatitis (n=1)
- hepatic encephalopathy (n=1).

HCV infection was one of the causes of death listed on the first part of the death certificate for forty 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.

Liver-related mortality was significantly higher in participants who were currently chronically infected with HCV (n=43, 7.2%) and those with no RNA results in their charts (n=8, 17.4%) compared to those who never became chronically infected (n=2, 0.4%) and those who had been chronically infected in the past and had since cleared the virus (mostly through treatment) (n=2, 1%) (figure 15).

High alcohol intake was a highly significant predictor of liver-related mortality. Information on alcohol consumption was available for 82% of those whose death was caused by liver disease. Forty four percent had indicators of high levels of alcohol consumption in their medical charts. Liver-related mortality rates were also higher in males and in those infected through blood transfusions or clotting factors.

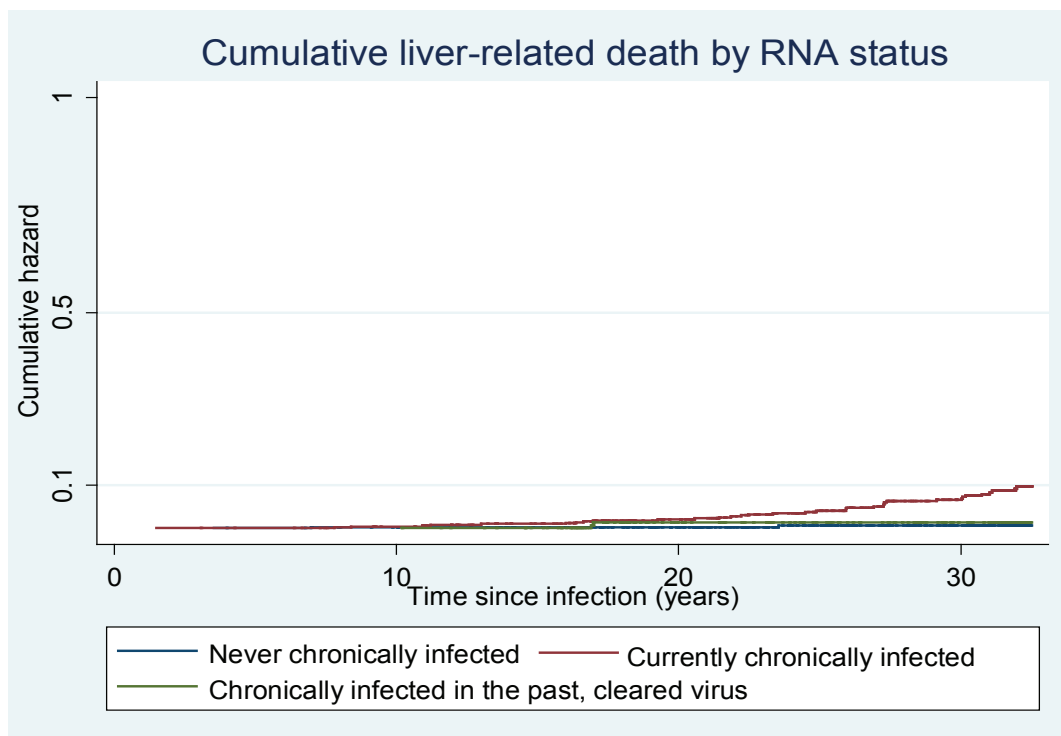


Figure 15. Comparison of liver-related mortality rates for participants who are currently chronically infected, were chronically infected in the past and have since cleared the virus, and those who were never chronically infected.

Table 19. Number and percentage of ever chronically infected participants who died directly from liver-related disease, by gender and source of infection

Gender and source of infection	Number who died directly from liver-related disease	% who died directly from liver-related disease	Median age at death	Median duration RNA positivity at death in years (range)
Gender				
Females	24	4.1	62.5 (37-74)	27 (11-41)
Males	21	9.8	54 (39-82)	22 (8-38)
Source of infection*				
Anti-D	11	2.6	54 (44-69)	30 (19-32)
Transfusion or renal	21	7.8	71 (43-82)	21 (8-41)
Clotting factors	12	11.3	47.5 (37-58)	26 (16-38)

*Information relating to source of infection was missing on one participant who died directly from liver-related disease

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

HCV disease progresses particularly after two to four decades of infection.⁶ The median time since infection for the database population is now 30 years and the median duration of RNA positivity for those who became chronically infected is also 30 years (currently RNA positive: 32 years, RNA positive in past: 19 years). This is the fourth round of data collection and increases can be seen in the prevalence of liver-related health outcomes since baseline data were collected (figure 16).

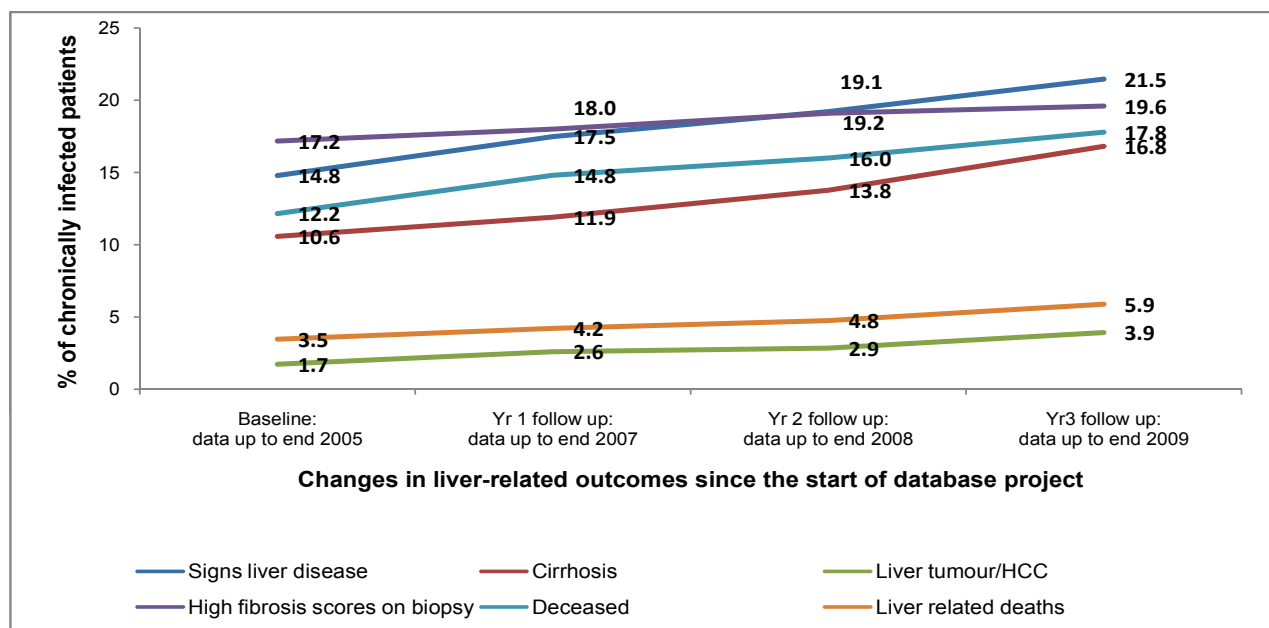


Figure 16. Changes in the prevalence of all cause mortality and liver-related outcomes for chronically infected participants since baseline data were collected.

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

Summary of disease progression and factors associated with disease severity

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

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

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

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

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

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

Using these criteria, 31% (n=190) of currently chronically infected participants, 20% (n=43) of participants who were chronically infected in the past, 22% (n=11) of those with no RNA results and 2% (n=7) of those who were never chronically infected were classified as having severe liver disease by latest follow-up.

Tables 20 and 21 show the effects of some key host and virus characteristics on the odds of having severe liver disease. Only participants who tested RNA positive at some stage (ever chronically infected) were included in these analyses as 93% of the participants with severe disease had tested RNA positive at some stage and this approach allowed the effects of genotype to be assessed.

The determinants of having severe liver disease in the database cohort were high alcohol intake, older age at end of latest follow-up, male gender, longer duration of RNA positivity and HCV genotype 3 (table 20). Table 21 shows the same model with source of infection substituted for gender. These factors cannot be assessed together using a logistic regression model as gender is too closely linked to source of infection in the database population. This model indicates that participants infected through blood transfusions/treatment for renal disease and those

infected through clotting factors were more likely to have severe liver disease by latest follow-up compared to those infected through anti-D. All associations between these characteristics and severe liver disease were statistically significant and the influence of each of these factors on disease severity was independent of the effects of all of the other factors in the table.

The most important factor in disease progression was alcohol intake. Participants who had high alcohol intake had more than five times higher odds of having severe disease compared to those without. However, the number of chronically infected database participants with high alcohol intake was low (n=63, 8.3%) and due to its sensitivity, alcohol consumption data may be inaccurately reported. Figures 17 and 18 show the prevalence of severe liver disease by duration of RNA positivity, alcohol intake, gender and source of infection.

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

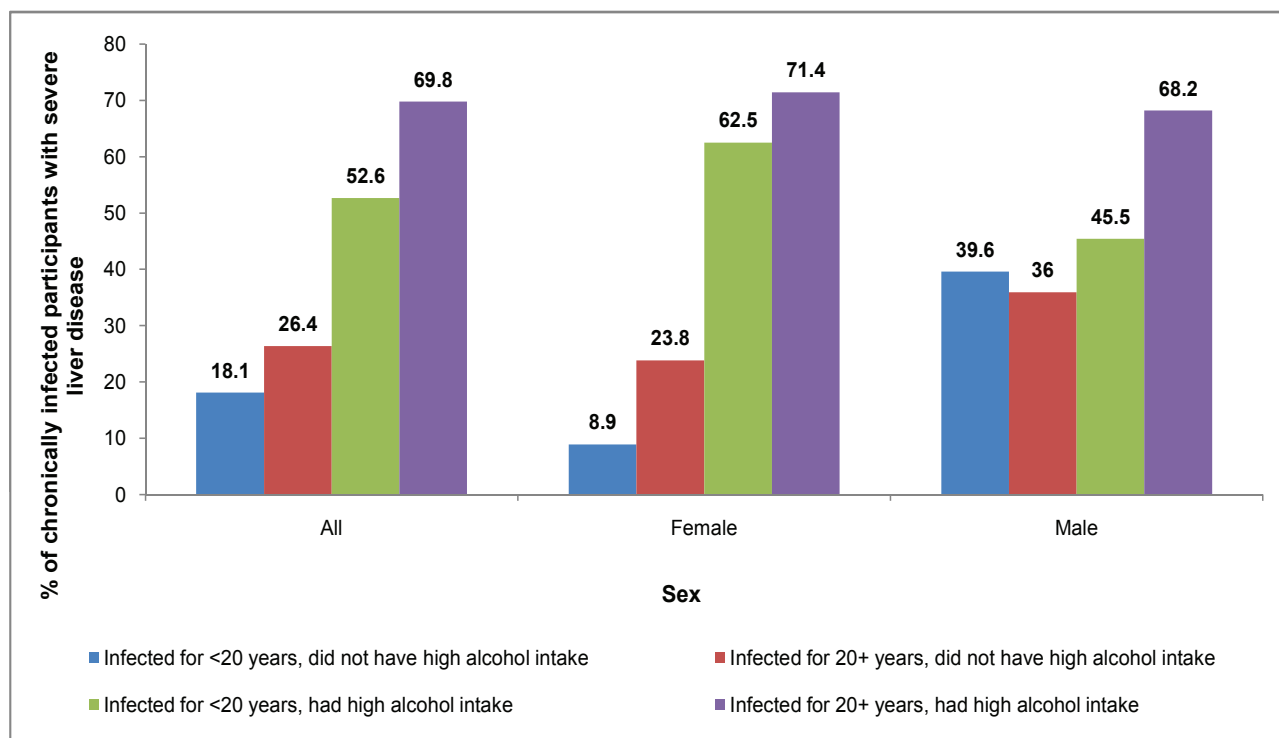
Table 20. Factors associated with severe liver disease in chronically infected participants - logistic regression model including gender (n=727)

Factors associated with having severe liver disease	Odds Ratio	P-value	95% Confidence interval
Alcohol consumption			
Non drinker/within recommended limits/moderately high	1	Reference	Reference
High (>40 units per week or alcohol abuse in chart)	5.6	<0.001	3.02 - 10.52
Age at end of latest follow-up			
<50 years	1	Reference	Reference
50 to 64 years	2.7	<0.001	1.60 - 4.55
65+ years	3.7	<0.001	2.11 - 6.53
Gender			
Female	1	Reference	Reference
Male	2.8	<0.001	1.83 - 4.37
Genotype			
Genotype 1	1	Reference	Reference
Genotype 2	0.9	0.762	0.35 - 2.14
Genotype 3	2.2	0.002	1.32 - 3.61
Duration of RNA positivity			
<20 years	1	Reference	Reference
20+ years	2.2	0.002	1.32 - 3.58

Table 21. Factors associated with severe liver disease in chronically infected participants - logistic regression model including source of infection (n=725).

Factors associated with having severe liver disease	Odds Ratio	P-value	95% Confidence interval
Alcohol consumption			
Non drinker/within recommended limits/moderately high	1	Reference	Reference
High (>40 units per week or alcohol abuse in chart)	5.5	<0.001	2.97 - 10.36
Age at end of latest follow-up			
<50 years	1	Reference	Reference
50 to 64 years	2.2	0.003	1.31 - 3.66
65+ years	2.6	0.001	1.47 - 4.55
Source of infection			
Anti-D	1	Reference	Reference
Transfusion or renal	2.8	<0.001	1.85 - 4.35
Clotting factors	2.1	0.025	1.09 - 3.93
Genotype			
Genotype 1	1	Reference	Reference
Genotype 2	0.6	0.286	0.25 - 1.51
Genotype 3	1.9	0.016	1.12 - 3.10
Duration of RNA positivity			
<20 years	1	Reference	Reference
20+ years	2.4	0.001	1.47 - 4.02

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

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

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

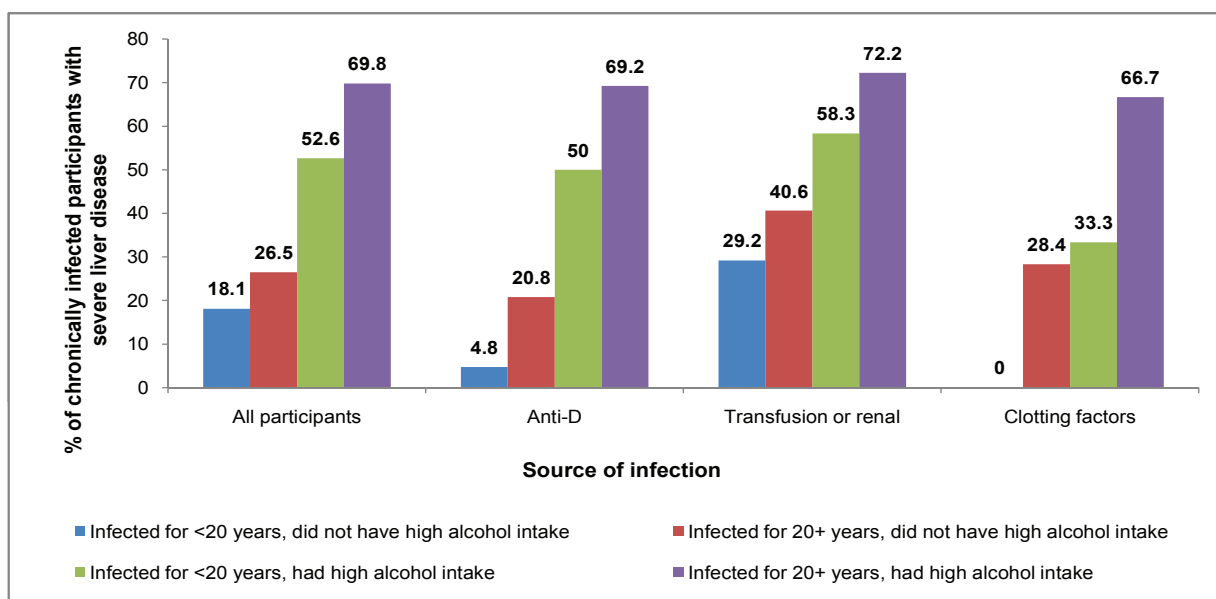


Figure 18. Percentage of chronically infected participants with severe liver disease by source of infection, duration of RNA positivity and alcohol consumption

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

Anti-viral treatment for hepatitis C

Forty two percent (n=344) of chronically infected participants had one or more courses of anti-viral treatment by latest follow-up. Participants stopping treatment early are included when calculating sustained virological response (SVR). The SVR rate has improved in recent years with the advent of combination therapy with pegylated interferon (peg-IFN) and ribavirin (RBN) (figure 19). Tolerance of anti-viral treatment remains an issue, with 24% (n=104) of all treatment courses stopped early due to side-effects. The percentage stopping treatment early was lower for combination therapy with peg-IFN and RBN (17%, n=32) than for combination therapy with IFN and RBN (28%, n=24) or monotherapy with IFN or peg-IFN (28%, n=48).

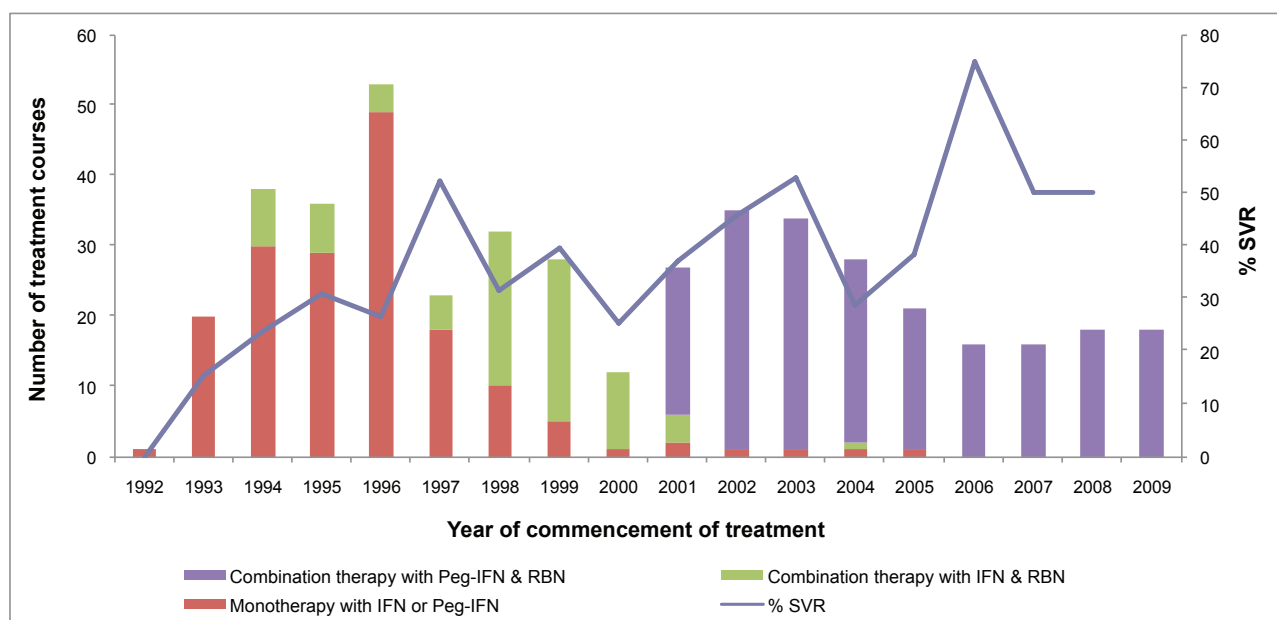


Figure 19. Treatment courses by type of treatment and percentage sustained virological response, 1992-2009

Note: Outcome is awaited for 13 participants who were treated in 2009 and 4 participants who were treated in 2008. These are not included when calculating SVR

Younger participants, 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 were more likely to have been treated (table 22). However, of the 52 participants who commenced treatment between 2007 and 2009, 43 (83%) were genotype 1. This was the first course of treatment for 36 (69%), second for 14 (27%) and third for 2 (4%) participants. A high fibrosis score was recorded for 10 (19%) of these recently treated participants.

Treatment response

Seventy three percent of genotype 2 or 3 treatment naïve participants on peg-IFN and RBN combination therapy achieved an SVR compared to 41% of genotype 1 participants on the same treatment (table 22). Treatment response for treatment naïve participants on peg-IFN and RBN, by genotype and type and duration of treatment, are shown in figure 20.

Table 22. Number and percentage of chronically infected participants treated, and percentage SVR, by source of infection, gender, fibrosis scores, hepatitis C genotype and age at latest follow-up

Characteristic	Number of participants treated - any drug regimen	% treated - any drug regimen	% SVR on first treatment - any drug regimen	% SVR on first treatment with Peg-IFN & RBN - treatment naïve participants	% SVR on first re-treatment with Peg-IFN & RBN - previously failed tx on other drugs
Source of infection					
Anti-D all*	151	35.0	35.9	44.2	28.6
Anti-D 77-79	109	28.8	23.8	44.2	16.7
Anti-D 91-94	33	86.8	75.8	57.1	100.0
Blood clotting factors	54	50.5	34.6	54.2	27.3
Blood transfusion/renal	139	50.9	38.2	57.1	36.4
Gender					
Female	236	39.7	36.9	45.1	27.3
Male	108	49.1	36.2	62.8	38.1
Ever had a high fibrosis score on biopsy					
No	201	40.7	44.1	48.6	40.7
Yes	99	61.9	19.4	45.2	15.0
Genotype					
1	208	35.1	23.6	41.0	18.9
2	25	69.4	44	72.7	75.0
3	99	69.2	57.6	73.3	53.8
Age at latest follow up					
0 to 49 years	111	55.5	50.9	70.7	47.1
50 to 59 years	128	46.7	35.5	51.1	23.8
60+ years	105	30.8	22.8	30.8	25.0
All	344	42.2	36.7	51.2	31.5

*Includes participants infected through anti-D in non-outbreak years.

Genotype not available for 10 participants who were treated. Participants with genotypes 4/5 (n=4) omitted from analysis of treatment data. Fibrosis scores not available for 34 of the participants who were treated. Treatment outcome for the first course of treatment awaited for 14 participants – these participants were not included when calculating SVR.

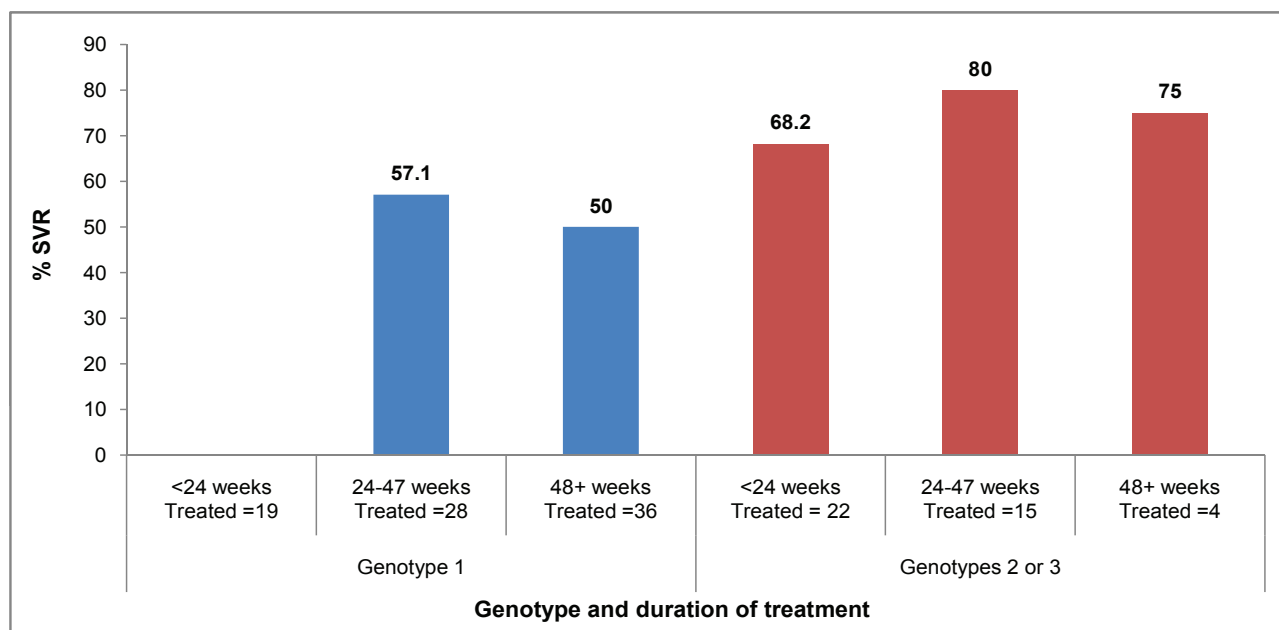


Figure 20. Percentage sustained virological response for treatment-naïve participants treated with combination therapy with Peg-IFN and RBN (n=124), by genotype and duration of therapy

The factors associated with SVR on first treatment were: treatment with combination therapy with peg-IFN and RBN rather than combination therapy with IFN & RBN or monotherapy, having HCV genotypes 2 or 3 rather than genotype 1, longer duration of treatment and lower fibrosis scores on biopsy.

Treatment response: previously treated participants

Fifty four participants were re-treated with peg-IFN and RBN having failed to achieve SVR on previous treatment courses with other drug regimens. Their overall treatment response rate was 31.5%. However, response rates were good for genotype 1 participants who were treated for 48 or more weeks (50%) and for genotype 2 or 3 participants who were treated for 24 or more weeks (67%). Response rates by genotype and duration of treatment are shown in figure 21.

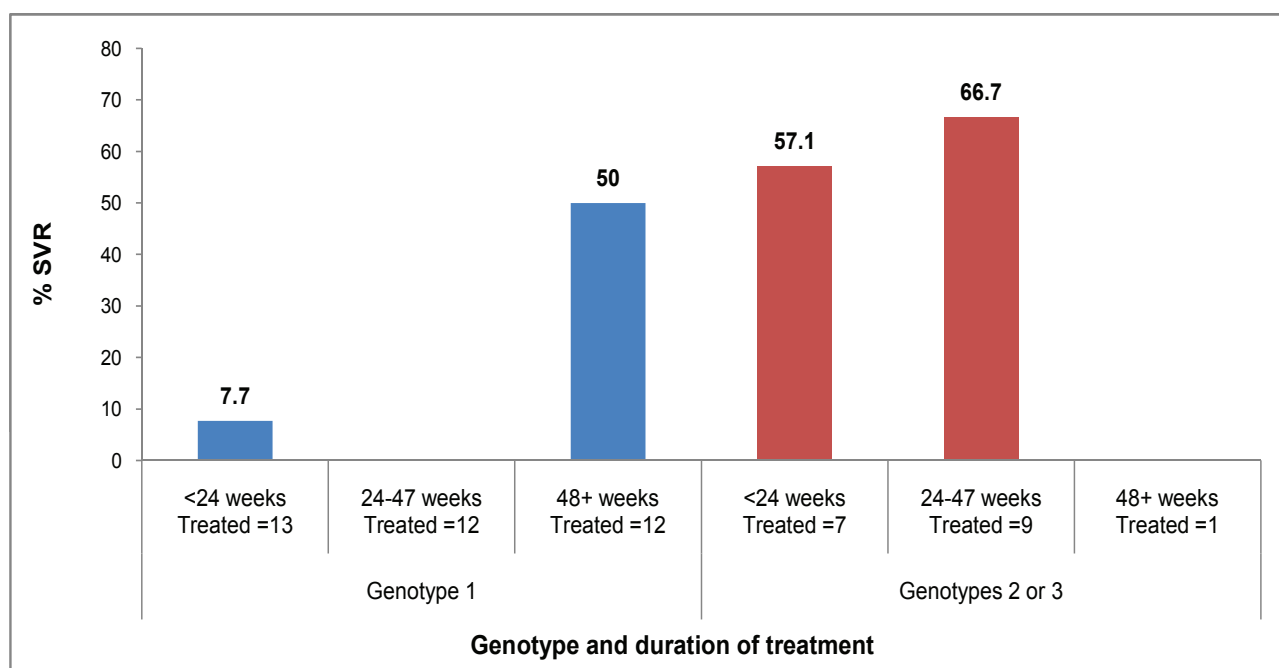


Figure 21. Percentage sustained virological response for re-treated participants (previously failed to achieve SVR on other drug regimens) treated with combination therapy with Peg-IFN and RBN (n=54), by genotype and duration of therapy

Liver transplants

Nineteen database participants had received twenty one liver transplants by the end of 2009. Fifteen received transplants in 2007 or earlier, three were transplanted in 2008 and one was transplanted in 2009. The median age at transplant was 53 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=16) remained RNA positive. Five transplant recipients (26%) had evidence of high alcohol consumption at some stage.

Fourteen transplant recipients had a diagnosis of cirrhosis before their liver transplant and one had HCC. Post-transplant biopsy or other staging results were available for ten participants. Within five years of transplant, two developed HCC, two developed cirrhosis, two had moderate or advanced fibrosis, two had mild fibrosis and one had no fibrosis. One further participant developed cirrhosis many years after transplant.

Five of the liver transplant patients have since died. Three died from non-liver related causes, one from hepatocellular carcinoma and no death certificate was available for the fifth. The median time between transplant and death for these patients was 21 months.

Medical conditions

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

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

Table 23 shows common medical conditions and other medical conditions of interest, recorded by RNA status, and indicates conditions 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.

Depression was significantly more likely to be recorded in the medical charts of chronically infected participants (n=271, 33%) compared to those who never became chronically infected (n=95, 21%). Females were more likely to report depression than males after accounting for the effects of RNA status. Participants who had received anti-viral treatment were also more likely to have depression recorded in their medical charts. Long-term medications for depression, sleep disorders or anxiety were noted in the charts of 68% (n=183) of chronically infected participants with depression.

Fibromyalgia was significantly more prevalent in chronically infected females compared to females who did not become chronically infected. Age also had an impact and females aged 50 years or older were more likely to have fibromyalgia than younger females.

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

Table 23. Medical conditions recorded in charts of participants – most common conditions, 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	%			
Depression	271	33.3	95	21.1	Yes	Yes	No
Fatigue and lethargy	262	32.1	133	29.5	No	Yes	No
Arthralgia or joint pain	194	23.8	115	25.5	No	No	No
Hysterectomy [‡]	118	19.8	68	16.4		No	
Fibromyalgia	103	12.6	42	9.3	No	Yes	No
Osteoarthritis	91	11.2	44	9.8	No	No	No
Osteopenia	77	9.4	36	8	No	No	No
Dermatitis and eczema	70	8.6	21	4.7	Yes	No	Yes
Diabetes mellitus	68	8.3	20	4.4	Yes	No	No
Osteoporosis	60	7.4	11	2.4	Yes	Yes	No
Dry eyes/conjunctivitis	56	6.9	23	5.1	No	No	No
Anxiety	45	5.5	14	3.1	No	Yes	No
Arthritis, unspecified	31	3.8	14	3.1	No	No	No
Sicca/Sjorgen syndrome	22	2.7	8	1.8	No	No	No
Thrombocytopenia or other purpura	17	2.1	2	0.4	Yes	No	No
Rheumatoid Arthritis	14	1.7	6	1.3	No	No	No cases
Parkinson's Disease	6	0.7	2	0.4	No	No	No
Ovarian Cancer [‡]	5	0.8	0	0		No	
Brain tumour	4	0.5	0	0	No	No	No cases
Non-Hodgkin's Lymphoma	4	0.5	0	0	No	No	No

*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.

[†]P < 0.05

[‡]Percentage calculated using female denominator figures.

Focus on the different patient groups

Database participants who became chronically infected with HCV through blood transfusions or treatment for renal disease had the highest prevalence of severe liver disease in spite of having the shortest median duration of RNA positivity at the end of latest follow-up. Thirty nine percent (n=107) of transfusion/renal participants were classified as having severe liver disease, including 26% (n=70) with cirrhosis, after a median duration of HCV RNA positivity by latest follow-up of 21 years. The prevalence of severe liver disease was also high in participants who were chronically infected through clotting factors, with 32% (n=34) classified as having severe liver disease and 16% (n=17) diagnosed with cirrhosis after a median duration of RNA positivity of 28 years. Chronically infected anti-D participants had better liver-related outcomes overall, with 21% (n=91) classified as having developed severe liver disease, including 11% (n=49) with cirrhosis, after a median duration of RNA positivity of 32 years.

There are several potential explanations for these differences in liver-related outcomes. Firstly, we would expect co-morbidities to be high in transfusion/renal participants in general, as many were infected with HCV as a result of treatment for serious medical conditions such as cancer. Transfusion/renal participants were also slightly older overall when infected with HCV, with a median age at infection of 32 years, compared to 28 years for anti-D participants and 14 years for participants infected through clotting factors. Gender may also be a factor as chronically infected female participants have a lower prevalence of serious liver-related outcomes than males in spite of having longer durations of RNA positivity. Alcohol intake also varies by gender and hence by source of infection, with 12% of chronically infected transfusion/renal participants and 17% of chronically infected clotting factor participants consuming high levels of alcohol at some stage, compared to 4% of anti-D participants.

Participants infected through anti-D

In spite of having the longest median duration of RNA positivity, database participants infected through anti-D have the lowest prevalence of serious liver-related outcomes. This is likely to be attributable, in part, to the fact that this group was entirely composed of females who were infected during or after pregnancy and who were likely to have been in relatively good health when infected with HCV. Reported alcohol consumption was also lower for female database participants. Their median age at infection was 28 years, which makes them younger overall compared to the transfusion/renal group but significantly older than those infected through clotting factors.

Anti-D participants infected between 1977 and 1979 have had the lowest uptake of antiviral treatment to date (n=109, 29%). This is probably due to the relatively low prevalence of progressive fibrosis in this group, combined with published information showing poorer treatment responses in genotype 1 patients.^{11,30} The overall SVR was 32% (n=32) in participants infected during the 1977-79 anti-D outbreak and 34% (n=32) in other genotype 1 database participants. Treatment uptake in participants infected during the second anti-D outbreak (1991-1994) has been extremely high (n=33, 87%). The percentage achieving SVR has also been very high (91%), even in comparison with other genotype 3 database participants (65%, n=42).

Demographic characteristics, liver-related outcomes and treatment data for participants infected during each anti-D outbreak period are shown in table 24.

Table 24. 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	
	Number	%	Number	%
Hepatitis C genotype	Genotype 1		Genotype 3	
Chronically infected with hepatitis C	378		38	
Median age at infection (years)	28		30	
Median age at end of follow up (years)	59		46	
Median years since infection at end of follow up	32		16	
Mean duration RNA positivity (years)	32		6	
Alcohol intake				
Alcohol data available (highest reported)	368		37	
≤14 units per week	337	91.6	32	86.5
15 to 40 units per week	17	4.6	2	5.4
>40 units per week or alcohol abuse in chart	14	3.8	3	8.1
Serum alanine aminotransferase levels				
Data available	377		36	
Normal	118	31.3	25	69.4
Slightly elevated (from upper normal limit to <2.5 times upper normal limit)	183	48.5	7	19.4
More highly elevated (≥2.5 times upper normal limit)	76	20.2	4	11.1
Liver disease severity				
Mild or no liver disease	205	54.2	19	50.0
Moderate	89	23.5	14	36.8
Severe	84	22.2	5	13.2
Outcomes				
Signs of liver disease	53	14.0	5	13.2
Cirrhosis	44	11.6	3	7.9
HCC	5	1.3	0	0.0
High fibrosis score on biopsy	70	18.5	2	5.3
Deceased	36	9.5	0	0.0
Liver-related disease directly caused death	11	2.9	0	0.0
Hepatitis C treatment				
Treated	109	28.8	33	86.8
Treated and treatment response available	99	26.2	33	86.8
SVR on peg-IFN & RBN - treatment naïve participants	19 (of 43)	44.2	4 (of 7)	57.1
Overall SVR on last treatment with any drug regimen	32 (of 99)	32.3	30 (of 33)	90.9

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 three, but where results were available, 82% (n=273) were chronically infected and 18% (n=61) had cleared the HCV virus by this time.

The group of participants infected through blood transfusions or treatment for renal disease 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 liver disease severity. Logistic regression was used to model the factors that were independently and significantly associated with severe liver disease in this population (table 25).

High alcohol intake, older age at the end of latest follow-up, male gender, longer duration of infection and HCV genotype 3 were all found to be independently associated with severe liver disease (as defined on page 37) in chronically infected blood transfusion/renal patients (table 25).

Table 25. Factors associated with severe liver disease in chronically infected participants infected through blood transfusions/treatment for renal disease - logistic regression model (n=236).

Factors associated with having severe liver disease	Odds Ratio	P-value	95% Confidence interval
Alcohol consumption			
Non drinker/within recommended limits/moderately high	1	Reference	Reference
High (>40 units per week or alcohol abuse in chart)	3.6	0.005	1.49 - 8.78
Age at latest follow-up			
<50 years	1	Reference	Reference
50+ years	4.0	<0.001	1.92 - 8.51
Gender			
Female	1	Reference	Reference
Male	2.8	0.001	1.50 - 5.28
Duration of RNA positivity			
<20 years	1	Reference	Reference
20+ years	2.5	0.004	1.35 - 4.72
Genotype			
Genotype 1	1	Reference	Reference
Genotype 2	0.7	0.53	0.25 - 2.05
Genotype 3	2.5	0.005	1.32 - 4.75

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 22). These patients had all died prior to RNA testing but had similar prevalence of serious liver-related outcomes to the chronically infected participants and it is likely that they were chronically infected with HCV when they died. The remaining 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.

Thirty five percent (n=37) of the chronically infected participants and 84% (n=31) of those with no HCV RNA results were co-infected with HIV. It was difficult to ascertain the true effects of HIV co-infection on HCV disease progression as 66% (n=45) of the co-infected participants have died. However, 34% (n=23) of those who were HIV positive had clinical signs of liver disease by latest follow-up compared to 17% (n=13) of those who were HIV negative, even though they had a shorter median duration of follow-up (25 years compared to 28.5 years) (figure 22). High alcohol intake was also found to be associated with severe liver disease in HIV negative participants. Fifty six percent (n=5) of HIV negative participants with high alcohol consumption were classified as having severe liver disease by latest follow-up compared to 17% (n=9) 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 severe disease compared to 42% (n=13) of those without. However, as alcohol data were not available for all, these data comprise small numbers of participants and may not be representative.

Death certificates were available for 42 of the 45 HIV positive participants who had died. The underlying cause of death was liver-related disease for ten and directly related to HIV infection for twelve. A further ten had causes of death relating to immunodeficiency, but the term HIV was not specifically mentioned on their death certificate.

The underlying cause of death was classified as directly liver-related for 9 of the 25 HIV negative participants who had died, not liver-related for 15 and the death certificate was missing for the remaining patient. Of the nine liver-related deaths, four were caused by HCC, two were caused by cirrhosis, one was due to hepatorenal syndrome, one was due to hepatitis C and the remaining death was due to hepatitis B induced liver failure.

Fifty four (50%) participants chronically infected through blood clotting factors had received anti-viral treatment for HCV by latest follow-up. The percentage treated did not vary significantly by HIV status (49% HIV positive, 51% HIV negative). Treatment outcome was available for 52 and the percentage who achieved SVR on any drug regimen did not differ by HIV status (56% HIV positive, 50% HIV negative).

Twenty six treatment naïve participants were initially treated using peg-IFN and RBN combination therapy. Outcome was available for twenty four (12 HIV negative and 12 HIV positive) and SVR was achieved by 58% of HIV positive participants and 50% of HIV negative participants. The proportion who were genotype 1 was slightly higher in the HIV positive group (58% compared to 50%). The numbers treated were too low to reliably assess if treatment response in genotype 1 patients varied with HIV status, but treatment response rates look similar between HIV positive and negative clotting factor participants. The combined (HIV positive and negative) response rates on initial treatment with peg-IFN and RBN were 39% for genotype 1 participants and 73% for genotype 2/3 participants. These SVR rates were comparable to those achieved by participants infected through other means (41% SVR for genotype 1 and 73% for genotype 2/3).

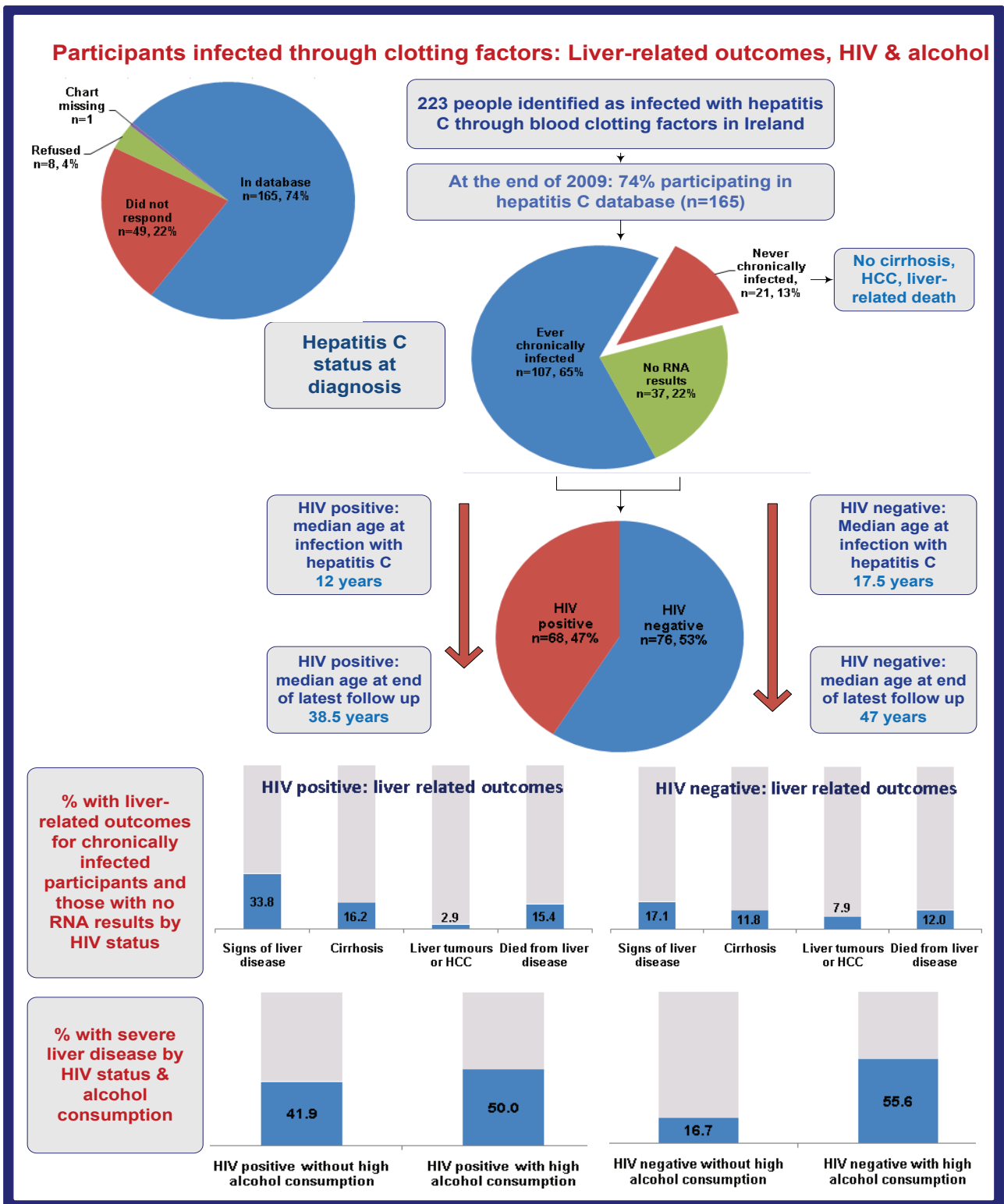


Figure 22. Summary of hepatitis C infection and disease progression in participants infected through clotting factor, by HIV status.

Clinical management and health service usage

Specialist health services and procedures

Since last follow-up, 40% (n=265) of ever chronically infected living participants and 21% (n=91) of those who were never chronically infected attended one or more specialist hospital services other than hepatology. The most common services used by chronically infected participants were haematology (9%), endocrinology (6%), rheumatology (5%) and psychiatry/psychology/counselling (5%) (table 26). As expected, a high proportion of participants infected through clotting factor attended haematology and physiotherapy services and a very high proportion of participants infected as a result of treatment for renal disease attended nephrology services.

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

Table 26. Most common specialist services, other than hepatology, attended by living participants since the last round of follow-up data collection.

Most common services attended	Ever chronically infected		Never chronically infected	
	Num	%	Num	%
Haematology	63	9.4	14	3.3
Endocrinology	38	5.7	11	2.6
Rheumatology	32	4.8	9	2.1
Psychiatry/psychology/counselling	31	4.6	1	0.2
Dermatology	30	4.5	6	1.4
Physiotherapy	28	4.2	15	3.5
Surgical	27	4.0	13	3.1
Ear, nose and throat	24	3.6	4	0.9
Cardiology	20	3.0	11	2.6
Neurology	17	2.5	11	2.6
Orthopaedic	17	2.5	4	0.9
Nephrology	16	2.4	2	0.5
Dietitian/nutritionist	15	2.2	4	0.9

Since last follow-up, 35% (n=233) of ever chronically infected living participants and 7% (n=28) of those who were never chronically infected underwent one or more liver-related procedures aside from liver biopsies. The most common liver-related procedures were ultrasounds (32% of chronically infected living participants) and CT scans (5% of chronically infected living participants) (figure 23). The number of liver biopsies being carried out has been decreasing in recent years (figure 11). Because ultrasounds are less invasive and more acceptable to patients, it is likely that they are increasingly being used to monitor disease progression where possible. Some of the hepatology units have also started to use fibroscans to assess liver elasticity. Very little data were available to the end of 2009 on fibroscans.

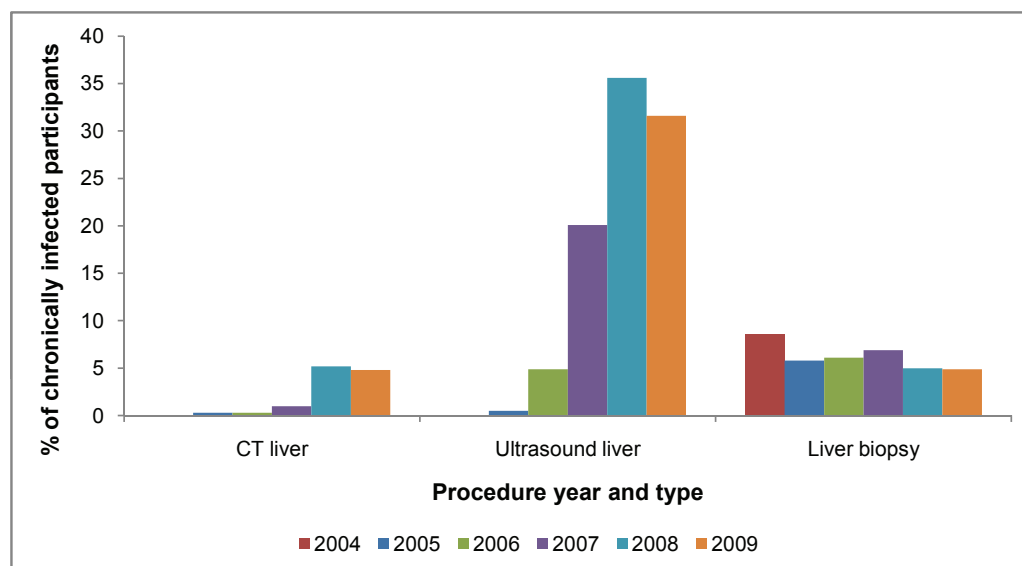


Figure 23. Percentage of ever chronically infected living participants undergoing liver-related procedures, by year.

Chapter 5 Discussion

This report describes the current health of a large group of people who were infected with hepatitis C virus through the administration of blood or blood products many years ago. Almost half of this population still have chronic hepatitis C infection. Despite this, the majority do not have evidence of serious liver disease after an average of more than 30 years of infection. However, the findings of this latest round of data collection have demonstrated further progression of liver disease in a small number of participants.

There is no evidence of cirrhosis or hepatocellular carcinoma in those participants who never developed chronic infection. In those who developed chronic infection, there has been a small increase in the proportion with cirrhosis, HCC and liver-related death compared with the previous round of data collection one year ago (17%, 4% and 6% respectively, compared with 14%, 3% and 5% one year ago).¹⁷

The factors found to be associated with progression of liver disease in the chronically infected database participants have been well described in the literature: male gender, duration of infection, older age, high alcohol intake.^{1,6,9} The odds of having severe liver disease were almost three times higher for males compared with females in the database population.

Genotype 3 was also found to be independently associated with having severe liver disease in the database population, as noticed previously.¹⁷ The published data on the impact of HCV genotypes on fibrosis progression rates, development of cirrhosis, and the risk for HCC, have been conflicting.³¹ However, a recent study on a large dataset, The Swiss Hepatitis C Cohort, found that HCV genotype 3 was associated with accelerated fibrosis.³² Conflicting results were reported from the UK HCV Register which found that type 1 infection is associated with greater aggressiveness than type 2 or 3 infections, with type 1 infection being independently associated with more advanced stages of liver disease on biopsies carried out by the Registry.³³

The most important factor in disease progression was alcohol intake. Participants who had high alcohol intake had more than five times higher odds of having severe liver disease compared to those without. This finding has been described in previous reports from the database.^{15,16,17} There is clear evidence from international sources that heavy alcohol use accelerates fibrosis progression and increases the risk of cirrhosis, HCC and end stage liver disease.^{34,35,36} The exact amount of alcohol required to increase the risk of disease progression in patients with HCV is unknown.

Although the number of participants with a history of high alcohol intake was small, accounting for only one third of those with severe liver disease, it is an important issue as it is one area where intervention is possible to reduce the risk of progression of disease. Patient information and education initiatives among people with HCV infection should focus on raising awareness of the risks associated with alcohol consumption.

We would like to have better quality data on alcohol intake. Much of the alcohol consumption data on participants was last recorded many years ago. It is hoped that there may be more active recording of up to date information on alcohol consumption in the patient medical notes by the time of the next period of data collection.

In general, those infected through anti-D immunoglobulin have demonstrated a more benign course than those infected through receipt of blood transfusion or clotting factors. This is likely to be related to the younger age at infection, female gender, relative lack of co-morbidity and lower alcohol use among the anti-D cohort.

Twenty two percent of participants with chronic infection have been successfully treated, having cleared the virus. Responses following treatment with combined pegylated interferon and ribavirin in database participants have been in line with internationally published figures, being 41% for genotype 1 and 73% for genotype 2 or 3 in treatment naïve patients.^{10,11} There is also evidence from serial biopsy results on successfully treated database patients that fibrosis scores have improved in over half of these and have not progressed in most of the others. The uptake of anti-viral therapies has been highest in genotype 2 and 3 participants (69%), with only 35% of genotype 1 participants having been treated. This is understandable given the poorer response to treatment in genotype 1 infection.¹¹ However, most of those commencing treatment since 2007 have had genotype 1 infection. The recent addition of protease inhibitors into the management of genotype 1 infection will be captured in the next round of data collection and reported in the next report.

In recent years, there has been increasing use of non-invasive diagnostic techniques such as ultrasound, CT scan and fibroscans to monitor progression of liver disease. Many of the hepatology units in Ireland have now adopted the use of fibroscans. There was little information recorded on fibroscan results up to the end of 2009 and so this information is not included in the present report. However, we hope to have useful data on fibroscan findings in the next report.

Almost 90% of chronically infected participants attended their hepatology unit for follow-up within the past 1-2 years. It is interesting to note that over half of those who never developed chronic infection had also attended the hepatology unit during that time.

Depression was commonly recorded in the medical notes of many participants, particularly women, those with chronic infection and those who received anti-viral treatment. Many of these patients were on long-term medications for depression. Fibromyalgia is also frequently diagnosed in database patients with chronic HCV infection, again more often in women than in men. An association between fibromyalgia and HCV infection was demonstrated in an American study of 90 HCV-infected patients, with 16% of cases being diagnosed with fibromyalgia while none of the control group were diagnosed with fibromyalgia.³⁷

Several amendments to the database are planned for 2013. These include new data fields for IL-28B genotype, and Child-Pugh and MELD scores (scores for severity of liver disease). In addition, the treatment section has been revised to capture details of new therapies, of adherence to treatment dose and schedule, and details of treatment responses at specified time points.

We hope that in the next round of data collection we will have useful information on genetic and metabolic factors affecting disease progression. The information on height and weight contained in patient medical notes to date has been limited and thus it has not been possible to examine the effect of BMI on disease progression in the database population. Data on steatosis were also infrequently available. We hope to be able to comment on these areas in future reports if the relevant data are recorded in the patients' charts.

This report is based on the findings of the fourth round of data collection, and contains information on developments over the one year period since the previous data collection period. When the database was first set up it was envisaged that data would be collected every year. However, it is apparent now that little change in health status is likely to be evident in the space of one year and that annual data collection is not warranted. Therefore, the next round of data collection is planned for mid-2013 and will cover the three year period from 2010 to 2012 inclusive.

The national hepatitis C database allows us to study the health of a large number of people who were infected with hepatitis C over 30 years ago. The participation rate in the database project is high at 77%. 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.

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Glossary of definitions, terms and abbreviations

Definitions

Case of hepatitis C for the purpose of this database

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

Confirmed positive case of hepatitis C

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

Ever hepatitis C RNA positive (PCR positive)

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

Definition of alcohol use in excess of recommended limits (as per guideline that was current at the time of this study)

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 the study – 2009) 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.²⁸

(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).²⁹

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.

Early Virological Response

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

Extrahepatic manifestations of hepatitis C

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

Fibrosis

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

Genotype testing

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

Health Amendment Act (HAA) card

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

Hepatic encephalopathy

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

Hepatitis C EIA (Enzyme Immunoassay) /ELISA (Enzyme-Linked Immunosorbent assay)

An assay that detects antibodies to specific hepatitis C antigens in a patient's blood. The hepatitis C EIA test is usually used as an initial screening test for hepatitis C antibodies.

Hepatitis C PCR test (Polymerase Chain Reaction)

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

Hepatocellular carcinoma (HCC)

Primary malignancy (cancer) of the liver.

Hepatomegaly

Enlarged liver.

Liver biopsy

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

Liver function tests (LFTs)

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

Mean (average)

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

Median

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

Meta-analysis

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

Multivariate logistic regression

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

Odds ratio

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

Oesophageal varices

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

Portal hypertension

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

Positive predictive value

This is the proportion of all those who test positive who really have the disease or condition.

P-value

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

Rapid Virological Response

HCV RNA undetectable at week 4 of treatment

Recombinant immunoblot assay (RIBA)

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

Renal

The term renal refers to the kidney.

Sensitivity

This measures how often a test turns out positive when it is being used on people who have the disease or condition.

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.

Specificity

This measures how often a test turns out negative when it is being used on people who do not have the disease or condition.

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

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

Appendix A

Members of the National Hepatitis C Database Steering Committee

Dr Barbara Coughlan, UCD School of Nursing

Ms Anne Duffy, Irish Haemophilia Society

Ms Susan Gaughran, Transfusion Positive

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

Ms Lara Hynes, Department of Health and Children

Ms Helena Irish, St James's Hospital

Ms Maura Long, Transfusion Positive

Mr Mark Murphy, Irish Kidney Association

Ms Niamh Murphy, Health Protection Surveillance Centre

Ms Joanne Deveney, Positive Action

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

Dr Lelia Thornton, Health Protection Surveillance Centre

Ms Noeleen White, Positive Action

Appendix B

Members of the National Hepatitis C Database Scientific and Technical Group

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

Prof Garry Courtney, St Luke's Hospital, Kilkenny

Dr Orla Crosbie, Cork University Hospital

Prof John Crowe, Mater Misericordiae University Hospital

Prof John Hegarty, St Vincent's University Hospital

Dr John Lee, University College Hospital, Galway

Ms Carol McNulty, St Vincent's University Hospital

Ms Niamh Murphy, Health Protection Surveillance Centre

Prof Frank Murray, Beaumont Hospital

Dr Niamh Nolan, St Vincent's University Hospital


Prof Suzanne Norris, St James's Hospital

Prof Cliona O'Farrelly, Trinity College Dublin

Dr Lelia Thornton, Health Protection Surveillance Centre

Dr Stephen Stewart, Mater Misericordiae University Hospital

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



National Hepatitis C Database
for infection acquired through
blood and blood products

National Hepatitis C Database

for infection acquired through blood and blood products

Follow-up Form

Year 3

1. Database ID _____

2. Date consent given _____

3. Form completed by _____

4. Date form completed _____

5. Hepatology Unit

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

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

Section 5. Treatment

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

Date	Medication 1		Medication 2		Response (see codes below)
	Started	Finished	Name/schedule	Start Dose	

1: Not relevant (still on treatment)
 2: No response (never became PCR negative)
 3: Breakthrough 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)
 8: Treatment stopped early (e.g. due to side effects) If Yes, details _____

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

Medication	Dose

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

45. Other treatments recorded Yes No If yes, give details below

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

46. 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

Thank you very much for your help.
 Please return this form to:
 Nianah Murphy
 Health Protection Surveillance Centre
 25-27 Middle Gardiner Street
 Dublin 1
 Tel: 01 87665300

Appendix D Biopsy scoring

Fibrosis scoring systems

Score	Original HAI or Knodell ¹⁸	Modified HAI or Modified Knodell or Ishak ¹⁹ or Desmet ²⁰	Scheuer ²¹	International group of Hepatopathologists
0	No fibrosis	No fibrosis	None	No fibrosis
1	Fibrosis portal expansion	Fibrosis expansion of some portal areas, with or without short fibrous septa	Enlarged, fibrotic portal tracts	Fibrous portal expansion
2		Fibrosis expansion of most portal areas, with or without short fibrous septa	Periportal or portal-portal septa with intact architecture	Portal septa with normal vascular relationships
3	Bridging fibrosis (portal-portal or portal-central linkage)	Fibrosis expansion of most portal areas, with occasional portal to portal bridging	Fibrosis with architectural distortion but no obvious cirrhosis	Distorted structure or incomplete cirrhosis (focal nodules)
4	Cirrhosis	Fibrosis expansion of portal areas, with marked bridging (portal to portal as well as portal to central)	Probable or definite cirrhosis	Cirrhosis, probable or definite
5		Marked bridging with occasional nodules (incomplete cirrhosis)		
6		Cirrhosis, probable or definite		

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

Appendix E Contact Information

Support Groups

Positive Action

56 Fitzwilliam Square, Dublin 2. Tel: 01-676 2853, Fax: 01-662 0009
www.positiveaction.ie

Transfusion Positive

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

Ms Michele Tait, National Co-ordinator of Hepatitis C Services, Health Service Executive,
Mill Lane, Palmerstown, Dublin 20. Tel: 01 620 1712 or 01 620 1750

HSE Dublin North East

Dublin North/North West/North Central, Cavan, Monaghan, Louth & Meath

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

HSE Dublin Mid Leinster**Dublin South/ South West/West/ East Coast, Kildare & Wicklow**

Ms Michelle Hayes, Health Service Executive, Mill Lane, Palmerstown, Dublin 20 Tel 01 6201840

Laois, Longford, Offaly & Westmeath

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

HSE West**Clare, Limerick & Tipperary North**

Ms Ellen Rush, Tyone Health Centre, Tyone, Nenagh, Co Tipperary. Tel: 067 46449

Leitrim, Sligo & Donegal

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

Galway, Mayo & Roscommon

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

HSE South**Carlow, Kilkenny, Tipperary South, Waterford & Wexford**

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

Cork/Kerry

Mr Donal Murphy, Primary Care Unit, Health Service Executive, 26/27 South Mall, Cork.
Tel: 021 4921872 / 021 492 1871

For all queries that cannot be resolved at local level and within the hospital services:

Ms Michele Tait, Health Service Executive, Mill Lane, Palmerstown, Dublin 20. Tel: 01 620 1712

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: cchepec@health.irlgov.ie, Website: <http://www.consultativecouncilonhepc.ie/>

Appendix F Newsletter

Database News

Issue 3 October 2010

Newsletter of the National Hepatitis C Database


HCV

National Hepatitis C Database

Welcome to the third edition of Database News, the newsletter of the National Hepatitis C Database. We would like to thank everyone who has taken part in the database and those who have supported the development of the database, especially the hepatology units and patient support groups.

Background

Everybody who was infected with hepatitis C through blood or blood products in Ireland is eligible to participate in the database. Information is collected on people who still have circulating virus (PCR/RNA positive) and also people who cleared the virus or have undetectable virus levels (antibody positive, but not PCR/RNA positive). The collection of information about all participants who consented to be included in the database began in 2005. Follow up data is collected each year from patients' medical notes, and the third round of data collection is now completed. Names and addresses are not collected in the database and there is no direct contact made with patients.

Please contact with your hepatology unit or patient support group if you wish to participate and have not yet given your consent.

What information is collected in the database?

Information is collected on the source of infection, current state of health, use of health services, liver biopsy and other test results, and treatment.

The database population

- The total number of participants in the database is 1,303.
- 28 people have been added to the database since 2008
- 62% of the total database population were infected through anti-D immunoglobulin, 26% were infected through receipt of blood transfusions or treatment for kidney disease, and 12% through blood clotting factors
- 7.6% are HCV genotype 1 and 1.9% are genotype 3
- 73% are females
- The average age of the database population is now 57 years
- The average duration of infection is 30 years. This varies by source of infection



Contents

Welcome

Background

What information is collected in the database?

The database population

Main Findings

Medical conditions

Clinical management

Liver Biopsy results

Anti-viral treatment

Alcohol consumption

Deceased participants

Support

Contact information


**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

Areas we hope to improve upon in the database

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

What you can do to improve your health

- Consider anti-viral treatment for hepatitis C, if recommended by your doctor
- Decrease or give up alcohol
- Maintain a healthy weight
- Live a healthy lifestyle



Michael Griffin and Lary Bathe at the launch of the 2010 Database Report

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

 Database website: www.hcvdatabase.ie

Support & Contact Information

Support Groups

Positive Action

 56 Fitzwilliam Square, Dublin 2.
Tel: 01-676-2853, Fax: 01-662 0009.
www.positiveaction.ie

Transfusion Positive

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

Irish Haemophilia Society

 3 Clonwilliam Square, Dublin 8.
Tel: 01-657 9900, Fax: 01-657 9901
Email: info@haemophilia.ie
Website: www.haemophilia-society.ie

Irish Kidney Association

 Donor House, Block 43a Park West, Dublin 12.
Tel: 01-620 5306, Fax: 01-620 5366,
Local: 1890-543 639
Email: info@ika.ie, Website: www.ika.ie

HPSC: HCV Database Team

 Dr Leila Thornton, Project co-ordinator
Ms Niamh Murphy, Surveillance Scientist
Ms Paula Flanagan, Research Nurse
Ms Margaret McIver, Surveillance Assistant

HPSC-Health Protection Surveillance Centre

Tel: 01 8765 300

Email: hcvdatabase@hpsc.ieWebsite: www.hpsc.ieDatabase website: www.hcvdatabase.ie

Main findings so far

Table 1. Focus on the different patient groups

Anti-D	Blood transfusion/renal	Inherited bleeding disorders
1977-79 outbreak (Genotype 1) - 27% uptake of anti-viral treatment.	Fifty seven percent of chronically infected participants were female and forty three percent were male	Predominantly male (94%) and 42% were co-infected with human immunodeficiency virus (HIV).
1991-94 outbreak (Genotype 3) - 89% uptake of anti-viral treatment.	Most were infected in the late 1970s and 1980s	Most were infected as children in the mid-1970s to early 1980s.
Lowest prevalence of serious liver-related outcomes.	This group had the highest prevalence of severe liver disease (36% of those with chronic infection) and of cirrhosis (22% of those with chronic infection)	Of those with chronic infection, thirty one percent were classified as having severe liver disease and fourteen percent were diagnosed as having cirrhosis
Of those who had developed chronic (long term) infection nineteen percent were classified as having severe liver disease and nine percent had developed cirrhosis.		

Medical conditions

- Depression, hypertension, fibromyalgia/myalgia, dermatitis, diabetes, osteoporosis, and gastro-oesophageal reflux were all recorded more often for those chronically infected than those who were never chronically infected.

Clinical management

- The proportion of chronically infected participants taking long-term medications to treat depression, anxiety or diabetes was higher than for those not chronically infected.
- The specialist hospital services, other than hepatology, most commonly attended by chronically infected participants were haematology, psychiatry/psychology/ counselling, endocrinology and rheumatology.

Liver biopsy results

- Nineteen percent of chronically infected participants had a high fibrosis score on their most recent biopsy and 14% had cirrhosis
- A high fibrosis score was associated with high alcohol intake, older age at biopsy, longer duration of infection, male gender, infection through blood transfusion or renal disease and genotype 3.

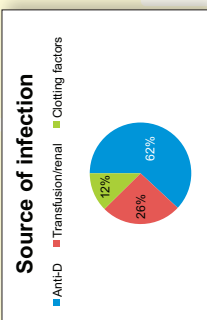


Figure 1. Database population by source of infection

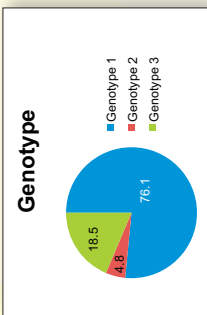


Figure 2. Genotype

Deceased participants

- One hundred and eighty eight participants had died by latest follow up. This represents fifteen additional deceased participants compared to the previous round of data collection.

- Death was directly caused by liver disease for 48 participants
- Death rates were higher in males or participants infected through blood transfusions or clotting factors, those who had high alcohol intake and participants who were older at infection.

Alcohol consumption

- Males and females differed in their reported exposure to alcohol with 32% of chronically infected males exceeding the recommended national limits for alcohol intake compared to 9% of females
- Alcohol consumption also differed by source of infection with participants infected through anti-D less likely to consume alcohol in excess of recommendations

- Compared to those infected through other means
- Participants who had high alcohol intake were almost 5 times as likely to have severe liver disease

Summary

Although there is evidence of progression of disease in some people, the majority of the database population, even those chronically infected, do not have any evidence of serious liver disease. The factors found to be linked to more severe liver disease were:

- Testing PCR/RNA positive
- High alcohol intake
- Male gender
- Older age at end of latest follow-up
- Longer duration of RNA positivity
- Genotype 3

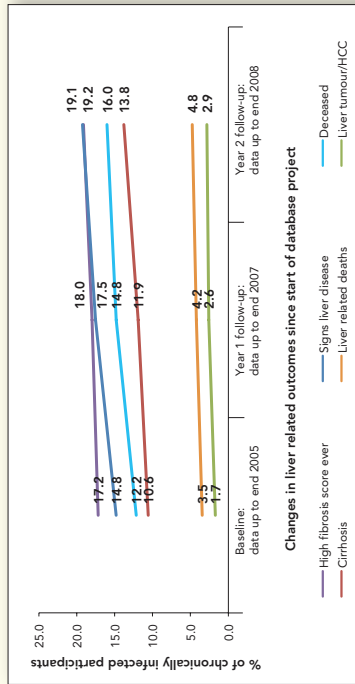


Figure 3. Changes since baseline data collection

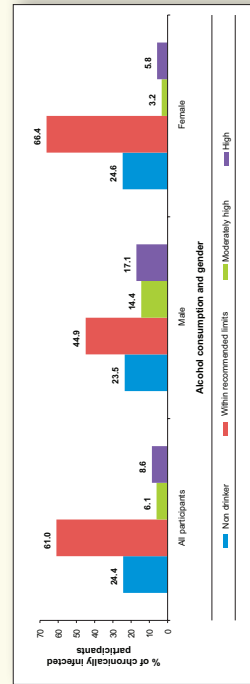


Figure 4. Highest reported alcohol consumption by gender for participants who became chronically infected.



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

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

Health Protection Surveillance Centre
25-27 Middle Gardiner Street Dublin 1 Ireland
Tel: +353 1 876 5300 Fax: +353 1 856 1299
Email: info@hpsc.ie www.hpsc.ie