National Hepatitis C Database

for infection acquired through blood and blood products

Final report

Data up to the end of 2017

Health Protection Surveillance Centre

Contents

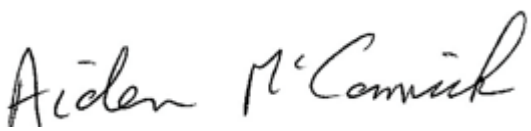
Report

Foreword

This is the sixth report of the National Hepatitis C Database. The fifth report included outcomes up till 2013. Since then, the landscape for hepatitis C treatment has changed dramatically. In 2020 the Nobel prize was awarded to Michael Houghton, Harvey Alter and Charles Rice for their work on the discovery of and characterisation of the hepatitis C virus. Their work, along with thousands of other clinicians, scientists, patient support and advocacy groups made possible the highly effective curative treatments we have today. It is now standard practice to cure hepatitis C in more than 95% of individuals with once daily tablets taken for 8-12 weeks. The majority of non-responders can be treated and cured with a second course of treatment. These medications have changed hepatitis C from a potentially fatal disease to an easily curable viral infection. The medications are expensive but very cost effective. In 2015 Department of Health and HSE set up The National Hepatitis C Treatment Program (NHCTP) and tasked it with providing treatment, free of charge, to all who need it. In this current report it is very encouraging to see that 99% of state infected hepatitis C patients treated with these highly effective treatments cleared the virus (page 55).

Over the years there have been improvements in diagnosis and management as well as treatment for hepatitis C. Figure 10 on page 46 very nicely illustrates that liver biopsies are a thing of the past for most patients. The place of liver biopsy has been taken by non-invasive tests including Fibroscan, ultrasound or MRI scans. Most liver clinics now have a Fibroscan on site so rapid assessment of liver fibrosis can be made at the time of the clinical consultation. One particularly interesting aspect of the report is the spontaneous viral clearance rate. In this cohort of patients approximately 37% of patients with hepatitis C antibodies were found to have cleared the virus at the time of diagnosis. In a recent large epidemiological study, the National Treatment Program found that 84% of individuals with hepatitis C antibodies in the community had cleared the virus. Given an expected spontaneous clearance rate of about 37% this suggests a significant impact of antiviral treatment on the prevalence of chronic hepatitis C infection in the general population.

The success of hepatitis C treatment prompted the World Health Organization to set ambitious elimination targets to make hepatitis C a rare disease by 2030. Many countries, including Ireland, are well on the way to achieving these goals. Hepatitis C is easily curable and there is no animal or environmental reservoir of infection. If we can identify all infected individuals and treat them, the infection can be eliminated from the world. It would be fantastic if we could relegate Hepatitis C infection to the history books along with other previous scourges like smallpox and polio.



Professor Aiden McCormick, Clinical Lead for the HSE National Hepatitis C Treatment Programme

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Executive summary

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

Between 55% and 85% of those infected with hepatitis C develop chronic infection and are at risk of progressive liver disease. Cirrhosis of the liver develops in 15 to 35% of chronically infected individuals after 25-30 years of infection. Between 1 and 4% of patients with cirrhosis develop hepatocellular carcinoma (HCC) per year.

The National Hepatitis C Database was set up in 2004 to collect data on people infected with HCV through the receipt of contaminated blood or blood products in Ireland. Approximately 1,700 people were infected through blood transfusions, anti-D immunoglobulin, blood clotting factors or treatment for renal disease. The purpose of the database project is to follow the natural history of infection, evaluate the outcomes of treatment, provide information for planning of services, and serve as a resource for research. Information is gathered from participants' medical records in the eight hepatology units. This report is based on the sixth round of data collection and includes information on database participants up to the end of 2017.

Main findings

Profile of participants

- 1,322 people are now included in the database, a participation rate of 77%.
- 1,016 (77%) were still alive at the end of 2017.
- The most common source of infection was anti-D immunoglobulin (61%), followed by blood transfusion or treatment for renal disease (26%) and blood clotting factors (12%). A small number of participants were infected through contact with cases infected through blood/blood products, rather than directly from blood/blood products (<1%).
- The average age at last follow-up was 63 years
- Participants included 1026 (78%) females and 296 (22%) males.
- The average time interval from infection to last follow-up for all patients was 35 years (38 years for patients who were still alive at last follow up)
- The average duration of hepatitis C RNA positivity for those who ever tested RNA positive was 32 years (36 years for patients who were still alive at last follow up)

Hepatitis C status

- The spontaneous viral clearance rate in this population is between 20% and 37% (depending on whether participants with no confirmatory antibody results are included in the denominator).
- 258 participants have been successfully treated in the four years since the previous round of data collection.

- 98 database participants were reported as still alive and chronically infected at the end of 2017
- About a third of those remaining chronically infected are likely to be lost to follow up (had not attended in the past five years or were known to be living abroad). Some of these patients may be deceased. A further third refused treatment and a small number of patients were not treated on medical grounds. At the time of data collection, the hepatology units were actively following up patients who remained chronically infected with a view to treatment.

Alcohol consumption

- Alcohol consumption in excess of recommended levels was recorded at some stage for 18% of those with chronic infection. However, the latest reported alcohol intake data indicated that this had reduced to 6%.
- Alcohol intake was higher in males and in younger people.

Body mass index (BMI)

- BMI was only available for 48% of participants.
- Any findings related to BMI may not be representative of the whole population as BMI is more likely to be recorded for those who are overweight or underweight.
- Where BMI was recorded, 36% of participants were categorised as overweight and a further 29% were categorised as obese.
- Obesity was not found to be significantly associated with cirrhosis or other signs of serious liver disease, but this finding is not robust due to the lack of data completeness.

Diabetes mellitus

- Diabetes was recorded for 9% of database participants.
- The prevalence of diabetes was higher in those who developed chronic infection (12%) than in those who never developed chronic infection (6%). However, the duration of follow up was shorter for participants who did not become chronically infected, and diabetes may be underreported in this group.

Outcomes

Liver-related disease was very rare in those who never developed chronic infection. Therefore, the results focus mainly on participants who developed chronic infection.

Clinical signs of severe liver disease

- Over one third (34%, n=278) of those who were ever chronically infected had clinical signs of severe liver disease (such as cirrhosis, hepatocellular carcinoma, oesophageal varices, portal hypertension, ascites and splenomegaly) recorded by latest follow-up, an increase from 29% in the previous round of data collection (data up to the end of 2013).
- The factors associated with having signs of serious liver disease were chronic infection, high alcohol intake, longer duration of infection and male sex.

- Participants infected through blood transfusion/ treatment for renal disease and those infected through blood clotting factors were more likely to have signs of serious liver disease than anti-D participants, despite shorter durations of infection.

Cirrhosis

- 28% (n=227) of those who ever developed chronic infection had developed cirrhosis by latest follow-up. This is an increase from 22% four years prior.
- Cirrhosis developed at an average age of 58 years and average duration of infection of 28 years.
- Aside from chronic infection, high alcohol intake and older age at infection were associated with higher rates of cirrhosis on multivariate regression analysis. Male sex was not significantly associated with having higher rates of cirrhosis after adjusting for age and alcohol intake.
- Participants infected through blood transfusion or treatment for renal disease had higher rates of cirrhosis than those infected through anti-D.

Hepatocellular carcinoma (HCC)

- HCC was recorded for 7% (n=57) of participants who had ever been chronically infected with hepatitis C, at an average duration of infection of 30 years and an average age of 66 years. This was an increase from 5% reported in the previous round of follow up, 4 years prior.
- Of the 57 chronically infected patients who developed HCC, almost three quarters (74%, n=42) had died by latest follow up.
- Aside from chronic infection, high alcohol intake, male sex and older age at infection were associated with higher rates of HCC on multivariate regression analysis.
- Participants infected through blood transfusion/treatment for renal disease and those infected through blood clotting factors had higher rates of HCC than those infected through anti-D.

Deaths

- By the end of 2017, 306 (23%) participants had died. This was an increase of 46 deaths since the previous round of follow up four years prior.
- Among participants who ever developed chronic infection, 27% had died, compared to 10% of those who never became chronically infected.
- Death from liver disease occurred in 86 participants: 10% (n=76) of chronically infected participants, 0.4% (n=2) of never chronically infected participants and 18% (n=8) of those with no RNA results (these patients had died before RNA testing began).
- The factors associated with liver-related mortality on multivariate regression analysis were chronic heptitis C infection, high alcohol intake, male sex and older age at infection.
    - Participants who became chronically infected had a 13-fold higher liver-related mortality rate compared to those who never became chronically infected, after adjusting for alcohol intake, sex and age at infection.

    - Participants with high alcohol intake had a sixfold higher liver-related mortality rate compared to those without high alcohol intake, after adjusting for hepatitis C status (ever chronically infected, never chronically infected), sex and age at infection.
- Participants infected through blood transfusion/treatment for renal disease and those infected through blood clotting factors had higher liver-related mortality rates than those infected through anti-D.

Antiviral treatment

- The first all-oral, direct acting antiviral (DAA) drug regimens for treating hepatitis C were approved In Ireland in late 2014. There are now several DAA combinations available, most with cure rates in excess of 95%.
- The efficacy and availability of these drug regimens, combined with a notable increase in liver disease among database participants, resulted in a significant increase in treatment uptake.
- 262 database participants were treated between 2014 and 2017: 84 had been previously treated and 178 were treated for the first time
- One was still on treatment when last followed up and the response to treatment was available for 261.
- The sustained virological response (SVR) rate for database patients treated using DAAs was 99% (258/261).
- Eighty five percent of living chronically infected database participants had been treated by the end of most recent follow up and 95% had achieved SVR on latest treatment (includes DAA and earlier treatment regimens).

Liver transplants

- Twenty five database participants had received a liver transplant by the end of most recent follow up. The average age at transplant was 54 years and the average duration of infection at transplant was 29 years.
- Sixteen of the liver transplant recipients had died by the end of 2017. The average time between transplant and death for these patients was 6 years.
- Of the remaining nine patients, eight have been successfully treated for their HCV infection (one prior to transplant and seven after transplant)

Focus on three individual patient groups

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

Summary tables

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

Conclusion

This report describes the health status of 1,322 people infected with HCV through the administration of blood or blood products in Ireland as of the end of 2017. At this stage, it had been over 35 years since infection occurred for more than half of the database population. It is clear that those who did not develop chronic HCV infection did not show signs of serious liver-related disease. Among those who developed chronic infection, a significant number had developed signs of serious liver disease such as cirrhosis and liver cancer, some of whom had died.

The most significant change since the previous round of data collection was the approval of new highly effective all-oral DAA drug regimens for treating hepatitis C. Although there was progression in the prevalence of adverse liver-related outcomes since the round of data collection four years prior, the vast majority of living patients, infected through blood or blood products in Ireland, were successfully treated by the end of 2017. International research has shown significantly reduced liver-related morbidity and mortality after SVR, especially in non-cirrhotic patients. Patients with cirrhosis also have a lower risk of developing liver failure and HCC once they have been successfully treated but remain at elevated risk compared to those with less severe pre-treatment liver disease and require long-term monitoring for complications. This is particularly true for patients with more advanced cirrhosis with varices, ascites or clinically evident portal hypertension.

Of the total database population, only 98 people were recorded as alive and still HCV infected at the end of the most recent data collection period. Some of these patients refused treatment, but many were patients who had not attended hepatology services for some time. Some may be deceased (but not reported as such to their hepatology units). At the time of data collection, the hepatology units were attempting to contact all remaining chronically infected patients who were not engaged in care, so that they could be encouraged to re-engage with hepatology services.

Summary tables

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

	All (n=1322)		Ever chronically infected (n=808)*		Currently chronically infected (n=299)†		Alive & currently chronically infected (n=98)		Chronically infected in the past (n=509)‡		Never chronically infected (n=465)§		No RNA results (n=49)	
All participants	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease ‖	293	22.2	278	34.4	134	44.8	22	22.5	144	28.3	8	1.7	7	14.3
Cirrhosis	234	17.7	227	28.1	108	36.1	18	18.4	119	23.4	2	0.4	5	10.2
Liver tumours or HCC	59	4.5	57	7.1	42	14.0	2	2.0	15	3.0	0	0.0	2	4.1
Deceased	306	23.2	221	27.4	201	67.2			20	3.9	45	9.7	40	81.6
Died from liver disease ¶	86	6.7	76	9.6	71	25.0			5	1.0	2	0.4	8	17.8

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

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

‡ At least one positive hepatitis C RNA result, now testing RNA negative, indicates viral clearance through antiviral treatment or late spontaneous clearance (small numbers).

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

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

¶ Liver-related disease directly caused death. Denominator for % calculation is all participants minus the 33 participants who have died but whose cause of death was not available (n=1289).

Table 2. Current RNA status for all participants

RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	%	Num	%	Num	%
Chronically infected*, never treated	214	16.2	74	7.3	140	45.8
Chronically infected, treated, no SVR	84	6.4	23	2.3	61	19.9
Chronically infected, treated, awaiting outcome, last RNA test positive	1	0.1	1	0.1	0	0
Past chronic infection†, treated, SVR	486	36.8	472	46.5	14	4.6
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	2	0.2	0	0	2	0.7
Past chronic infection, spontaneous resolution	21	1.6	17	1.7	4	1.3
Never chronically infected, confirmed positive‡	206	15.6	179	17.6	27	8.8
Never chronically infected, not confirmed positive§	259	19.6	241	23.7	18	5.9
No RNA results in chart	49	3.7	9	0.9	40	13.1
Total	**1322**	**100**	**1016**	**100**	**306**	**100**

* Hepatitis C RNA positive on most recent test

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

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

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

By source of infection

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

	All (n=811)*		Ever chronically infected (n=427)		Currently chronically infected (n=115)		Alive and currently chronically infected (n=54)		Chronically infected in the past (n=312)		Never chronically infected (n=374)	
Anti-D all	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	128	15.8	121	28.3	43	37.4	9	16.7	78	25.0	6	1.6
Cirrhosis	107	13.2	105	24.6	36	31.3	8	14.8	69	22.1	1	0.3
Liver tumours or HCC	13	1.6	13	3.0	6	5.2	0	0	7	2.2	0	0
Deceased	101	12.5	71	16.6	61	53.0			10	3.2	29	7.8
Died from liver disease †	23	2.9	21	5.0	21	18.9					1	0.3

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

This table includes participants infected in non-anti-D outbreak years (n=50) and those infected in outbreak years (1991-1994), but who did not have the relevant outbreak genotype (n=5).

† Denominator for this is all participants minus twelve participants who have died but whose cause of death was not available (n=799)

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

RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	**%**	**Num**	**%**	**Num**	**%**
Chronically infected, never treated	83	10.2	42	5.9	41	40.6
Chronically infected, treated, no SVR	31	3.8	11	1.5	20	19.8
Chronically infected, treated, awaiting outcome, last RNA test positive	1	0.1	1	0.1	0	0
Past chronic infection, treated, SVR	298	36.7	291	41.0	7	6.9
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	1	0.1	0	0	1	1.0
Past chronic infection, spontaneous resolution	13	1.6	11	1.5	2	2.0
Never chronically infected, confirmed positive	153	18.9	136	19.2	17	16.8
Never chronically infected, not confirmed positive	221	27.3	209	29.4	12	11.9
No RNA results in chart	10	1.2	9	1.3	1	1.0
Total	**811**	**100**	**710**	**100**	**101**	**100**

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

	All (n=683)*		Ever chronically infected (n=374)		Currently chronically infected (n=110)		Alive and currently chronically infected (n=49)		Chronically infected in the past (n=264)		Never chronically infected (n=303)	
Anti-D 1977-1979	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	119	17.4	112	30.0	42	38.2	8	16.3	70	26.5	6	2.0
Cirrhosis	99	14.5	97	25.9	35	31.8	7	14.3	62	23.5	1	0.3
Liver tumours or HCC	13	1.9	13	3.5	6	5.5	0	0	7	2.7	0	0
Deceased	97	14.2	67	17.9	61	55.5			6	2.3	29	9.6
Died from liver disease †	23	3.4	21	5.7	21	19.8					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 eleven participants who have died but whose cause of death was not available (n=672)

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

RNA status based on most recent RNA results	All		Currently alive		Deceased	
	Num	**%**	**Num**	**%**	**Num**	**%**
Chronically infected*, never treated	78	11.4	37	6.4	41	42.3
Chronically infected, treated, no SVR	31	4.5	11	1.9	20	20.6
Chronically infected, treated, awaiting outcome, last RNA test positive	1	0.1	1	0.2		0
Past chronic infection†, treated, SVR	253	37.0	248	42.7	5	5.2
Past chronic infection, spontaneous resolution	11	1.6	10	1.7	1	1.0
Never chronically infected, confirmed positive	142	20.8	125	21.5	17	17.5
Never chronically infected, not confirmed positive	161	23.6	149	25.6	12	12.4
No RNA results in chart	6	0.9	5	0.9	1	1.0
Total	**683**	**100**	**581**	**100**	**97**	**100**

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

	All (n=73)*		Ever chronically infected (n=37)		Never chronically infected (n=32)	
Anti-D 1991-1994	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	6	8.2	6	16.2	0	0
Cirrhosis	5	6.9	5	13.5	0	0
Liver tumours or HCC	0	0			0	0
Deceased	2	2.7	2	5.4	0	0
Died from liver disease †	0	0			0	0

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

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

Note: 5 participants who were reported as infected during this anti-D outbreak period, but who did not have this outbreak genotype are excluded from this table.

One participant remains currently chronically infected and alive and 36 were chronically infected in the past. Liver-related outcomes are not shown for these patients to ensure that they are not identifiable.

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

RNA status based on most recent RNA results	All		Currently alive	
Chronically infected, never treated	1	1.4	1	1.4
Past chronic infection, treated, SVR	34	46.6	33	46.5
Past chronic infection, spontaneous resolution	2	2.7	1	1.4
Never chronically infected, confirmed positive	5	6.8	5	7
Never chronically infected, not confirmed positive	27	37.0	27	38
No RNA results in chart	4	5.5	4	5.6
	73	**100**	**71**	**100**

Note: 5 participants who were infected during this anti-D outbreak period, but who did not have this outbreak genotype are excluded from this table.

Two participants were deceased. Further details are not shown for these patients to ensure that they are not identifiable

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

	All (n=339)*		Ever chronically infected (n=272)		Currently chronically infected (n=144)		Alive and currently chronically infected (n=39)		Chronically infected in the past (n=128)		Never chronically infected (n=65)	
Blood transfusion/renal	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	112	33.0	109	40.1	67	46.5	12	30.8	42	32.8	2	3.1
Cirrhosis	94	27.7	92	33.8	54	37.5	9	23.1	38	29.7	1	1.5
Liver tumours or HCC	33	9.7	33	12.1	28	19.4	2	5.1	5	3.9	0	0
Deceased	127	37.5	112	41.2	105	72.9			7	5.5	13	20.0
Died from liver disease †	41	12.7	40	15.3	36	26.9			4	3.1	1	1.7

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

† Denominator for this is all participants minus sixteen participants who have died but whose cause of death was not available (n=323)

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

RNA status based on most recent RNA results	All		Currently alive		Deceased	
Chronically infected, never treated	100	29.5	28	13.2	72	56.7
Chronically infected, treated, no SVR	44	13.0	11	5.2	33	26.0
Past chronic infection, treated, SVR	123	36.3	118	55.7	5	3.9
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	1	0.3	0	0	1	1
Past chronic infection, spontaneous resolution	4	1.2	3	1.4	1	0.8
Never chronically infected, confirmed positive	32	9.4	24	11.3	8	6.3
Never chronically infected, not confirmed positive	33	9.7	28	13.2	5	3.9
No RNA results in chart	2	0.6	0	0	2	1.6
Total	**339**	**100**	**212**	**100**	**127**	**100**

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

Outcomes	All (n=165)		Ever chronically infected (n=105)		Currently chronically infected (n=38)		Alive and currently chronically infected (n=4)		Chronically infected in the past (n=67)		Never chronically infected (n=23)		No RNA results (n=37)	
Blood clotting factors	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	52	31.5	47	44.8	23	60.5	1	25.0	24	35.8	0	0	5	13.5
Cirrhosis	32	19.4	29	27.6	17	44.7	1	25.0	12	17.9	0	0	3	8.1
Liver tumours or HCC	13	7.9	11	10.5	8	21.1	0	0	3	4.5	0	0	2	5.4
Deceased	77	46.7	37	35.2	34	89.5			3	4.5	3	13.0	37	100
Died from liver disease *	21	13.1	14	13.5	13	35.1			1	1.5	0	0	7	20.6

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

Table 12. Current RNA status for blood clotting factor participants

RNA status based on most recent RNA results	All		Currently alive		Deceased	
Chronically infected, never treated	29	17.6	3	3.4	26	33.8
Chronically infected, treated, no SVR	9	5.5	1	1.1	8	10.4
Past chronic infection, treated, SVR	63	38.2	61	69.3	2	2.6
Past chronic infection, spontaneous resolution	4	2.4	3	3.4	1	1.3
Never chronically infected, confirmed positive	19	11.5	17	19.3	2	2.6
Never chronically infected, not confirmed positive	4	2.4	3	3.4	1	1.3
No RNA results in chart	37	22.4	0	0	37	48.1
Total	**165**	**100**	**88**	**100**	**77**	**100**

By sex

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

Outcomes	All (n=1026)		Ever chronically infected (n=587)		Currently chronically infected (n=196)		Alive & currently chronically infected (n=81)		Chronically infected in the past (n=391)		Never chronically infected (n=426)		No RNA results (n=13)	
Females	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	188	18.3	179	30.5	79	40.3	16	19.8	100	25.6	7	1.6	2	15.4
Cirrhosis	160	15.6	157	26.8	67	34.2	15	18.5	90	23.0	1	0.2	2	15.4
Liver tumours or HCC	26	2.5	26	4.4	19	9.7	2	2.5	7	1.8	0	0	0	0
Deceased	168	16.4	130	22.2	115	58.7			15	3.8	34	8.0	3.4	30.8
Died from liver disease*	46	4.6	43	7.5	41	22.2			2	0.5	2	0.5	1	7.7

* Denominator for this is all participants minus twenty two participants who have died but whose cause of death was not available (n=1004)

Table 14. Current RNA status for females

RNA status based on most recent RNA results	All		Currently alive		Deceased	
Chronically infected, never treated	139	13.5	61	7.1	78	46.4
Chronically infected, treated, no SVR	56	5.5	19	2.2	37	22.0
Chronically infected, treated, awaiting outcome, last RNA test positive	1	0.1	1	0.1	0	0
Past chronic infection, treated, SVR	374	36.5	363	42.3	11	6.5
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	1	0.1	0	0	1	0.6
Past chronic infection, spontaneous resolution	16	1.6	13	1.5	3	1.8
Never chronically infected, confirmed positive	177	17.3	156	18.2	21	12.5
Never chronically infected, not confirmed positive	249	24.3	236	27.5	13	7.7
No RNA results in chart	13	1.3	9	1.0	4	2.4
Total	**1026**	**100**	**858**	**100**	**168**	**100**

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

Outcomes	All (n=296)		Ever chronically infected (n=221)		Currently chronically infected (n=103)		Alive & currently chronically infected (n=17)		Chronically infected in the past (n=118)		Never chronically infected (n=39)		No RNA results (n=36)	
Males	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**	**Num**	**%**
Signs of liver disease	105	35.5	99	44.8	55	53.4	6	35.3	44	37.3	1	2.6	5	13.9
Cirrhosis	74	25.0	70	31.7	41	39.8	3	17.7	29	24.6	1	2.6	3	8.3
Liver tumours or HCC	33	11.2	31	14.0	23	22.3	0	0	8	6.8	0	0	2	5.6
Deceased	138	46.6	91	41.2	86	83.5			5	4.2	11	28.2	36	100
Died from liver disease *	40	14.0	33	15.2	30	30.3			3	2.5	0	0	7	21.9

* Denominator for this is all participants minus eleven participants who have died but whose cause of death was not available (n=285)

Table 16. Current RNA status for males

RNA status based on most recent RNA results	All		Currently alive		Deceased	
Chronically infected, never treated	75	25.3	13	8.2	62	44.9
Chronically infected, treated, no SVR	28	9.5	4	2.5	24	17.4
Past chronic infection, treated, SVR	112	37.8	109	69.0	3	2.2
Past chronic infection, treated, no SVR, but subsequently tested RNA negative	1	0.3	0	0	1	0.7
Past chronic infection, spontaneous resolution	5	1.7	4	2.5	1	0.7
Never chronically infected, confirmed positive	29	9.8	23	14.6	6	4.3
Never chronically infected, not confirmed positive	10	3.4	5	3.2	5	3.6
No RNA results in chart	36	12.2	0	0.0	36	26.1
Total	**296**	**100**	**158**	**100**	**138**	**100**

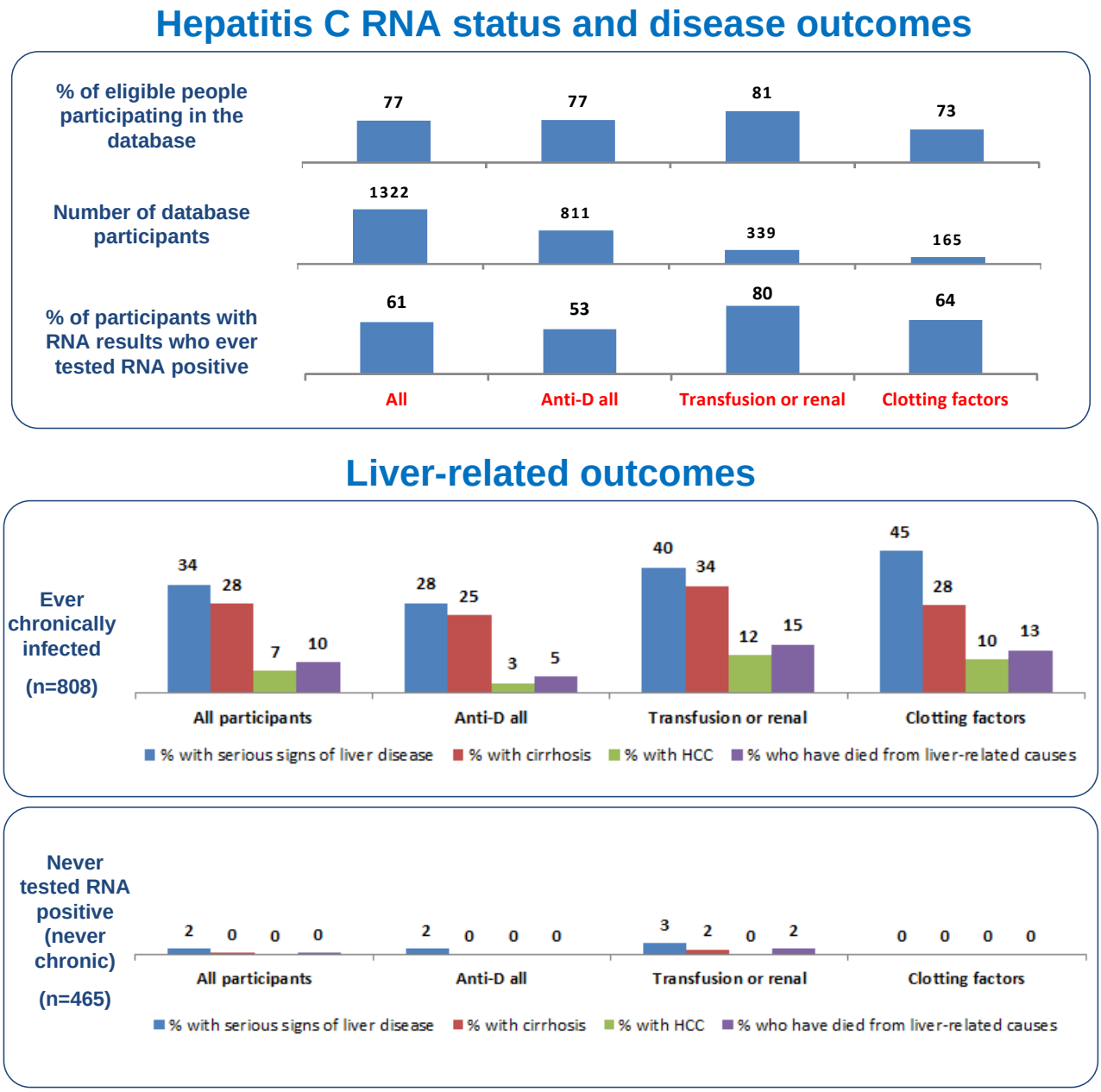


Figure 1. Summary of database participation, RNA status, and disease progression by RNA status, for all participants and by source of infection

Note: A small number of database participants who were infected through contact with cases infected through blood or blood products are included in the 'All' category but are not shown by source of infection.

Chapter 1. Hepatitis C virus infection

Hepatitis C (HCV) infection is caused by an RNA virus that was first identified in 1989. It primarily affects the liver but can have extrahepatic manifestations.[1-3] Six distinct but related genotypes and multiple subtypes have been identified. In Western Europe genotypes 1a and 1b are most common, followed by genotypes 3 and 2.[4]

HCV is transmitted by blood. Infection now occurs primarily through injecting drug use, and less frequently through sex with an infected partner, occupational exposure, and mother to infant transmission.[4,5] Transfusion-related HCV infection is rare since the introduction of routine screening of blood for HCV antibodies in the early 1990s.

Acute HCV infection, in general, is relatively mild with only 20%-30% of infected people developing symptoms or clinically evident acute infection.[2] In most people who become infected with HCV, viremia persists, that is, the virus continues to be present in the blood. Chronic HCV infection is marked by persistence of HCV RNA for at least 6 months after onset of infection. Between 55% and 85% of those infected with HCV develop chronic infection[6], the lower end of the range being accounted for mainly by young women.[7,8] Spontaneous resolution of chronic hepatitis C is relatively rare but can occur.[9]

Chronically infected people are at risk of progressive liver disease characterised by hepatocellular inflammation, hepatic fibrosis, cirrhosis and hepatocellular carcinoma (HCC).[6] These complications develop only in a proportion of patients and mostly after many years or decades of infection. It is estimated that between 15 and 35% of chronically infected individuals develop cirrhosis of the liver after 25 to 30 years of infection.[10] Approximately 1% to 4% of patients with cirrhosis develop HCC per year.[10] Factors that have been shown to be associated with progression of liver fibrosis include older age at infection, male sex, metabolic factors (steatosis, diabetes and obesity), co-infection with human immunodeficiency virus (HIV) or hepatitis B, longer duration of infection, and high alcohol intake.[1,3,4,6,9,10]

Chronic HCV infection has also 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]

There have been major advances in hepatitis C treatments in recent years. Until 2011, the standard of care was a combination of pegylated interferon (PegIFN) and ribavirin (RBV) for 24 to 48 weeks, depending on the hepatitis C genotype. This resulted in a successful response to treatment (SVR - sustained virological response) in more than 75% of patients with genotypes 2 or 3 HCV infection, and 40-50% of those with genotype 1 infection.[11] The addition of telaprevir or boceprevir to existing regimens, in 2011, increased the SVR rates in genotype 1 patients, but with additional side effects.[12]

The approval of all oral, interferon-free, direct acting antiviral (DAAs) drug regimens, in late 2014 and early 2015, completely changed the landscape of hepatitis C treatment in Ireland and elsewhere. There are now several highly effective DAA combinations available for hepatitis C treatment. The most commonly used combinations in Ireland, between 2014 and 2017, were Abbvie's viekirax (ombitasvir, paritaprevir and ritonavir) and exviera (dasabuvir) with or without ribavirin and Gilead's harvoni (ledipasvir and sofosbuvir) with or without ribavirin. Treatment with these drug regimens results in SVR for over 95% of patients, with fewer side effects and shorter treatment durations than interferon-based regimens.[13]

Studies have shown significantly reduced liver-related morbidity and mortality after SVR. This is particularly true in non-cirrhotic patients. Patients with cirrhosis also have a lower risk of developing liver failure and HCC once they have been successfully treated but remain at elevated risk compared to those with less severe pre-treatment liver disease and require long-term monitoring for complications. This is particularly true for patients with more advanced cirrhosis with varices, ascites or clinically evident portal hypertension.[14,15,16]

A national hepatitis C treatment programme was established by the HSE in 2015 (https://www.hse.ie/eng/national-hepatitis-c-treatment-programme/). The aim of this programme is to provide treatment for all people living with hepatitis C in Ireland. Given the efficacy of the DAA treatment regimes, elimination of hepatitis C is now achievable in Ireland, and with good treatment uptake, hepatitis C should become a rare disease in the near future.[17]

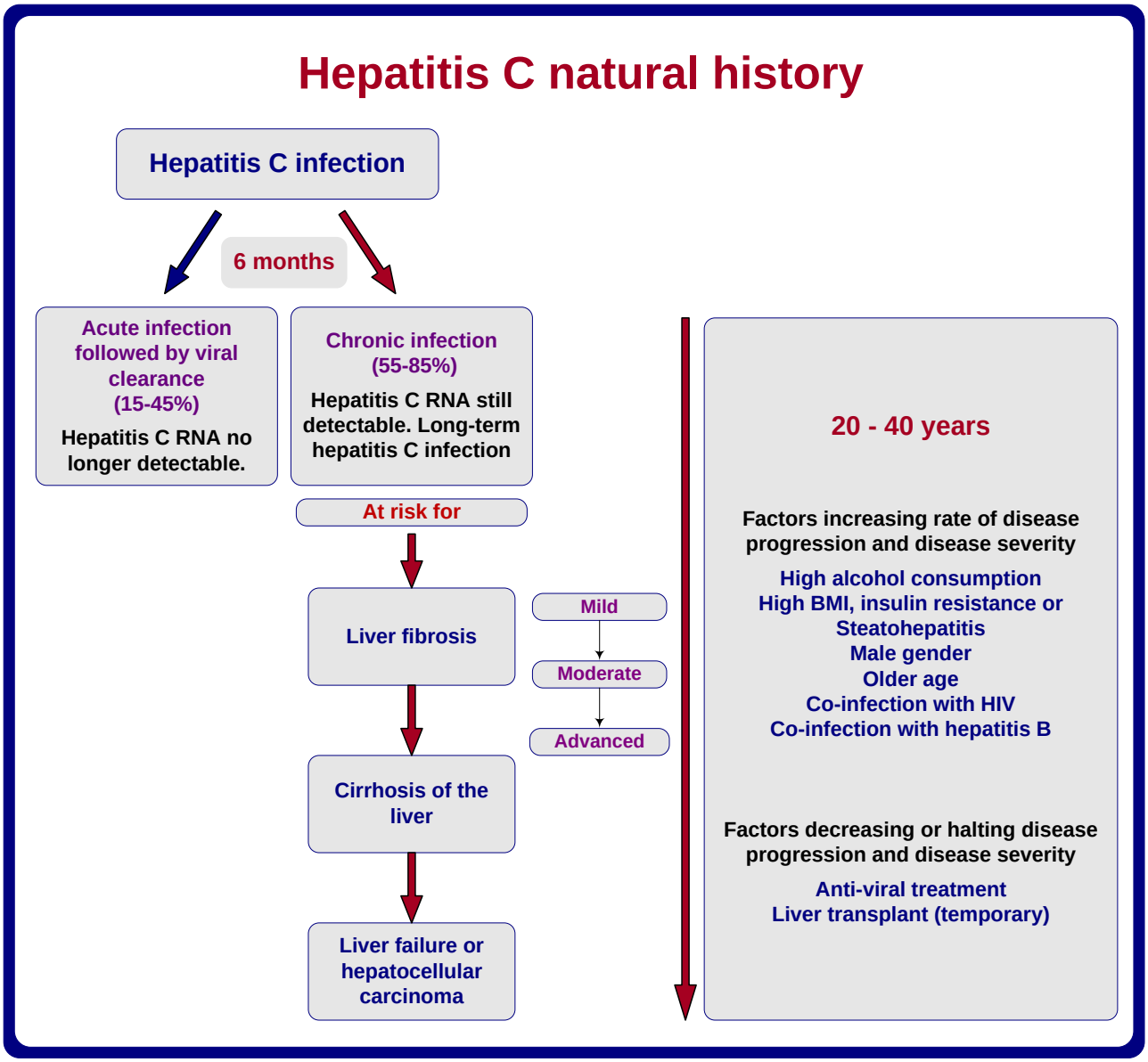


Figure 2. Summary of natural history of hepatitis C infection

Chapter 2. National Hepatitis C Database

2.1 Background to the database

The National Hepatitis C Database was set up in 2004 by the HSE-Health Protection Surveillance Centre (HPSC) in association with eight specialist hepatology units to collect data on people who were identified as having been infected with HCV through the receipt of contaminated blood and blood products in Ireland.

These included women infected through anti-D immunoglobulin, recipients of blood transfusions, people with haemophilia and other blood clotting disorders and people who received treatment for renal disease.[18] Specialist hepatology services were set up in eight designated hospitals to provide services for this group of 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 the database 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 was overseen by a Steering Committee (appendix A). A Scientific and Technical Group supported and advised HPSC on the scientific and technical development of the database (appendix B).

2.2 The objectives of the database were:

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

2.3 Data collection and reporting

Baseline data were collected in 2005 and 2006 and included all relevant data, from the date of diagnosis, on all patients who consented to participate and those who had died. A baseline report[19] describing these data was published in October 2007. Four follow-up reports have been published since baseline data collection, in 2009, 2010, 2012 and 2015.[20-23] This is the sixth report and includes information on all participants up to the end of 2017. Reports are available through the hepatology units, patient support groups, hepatitis C liaison officers and on the database website (www.hcvdatabase.ie).

2.4 Database population

Any person (alive or dead) who contracted HCV infection through the administration of blood or blood products within the state was eligible to be included in the database. Eligible patients were identified by the eight specialist hepatology units.[19]

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

People with positive or weak positive ELISA/EIA tests or indeterminate RIBA/INNO-LIA tests were included in the database as many patients were tested many years after the time of suspected infection, having had documented exposure to HCV, and some of these may have cleared the virus and since sero-reverted. HCV antibody levels have been demonstrated to drop below detection limits in some patients.[24-26]

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

2.5 Source of data

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

2.6 Data security

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

Chapter 3. Methods

3.1 Data Collection

The sixth round of data collection began in January 2018 and captured patient data up to 31st December 2017. Data were extracted from participants' medical notes by an HPSC research nurse and epidemiologist. Information collected included clinical, demographic and lifestyle data, which had been added to participants' medical records between the start of 2014 and the end of 2017. Data were entered into the database by a surveillance assistant in HPSC. Double entry was used to maximise accuracy. To improve the information available for participants, some additional data fields were included in the latest follow-up data collection form (appendix C).

3.2 Recruitment of new participants

Recruitment of new participants to the database was ongoing throughout the lifespan of the database project and eligible people were welcome to join at any time. These included people who did not consent to participate in the database when first invited to do so in 2004, and those who were newly identified as eligible since 2004. Patients were given the opportunity to consent at their hospital appointments. If they were interested in participating, they were given further information about the database by staff. Those who refused to consent at any time were not asked again. The patient support groups also encouraged their members to participate through their newsletters and meetings.

There were a small number of people living abroad (approximately 25; personal communication, Michelle Tait HSE), who met the eligibility criteria for the database but who did not attend a clinical service in Ireland. They were not included in the database due to the difficulties that would have arisen in terms of data collection, data quality, confidentiality and consent.

3.3 Assumptions

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

- Anti-D: If the person had received anti-D on multiple occasions, and one of these was the year of an outbreak period, i.e. 1977-1979 or 1991-1994, this year was taken as the year of infection. If none of the years fell into either of the outbreak periods, the earliest year that anti-D had been administered was used as the year of infection.
- Blood transfusion/treatment for renal disease: If the person had received multiple blood transfusions and none of them had been identified as being infectious, the earliest transfusion year was taken as the year of infection. Where the person had also been on dialysis for extended periods of time, the year of starting dialysis or of first blood transfusion, whichever was the earlier, was used as an estimate of the year of infection.
- Clotting factors: For people with haemophilia and other blood clotting disorders, if the year of infection was not available, the year that the patient first received clotting factors was

used as a proxy for the year of infection. Where the year of infection and the year when first factor was administered were missing, then the year of diagnosis of haemophilia was used as the year of infection.

- Where precise day or month were missing from a date (e.g. date of infection), the year was converted to 02/07/YYYY, where YYYY was the year (e.g. year of infection) and 02/07 was the midpoint of the year.
- All calculated ages were truncated (age as of last birthday) and all calculated durations were rounded.

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

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

3.5 Estimating duration of hepatitis C ribonucleic acid (RNA) positivity

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

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

3.6 Interpretation and presentation of HCV test results

3.6.1 HCV tests and their meaning

RNA tests (also known as PCR tests) are used to test for circulating virus (viraemia). Positive results indicate current infection. Antibody tests indicate if a person has ever been HCV infected, even if they no longer have circulating virus. In general, ELISA/EIA tests are used as screening tests for HCV antibodies, and line-immunoassay tests (e.g. RIBA/INNO-LIA) are used to confirm positive antibody results. The combination of a positive HCV antibody result and a negative RNA result indicates past infection.

3.6.2 Chronic HCV infection

As the vast majority of participants were diagnosed some years after infection, "ever testing RNA positive" can be taken to indicate that the person developed chronic long-term infection. Throughout this report, we treat participants who ever tested RNA positive as having been chronically infected with HCV and primarily focus on these participants when looking at clinical outcomes and liver disease progression.

3.6.3 Spontaneous viral clearance

There was no way of determining the timing of viral clearance for participants who cleared the HCV virus spontaneously prior to RNA testing (and thus had no positive RNA results). However, studies have found that spontaneous viral clearance usually occurs within one year of infection, so we assumed that these participants experienced acute infection only and were never chronically infected.[30,31]

3.6.4 Categorisation by RNA status

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 (ever chronically infected) and those who had RNA tests done but had no positive RNA results (never chronically infected). A small number of participants who had no RNA results in their charts were omitted from most of the results presented by RNA status as they could not be classified as either "ever" or "never" testing RNA positive. These were generally patients who had died prior to PCR testing being in common use in Ireland.

3.7 Categorisation of alcohol consumption

At the time the database was established, 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. [32] (Note: Low risk drinking guidelines have since been revised and are now defined as 17 standard drinks for men and 11 standard drinks for women, per week.[33]) 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 alcohol consumption were available for 94% of those who became chronically infected. However, it was unusual for alcohol consumption to have been recorded at every visit, and for many cases it was last recorded several years prior. Alcoholic liver disease or alcohol abuse was also mentioned in the medical records 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 (alcoholic liver disease, alcohol abuse or >40 units per week).

3.8 Coding of death certificates

Death certificates were collected for deceased participants from the General Register Office (GRO). This was done by the HPSC database research nurse, acting on behalf of the hepatology unit. 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 antibody or RNA status of the patient.

3.9 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: [34] fibrosis scored from 0-4
- Modified Knodell system,[35,36] also known as the Ishak or the modified HAI system: fibrosis scored from 0-6
- Scheuer system:[37] 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. Participants who had scores of 3 or 4 (0-4 scoring) or between 4 and 6 (0-6 scoring) were classified as having high fibrosis scores on biopsy. There has been a shift towards less invasive diagnostic procedures since the database project began and very few biopsies were carried out the last ten years of follow up.

3.10 Fibroscan results

Fibroscan results provide useful indicators of advanced fibrosis and cirrhosis but are not as accurate in distinguishing mild to moderate fibrosis. Results may also vary depending on the physiological features of the patient, particularly high BMI and abdominal adiposity. We

interpreted fibroscan scores of 9.5-14.4 kPa as indicating that the patient may have advanced fibrosis and scores of 14.5 kPa or higher as indicating that the patient may have cirrhosis.[38] High fibroscan results that were not consistent with other information in the patient's medical records were validated with the patient's hepatology unit.

3.11 Data analysis

Data analysis was done using Microsoft Access 2010, Microsoft Excel 2010 and Stata/SE version 15.1. Either Pearson's chi-square or the Wald test, with corresponding probability value (p-value) and 95% confidence intervals, were used to test for statistically significant differences between the occurrence of a given outcome in different categories of a variable (e.g. was cirrhosis more common in ever chronically infected patients than in never chronically infected patients?)

Multivariate regression (binomial) was used to investigate which patient and virus characteristics were independently and significantly associated with key outcomes. The regression models were mostly used to examine the determinants of key liver-related outcomes in participants who were ever chronically HCV infected and typically initially included sex, alcohol consumption, age at infection/age at end of follow up, duration of infection, HCV genotype and BMI. Only variables that were significantly associated with the outcome were maintained in the final model. Models were also created with source of infection instead of sex as these two variables were too closely linked for the effect of both to be examined in the same model. Poisson regression was used for modelling rates (cirrhosis/HCC/mortality) and survival curves were derived using the Kaplan Meier method. All statistical tests were 2-tailed and a p-value of <0.05 was taken as statistically significant.

Chapter 4. Main Findings

The summary tables 1-16 at the beginning of this report provide details of liver-related outcomes by RNA status, source of infection and sex and show current RNA status (as of most recent follow up) for all database participants by source of infection and sex.

4.1 Participation rates and representativeness of the database cohort

The overall participation rate in the database was 77%, including people who have died. The consent rate was 74% (figure 3). Three people consented and were added to the database since the previous round of data collection and one person was removed (found to be ineligible), bringing the total number of participants to 1,322. Figure 3 details the response rate by source of infection and sex.

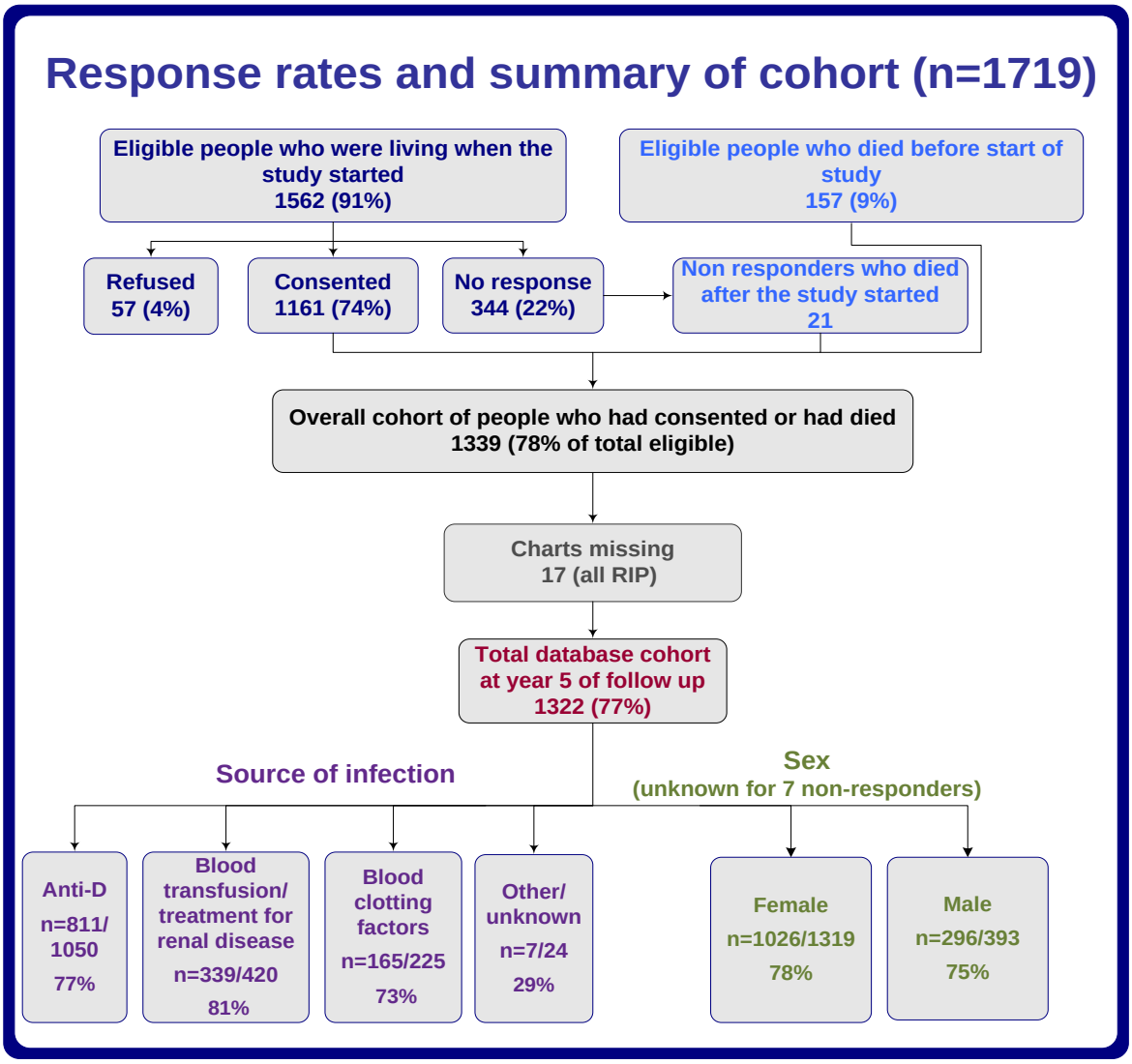


Figure 3. Summary of database cohort and participation rates by source of infection and sex

Note: Source of infection = "Other/unknown" included participants who were infected through contact with cases who were infected through blood or blood products.

Database participation increased with increasing age up to the mid-60s and declined slightly thereafter. This difference was statistically significant and was also evident when deceased patients were excluded from the analysis (consenting persons only). There was no significant difference in participation rate for females and males: 78% of females (n=1026) and 75% of males (n=296). People infected through blood clotting factors (73%) were significantly less likely to be included in the database compared to blood transfusion/renal patients (81%).

4.2 Hepatitis C infection status and RNA results

4.2.1 Hepatitis C test results

See Methods section 3.6 regarding interpretation of HCV test results.

Overall, 61% (n=808) of database participants had at least one positive RNA result in their charts (ever chronically infected), a further 35% (n=465) had RNA test results, but none were positive (never chronically infected) and the remaining 4% (n=49) had no RNA results in their medical records (all were deceased and most had died in the early to mid-1990s).

Over half (n=259) of the database participants who were classified as never chronically infected did not have positive confirmatory tests for HCV antibodies – they tested either ELISA/EIA positive or weak positive, or RIBA/INNO-LIA indeterminate. The remaining 206 participants had positive confirmatory tests for HCV antibodies (e.g. RIBA/INNO-LIA).

4.2.2 Viral clearance rate

Once participants with no RNA results were excluded (n=49), the overall spontaneous viral clearance rate, as determined by testing RNA negative at the time of first diagnosis, was 37% (465/1273). This varied by sex and source of infection. Females (n=426, 42%) were significantly more likely to have cleared the virus by the time of their diagnosis than males (n=39, 15%). As stated above, some participants did not have positive confirmatory results for HCV. A proportion of these may have had false positive ELISA/EIA results, making the viral clearance rate appear higher than it was. When only participants with positive confirmatory results for HCV were considered, 20% (206/1014) had cleared the virus spontaneously by the time they were diagnosed. The sex imbalance was also significantly reduced – the clearance rate was 23% for females compared to 12% for males. Therefore, the true spontaneous viral clearance rate after acute infection is likely to have been between 20 and 37%, with 63%-80% of those infected becoming chronically infected.

4.3 End of latest follow-up

Medical Information up to the end of 2017, where available, was 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.

Sixty five percent of all living database participants had attended their hepatology unit between 2014 and 2017. Attendance varied with RNA status. Eighty one percent of living ever chronically infected participants had attended their unit within these four years. Participants who had never become chronically infected were less likely to have attended recently, with 45% attending between 2014 and 2017. Some database participants are likely to have moved abroad and may have been lost to follow-up and some of the participants who never became chronically infected may have been discharged to the care of their GPs. Although we attempt to capture any new deaths at each round of follow up, it is likely that a small number of additional patients have died and are not identified as deceased in their hospital medical records.

4.4 Database participants: entire cohort

Date of infection and demographic characteristics for the entire database cohort are shown in figure 4 and table 17.

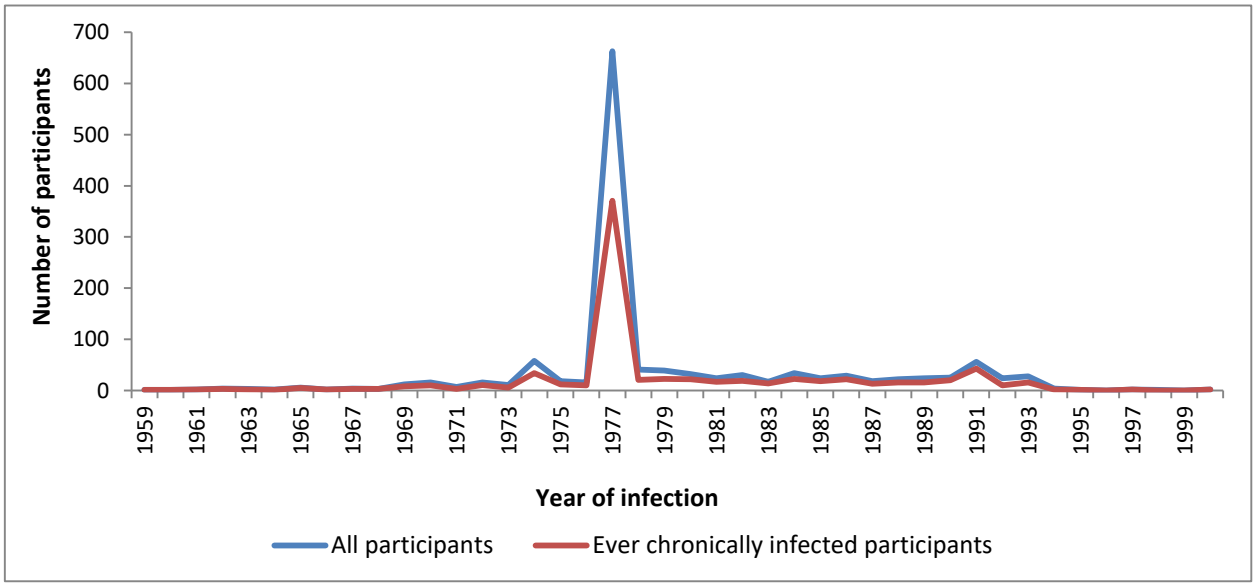


Figure 4. Number of database participants by year of HCV infection and RNA status

Table 17. Summary of demographic and virus characteristics for database participants by RNA status (n=1322)

All participants	All		Ever chronically infected		Alive & currently chronically infected		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%
All participants	**1322**		**808**		**98**		**465**	
Sex (n=1322)								
Females	1026	77.6	587	72.7	81	82.7	426	91.6
Males	296	22.4	221	27.4	17	17.4	39	8.4
Age at infection (n=1322)								
Median	**28**	**0-77**	**28**	**0-77**	**32**	**0-66**	**28**	**0-63**
<20	213	16.1	141	17.5	10	10.2	48	10.3
20-29	568	43.0	318	39.4	32	32.7	237	51.0
30-39	395	29.9	241	29.8	37	37.8	147	31.6
40+	146	11.0	108	13.4	19	19.4	33	7.1
Age at end of follow up (n=1322)								
Median	**63**	**12-91**	**64**	**16-91**	**69**	**24-90**	**59**	**15-91**
0-49	258	19.5	131	16.2	9	9.2	93	20.0
50-64	501	37.9	302	37.4	27	27.6	188	40.4
65+	563	42.6	375	46.4	62	63.3	184	39.6
Time since infection (n=1322)								
Median	**35**	**1-55**	**37**	**1-55**	**38**	**7-55**	**32**	**4-48**
<25 years	291	22.0	143	17.7	11	11.2	109	23.4
25-34 years	365	27.6	214	26.5	23	23.5	143	30.8
35+ years	666	50.4	451	55.8	64	65.3	213	45.8
Duration RNA positivity (n=808)								
Median	**32**	**1-55**	**32**	**1-55**	**38**	**7-55**	n/a	
<25 years	240	29.7	240	29.7	11	11.2		
25-34 years	216	26.7	216	26.7	23	23.5		
35+ years	352	43.6	352	43.6	64	65.3		
Highest alcohol intake (n=1210)								
Non drinker	290	24.0	175	23.0	30	32.6	109	25.3
Within recommended limits	735	60.7	446	58.7	51	55.4	281	65.2
Moderately high	91	7.5	65	8.6	5	5.4	25	5.8
High	94	7.8	74	9.7	6	6.5	16	3.7
HCV genotype (n=783)								
Genotype 1	598	76.4	598	76.4	81	82.7	n/a	
Genotype 2	38	4.9	38	4.9	4	4.1		
Genotype 3	143	18.3	143	18.3	13	13.3		
Genotype 4	2	0.3	2	0.3	0	0.0		
Genotype 5	2	0.3	2	0.3	0	0.0		
Body mass index (n=629)								
Normal or underweight	221	35.1	149	35.2	22	42.3	72	35.0
Overweight	224	35.6	153	36.2	18	34.6	71	34.4
Obese	184	29.3	121	28.6	12	23.1	63	30.6

*49 database participants had no RNA results in their medical records. They are included in the data for the "All" category, but not in the breakdown by RNA status. † High alcohol intake includes alcohol abuse or alcoholic liver disease recorded in participant's medical record. The alcohol breakdown represents the highest recorded alcohol intake for each participant. Alcohol data were not available for 112 database participants. n/a: not applicable

4.4.1 Sex, age and duration of infection

See Methods section 3.3 for assumptions about year of infection.

Of the 1322 database participants, 61% (n=808) were chronically HCV infected at diagnosis. Due to the large anti-D cohort, females predominate and account for 73% (n=587) of those who ever became chronically infected. The median age at infection for participants who were ever chronically infected was 28 years, the median age at end of follow-up was 64 years, the median time since infection was 37 years and the median duration of RNA positivity was 32 years.

At the time of data collection, there were only 98 living database participants who remained chronically infected (table 17). About one third of these patients are likely to be lost to follow up: 27 last attended hepatology services over five years ago and five are known to have moved abroad. Some of these patients may be deceased. Of the remaining chronically infected participants, 31 refused antiviral treatment, 9 were not treated due to other medical problems or advanced age, 1 was treated with DAAs, but treatment was stopped early due to medical issues, 1 was on treatment at the time of follow up, 1 was considering treatment and the reason for not being treated was not known for 23.

4.4.2 Body mass index (BMI)

BMI data were available for 48% (n=629) of all database participants and 52% (n=423) of ever chronically infected participants. Overall, 36% (n=224) were overweight and a further 29% (n=184) were obese (table 17). These data may not be representative of all participants as it is likely that BMI data are recorded more often for those who are either overweight or underweight. BMI did not vary significantly by sex, source of infection or RNA status, but did vary by age at end of latest follow-up, with participants aged between 50 and 69 years more likely to be obese than both younger and older participants.

4.4.3 Alcohol consumption

See Methods section 3.7 for categorization of alcohol consumption.

Moderately high alcohol intake was recorded in the medical charts of 9% of ever chronically infected participants for whom data were available, and high alcohol consumption was recorded for a further 10% (table 17). Males and females differed in their reported exposure to alcohol with 35% (n=70) of chronically infected males having moderately high or high alcohol intake at some stage compared to 12% (n=69) of females (figure 5). Younger participants were also more likely to

have had excessive alcohol consumption recorded in their medical notes. Alcohol consumption differed significantly by source of infection with participants infected through anti-D (12%) (table 18) less likely to consume alcohol in excess of recommendations compared to those infected through blood transfusion or treatment for renal disease (22%) (table 19) and those infected through clotting factors (36%) (table 20). However, this is largely attributable to the differences in age and sex profiles by source of infection.

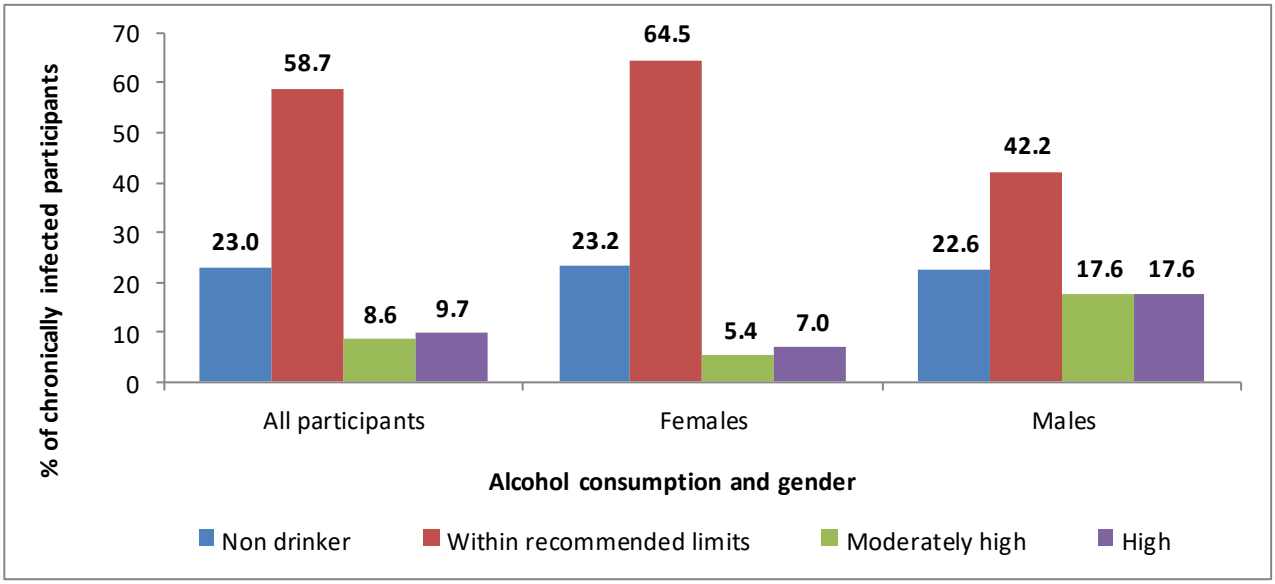


Figure 5. Distribution of highest reported alcohol consumption by sex for participants who became chronically infected (n=760)

4.4.4 HCV genotype

The HCV genotype was available for nearly all of the database participants who became chronically infected (n=783, 97%). Genotype 1 predominated; 77% (n=598) were infected with genotype 1, 18% (n=143) with genotype 3, 5% (n=38) with genotype 2 and four participants were infected with genotypes 4 or 5 (table 17).

4.5 Outcomes

Liver-related disease can be caused by factors other than hepatitis C. However, summary table 1 shows that liver-related disease was rare in database participants who did not develop chronic HCV infection and this results section focuses more on participants who became chronically infected with HCV.

4.5.1 Clinical signs of serious liver disease

Over a third (34%, n=278) of chronically infected participants had one or more clinical signs of serious liver disease (as listed in table 18) recorded in their charts by latest follow-up. The most common conditions or signs recorded were cirrhosis, varices, splenomegaly and portal hypertension. This was significantly higher than the 2% (n=8) of database participants who never became chronically infected with HCV who showed signs of serious liver disease when last followed up (crude risk ratio: 20, 95% CI: 1 – 40, p<0.001).

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

Clinical signs of liver disease	All participants (n=1322)		Ever chronically infected (n=808)		Never chronically infected (n=465)	
	Num	%	Num	%	Num	%
One or more signs of liver disease	**293**	**22.2**	**278**	**34.4**	**8**	**1.7**
Cirrhosis	234	17.7	227	28.1	2	0.4
Varices	96	7.3	94	11.6	0	0
Splenomegaly	90	6.8	88	10.9	2	0.4
Portal hypertension	84	6.4	83	10.3	0	0
Ascites	77	5.8	73	9.0	3	0.7
Liver Tumour/HCC	59	4.5	57	7.1	0	0
Hepatomegaly	38	2.9	34	4.2	4	0.9
Encephalopathy	34	2.6	32	4.0	1	0.2
Decompensated liver disease	24	1.8	23	2.9	0	0
Bleeding Varices	17	1.3	16	2.0	0	0
Hepatosplenomegaly	6	0.5	6	0.7	0	0
Hypersplenism	5	0.4	5	0.6	0	0
Oedema	3	0.2	3	0.4	0	0
Hepatic synthetic dysfunction	3	0.2	3	0.4	0	0
Portal gastropathy	2	0.2	2	0.3	0	0
Hepatopulmonary Syndrome	1	0.1	1	0.1	0	0
Hepatorenal syndrome	1	0.1	1	0.1	0	0

*7 participants with one or more signs of liver disease (including 5 with cirrhosis and 2 with liver tumours/HCC) had no RNA results in their charts (included under all, but not under 'ever chronically infected' or 'never chronically infected' categories)

The factors that were significantly associated with having one or more clinical signs of serious liver disease in chronically infected participants were high alcohol intake, longer duration of RNA positivity and male sex (table 19 –regression model a). Participants with high alcohol consumption had double the risk of having signs of liver disease compared to those without. However, the number of chronically infected participants with high alcohol intake was low (n=74, 10%) and due to its sensitivity, alcohol consumption data may be inaccurately reported.

The association between source of infection and sex on risk of developing serious signs of liver disease cannot be assessed in the same regression model as sex is too closely linked to source of infection in the database population. Chronically infected males had a slightly higher risk of developing signs of liver disease compared to females (table 19 – binomial regression model a). Blood transfusion/renal participants and participants infected through contaminated clotting factors were significantly more likely to have one or more signs of liver disease compared to anti-D participants after adjusting for alcohol consumption and duration of infection (table 20 – binomial regression model b). This may be largely attributable to differences in sex distribution by source of infection, but there may be additional unmeasured or inaccurately reported confounders associated with the different sources of infection (e.g. inaccurately reported alcohol consumption, other comorbidities). HCV genotype was not significantly associated with risk of developing signs of liver disease. BMI was not included in models as it was only reported for 52% of chronically infected participants.

Table 19. Factors associated with having one or more clinical signs of serious liver disease in ever chronically infected participants – binomial regression model a (n=760)

Factors associated with signs of serious liver disease	Risk ratio	p-value	95% confidence interval
Highest recorded alcohol consumption			
Non-drinker/within recommended limits/moderately high	1		
High (>40 units per week or alcohol abuse in chart)	2.0	<0.001	1.66 - 2.53
Duration of RNA positivity			
<20 years	1		
20-29 years	1.8	0.003	1.22 - 2.72
30+ years	2.4	<0.001	1.64 - 3.40
Sex			
Female	1		
Male	1.3	0.021	1.04 - 1.59

Explanatory note: The risk ratios shown are a measure of the risk of clinical signs of serious liver disease in one group (e.g. males) divided by the risk of serious disease in another group (the reference group e.g. females). A risk ratio of 1 indicates that signs of liver disease are equally likely in both males and females and a risk ratio of greater than 1 for males indicates that signs of liver disease are more likely in males. P-values of <0.05 were taken to indicate a statistically significant difference between the distribution of signs of liver disease in the category of the factor being assessed and the reference category of that factor. Each factor in the model is adjusted for the effect of the other factors in the model e.g. the effect of alcohol is adjusted for the duration of RNA positivity and sex and the estimated risk ratio for high alcohol use should be independent of the effect of duration of RNA positivity and sex.

Table 20. Factors associated with having one or more clinical signs of serious liver disease in ever chronically infected participants – binomial regression model b (n=757)

Factors associated with signs of serious liver disease	Risk ratio	p-value	95% confidence interval
Highest recorded alcohol consumption			
Non-drinker/within recommended limits/moderately high	1		
High (>40 units per week or alcohol abuse in chart)	1.9	<0.001	1.57 - 2.34
Duration of RNA positivity			
<20 years	1		
20-29 years	1.8	0.004	1.21 - 2.72
30+ years	2.5	<0.001	1.74 - 3.65
Source of infection			
Anti-D	1		
Transfusion or renal	1.5	0.001	1.17 - 1.85
Clotting factors	1.4	0.01	1.09 - 1.89

4.5.2 Cirrhosis

Cirrhosis also varied significantly by RNA status, with ever chronically infected participants much more likely to have developed cirrhosis compared to those who never became chronically infected (n=227, 28% compared to n=2, 0.4%, crude risk ratio 65, p<0.001). Table 21 shows the number and percentage of ever chronically infected participants who developed cirrhosis by key host and virus factors.

Table 21. Cirrhosis in ever chronically infected database participants (with univariate chi-square tests for differences in prevalence of cirrhosis across different categories of host and virus variables)

Ever chronically infected database participants	Number with cirrhosis	% with cirrhosis	p-value	Median age at cirrhosis diagnosis (years)	Median duration RNA positivity at cirrhosis (years)
All	227	28.1		58	28
Sex			0.165		
Females	157	26.8		60	30
Males	70	31.7		52	25
Source of infection			**0.030**		
Anti-D	105	24.6		59	33
Transfusion or renal	92	33.8		58	24
Clotting factors	29	27.6		49	31
Highest recorded alcohol intake			**<0.001**		
Non-drinker	51	29.1		61	29
Within recommended limits	102	22.9		59	31
Moderately high	16	24.6		55	30
High	45	60.8		53	23
Age at infection			**0.005**		
<25 years	70	16.0		49	31
25-34 years	95	15.8		59	30
35+ years	69	24.3		68	21
HCV genotype			0.841		
Genotype 1	168	28.1		59	31
Genotype 2	38	23.7		54	22
Genotype 3	143	29.4		53	23

The approximate date of cirrhosis was estimated for all database participants who developed cirrhosis. Database participants who ever became chronically infected had a 64-fold higher crude rate of cirrhosis compared to those who were never chronically infected (8.9 per 1,000 person years at risk versus 0.14 per 1,000 person years at risk, p<0.001) (figure 6).

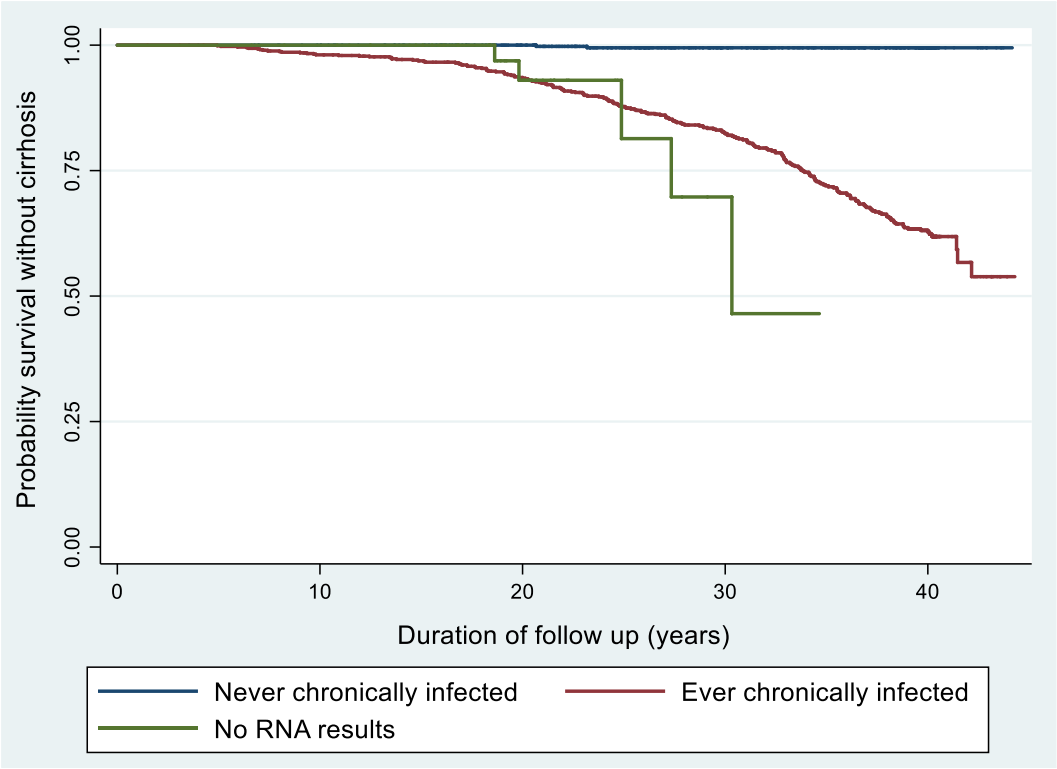


Figure 6. Proportion of participants who have not developed cirrhosis over the follow-up period by RNA status – Kaplan Meier survival estimates

For ever chronically infected database participants, the median duration of RNA positivity at the estimated date of cirrhosis (see Methods section 3.4 and 3.5 for methods used) was 28 years (mean: 27 years) and the median age at cirrhosis was 58 years (mean: 57 years). Of the 227 ever chronically infected participants who developed cirrhosis, just over half (52%, n=119) subsequently cleared the virus, mostly through successful treatment. Outcomes for patients who developed cirrhosis are shown in figure 7.

Only fourteen participants were estimated to have been diagnosed with cirrhosis after achieving SVR on treatment (see Methods section 3.4 regarding the method of assigning dates of cirrhosis diagnosis). Of these, five had not had biopsies for over 5 years prior to treatment, four had had high fibrosis scores before treatment and two had been diagnosed with serious signs of liver disease such as ascites, splenomegaly and portal hypertension prior to treatment. These participants were all likely to have been cirrhotic or pre-cirrhotic prior to treatment. Moderately high or high alcohol consumption was recorded in the medical records of the remaining three patients.

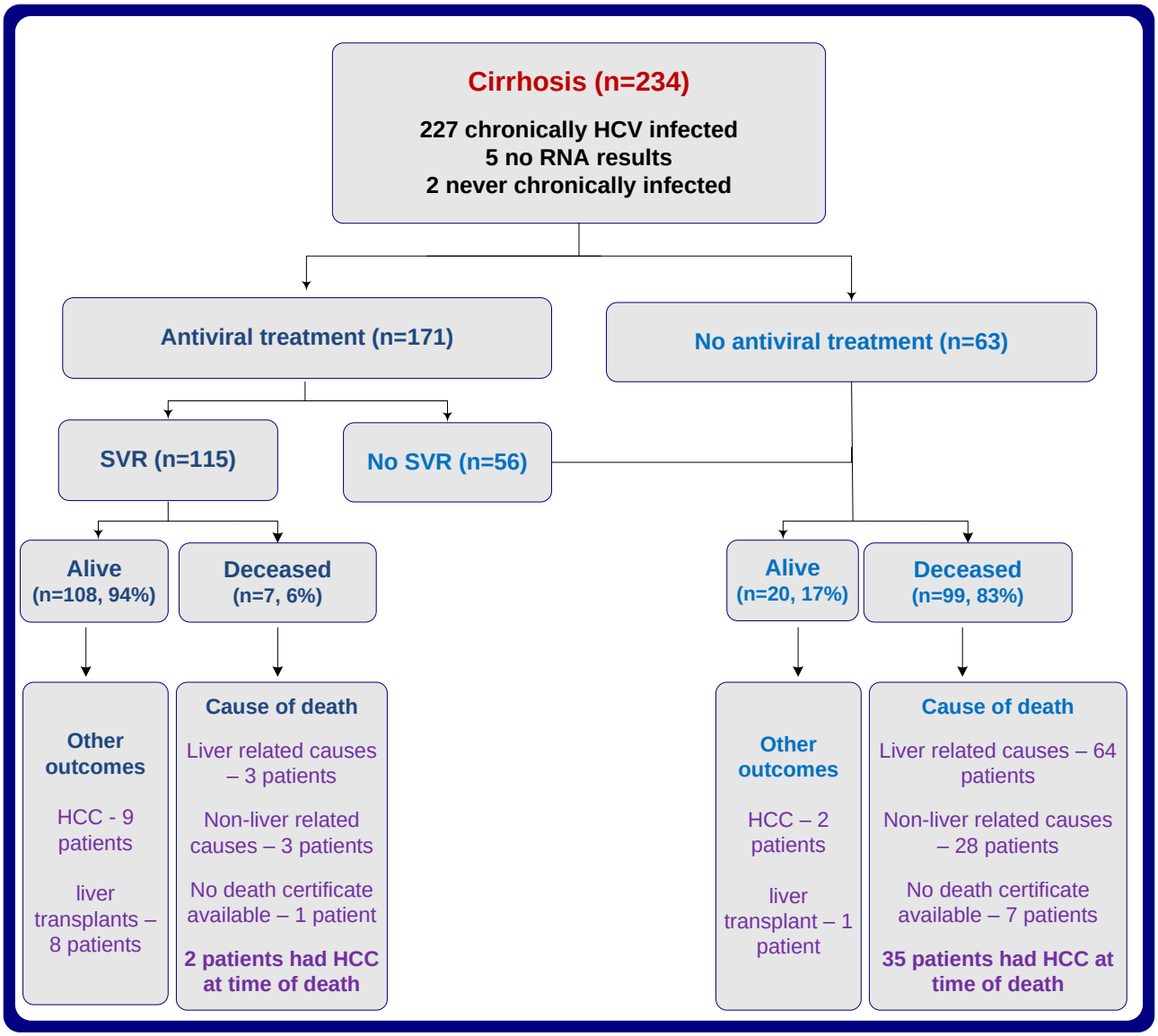


Figure 7. Outcomes for participants who developed cirrhosis

Poisson multivariate regression analysis was used to look at other factors associated with higher rates of cirrhosis in chronically infected participants. Other significant independent determinants of cirrhosis were high alcohol consumption (rate ratio 2.8, p<0.001), older age at infection (35+ years compared to <35 years) (rate ratio 1.5, p=0.02) and source of infection, with participants infected through blood transfusions/treatment for renal disease having higher rates of cirrhosis compared participants infected through anti-D (rate ratio 1.5, p=0.008) (table 22). Male sex was not significantly associated with higher rates of cirrhosis. Differences by source of infection, beyond those explained by differences in age, duration of infection and alcohol intake are likely to be due to differences in unmeasured/inaccurately reported health characteristics associated with the different patient groups.

Table 22. Factors associated with rate of cirrhosis in ever chronically infected participants – Poisson regression model (n=756)

Factors associated with cirrhosis	Rate ratio	p-value	95% confidence interval
Highest recorded alcohol consumption			
Non drinker/within recommended limits/moderately high	1		
High (>40 units per week or alcohol abuse in chart)	2.8	<0.001	2.01-3.98
Age at infection			
<35 years	1		
35+ years	1.5	0.02	1.06-2.00
Source of infection			
Anti-D	1		
Transfusion or renal	1.5	0.008	1.11-2.04
Clotting factors	1	0.856	0.67-1.61

4.5.3 Hepatocellular carcinoma (HCC)/liver cancer

By latest follow-up, 57 (7%) ever chronically infected participants and two participants with no RNA results (4%) had developed HCC (table 23, figure 8). There were no cases of HCC in participants who did not become chronically infected with HCV.

Forty four of the 59 participants (75%) who developed HCC were known to be deceased by latest follow up (figure 9). The cause of death was directly liver-related for thirty four, not directly liver-related for seven and the death certificate was missing for the remaining three patients. Of the 15 participants with HCC who were alive at most recent follow up, four had had liver transplants and 13 had achieved SVR on treatment.

For ever chronically infected database participants, the median duration of RNA positivity at date of diagnosis of HCC was 30 years (mean: 28.4 years) and the median age when HCC was diagnosed was 66 years (mean: 62 years) (see Methods sections 3.4 and 3.5 regarding methods used).

The median time from date of diagnosis of cirrhosis to date of diagnosis of HCC was two years (see Methods section 3.4 regarding the method of assigning dates of diagnosis). Cirrhosis was not specifically mentioned in the medical records of eleven of the participants with HCC. However, two of these patients had ascites, one had varices, one had splenomegaly and one had not attended their hepatology unit for several years.

Table 23. Hepatocellular carcinoma (HCC) in ever chronically infected database participants, (with univariate chi-square tests for differences in prevalence of HCC across different categories of host and virus variables)

Ever chronically infected database participants	Number with HCC	% with HCC	p-value	Median age at HCC diagnosis (years)	Median duration RNA positivity at HCC diagnosis (years)
All	57	7.1		66	30
Sex			**<0.001**		
Females	26	4.4		68	32
Males	31	14.0		58	27
Source of infection			**<0.001**		
Anti-D	13	3.0		68	36
Transfusion or renal	33	12.1		68	24
Clotting factors	11	10.5		54	32
Highest recorded alcohol intake			**0.001**		
Non drinker	16	9.1		69	33
Within recommended limits	21	4.7		62	29
Moderately high	4	6.2		54	27
High	13	17.6		63	30
Age at infection (years)			**0.03**		
<25 years	15	5.4		53	32
25-34 years	20	6.0		62	30
35+ years	22	11.2		72	25
HCV genotype			0.192		
Genotype 1	37	6.2		66	33
Genotype 2	3	7.9		49	21
Genotype 3	15	10.5		67	22

*Alcohol data not available for 3 participants with HCC, 2 participants with other HCV genotypes not shown under genotype in table

The factors associated with rate of HCC in ever chronically infected participants were assessed using Poisson multivariate regression. Participants with high alcohol intake (rate ratio 2.5, p=0.004), males (rate ratio 3.3, p<0.001) and those who were older at infection (35+ years compared to <35 years) (rate ratio 2.7, p<0.001) had higher rates of HCC. When source of infection was substituted for sex in the model, transfusion/renal participants (rate ratio 3.8, p<0.001) and clotting factor participants (rate ratio 3.4, p=0.004) had higher rates of HCC than anti-D participants and age at infection had a lesser impact (rate ratio 2.2, p=0.01).

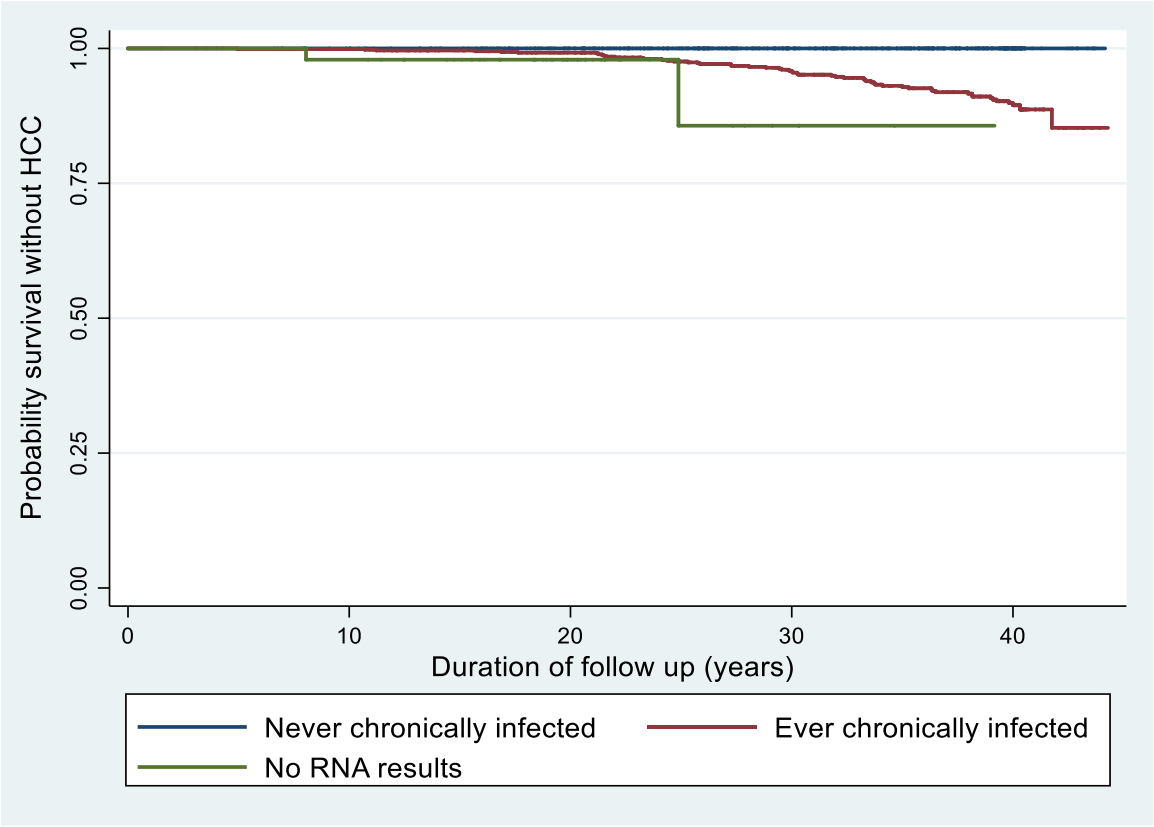


Figure 8. Proportion of participants who have not developed HCC over the follow-up period by RNA status – Kaplan Meier estimates

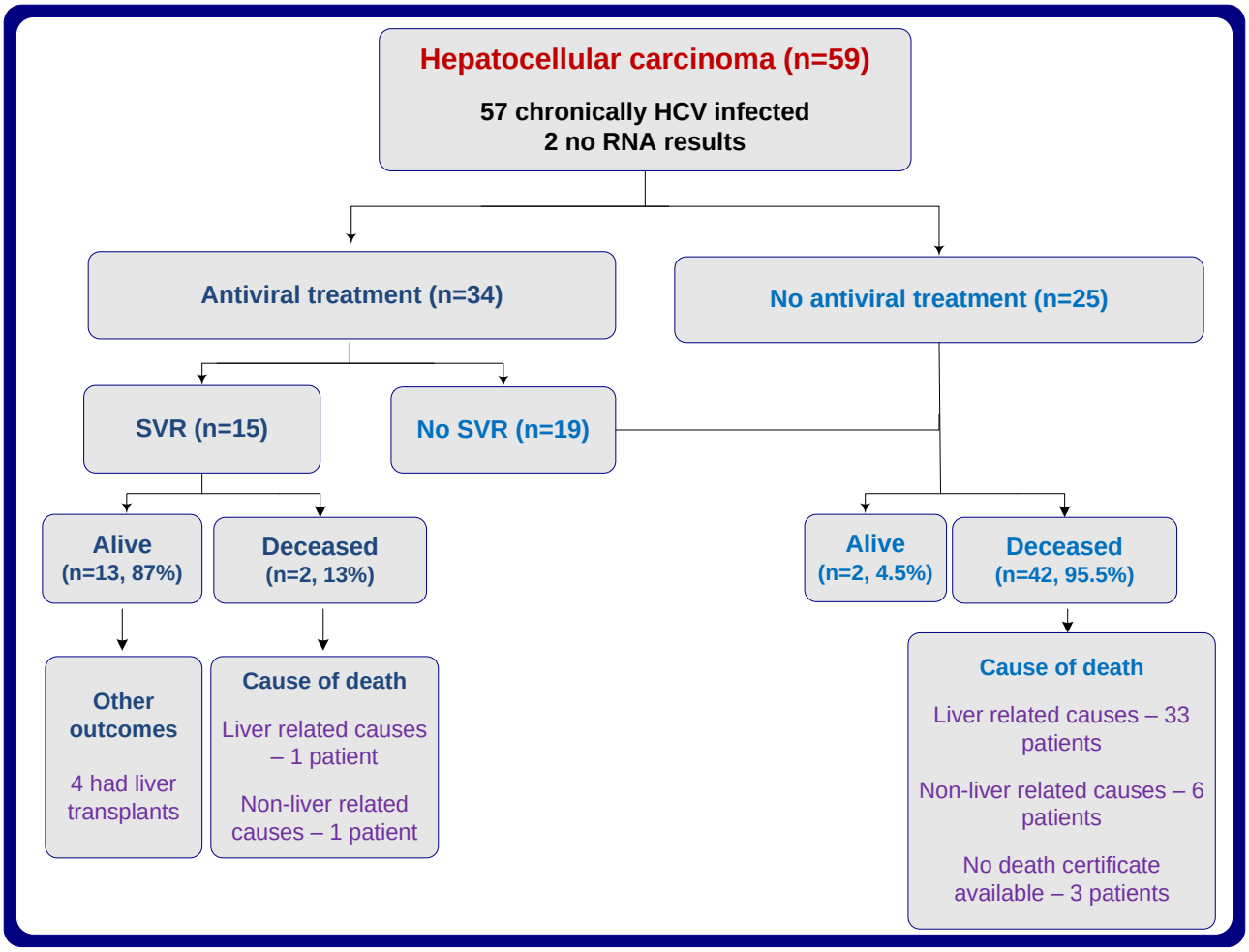


Figure 9. Outcomes for participants who developed hepatocellular carcinoma (HCC)

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

Most liver biopsies were carried out in the mid to late 1990s, with much smaller numbers being done in more recent years, therefore latest biopsy results alone are generally not a good indicator of current liver disease status (figure 10). Disease progression is now more likely to be monitored using less invasive diagnostic procedures such as fibroscans, ultrasounds, CT scans, MRI scans and blood tests of liver function.

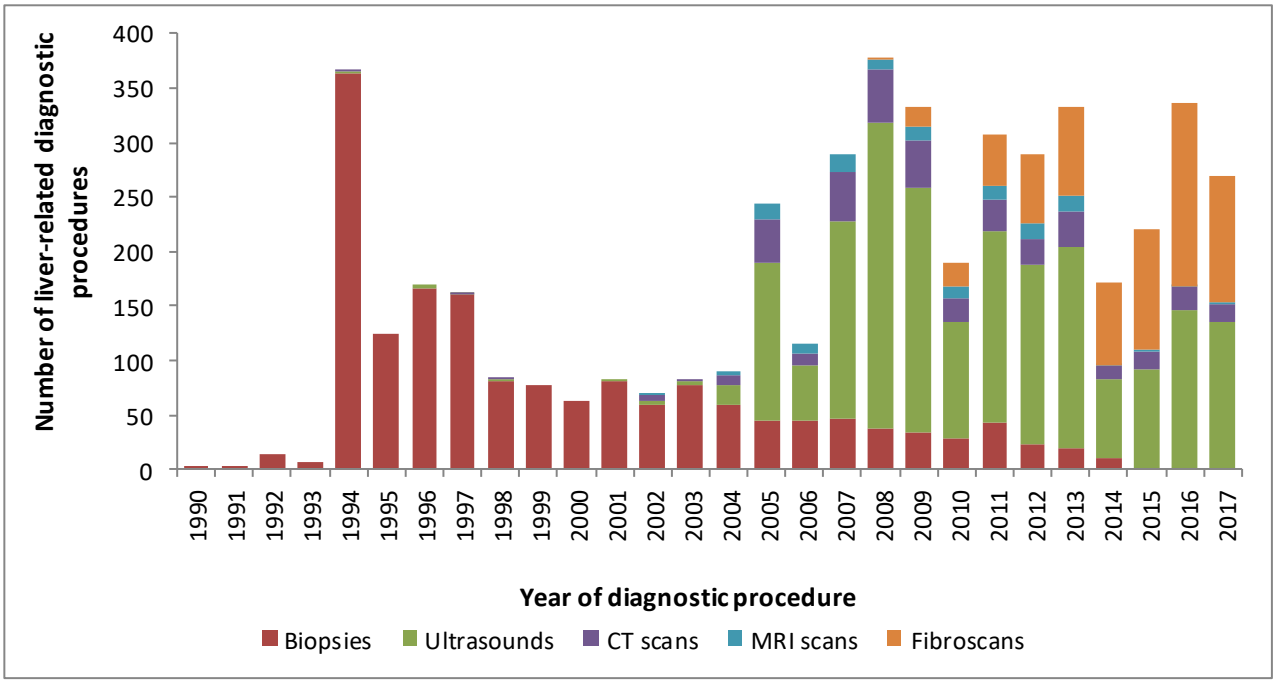


Figure 10. Number of liver-related diagnostic procedures by year and type of procedure for ever chronically infected participants

Note: multiple diagnostic procedures were carried out for most patients. Data on ultrasound, CT scans and MRI scans are more reliable since 2009, as the level of detail recorded has improved significantly since then.

4.6.1 Liver biopsies

Overall, 1,802 biopsies have been carried out on 804 database participants. Ninety seven percent (n=1740) of these had an inflammation grade and 90% (n=1614) had a fibrosis score recorded. Eighty one percent (n=655) of chronically infected participants had at least one biopsy with a documented fibrosis score and 84% (n=675) had at least one biopsy with a documented inflammation grade. The likelihood of having a biopsy varied by source of infection, with only 43% (n=45) of chronically infected clotting factor participants having biopsy results in their charts compared to 96% (n=412) of chronically infected anti-D participants and 82% (n=222) of those infected through blood transfusions or treatment for renal disease.

4.6.2 Results of liver biopsies

Inflammation

Twenty nine percent (n=195) of ever chronically infected participants had moderate or severe inflammation on last biopsy.

Fibrosis

Fibrosis was scored using different scoring systems in different hepatology units. Overall, 79% of biopsies were scored using a 0-6 scoring system, and a 0-4 system was used for the remaining 21%. Biopsy results scored from 0 to 6 were converted to the 0 to 4 scores (see Methods section 3.10) to allow all biopsy results to be analysed together. We categorised scores of 4-6 on biopsies scored using a 0-6 system, and scores of 3 or 4 on biopsies scored using a 0-4 system, as high fibrosis scores.

Twenty two percent (n=146) of chronically infected participants had a high fibrosis score on their most recent biopsy (where fibrosis score was recorded, n=655). Fibrosis varied by source of infection, with 33% (n=68) of chronically infected blood transfusion or renal participants having a high fibrosis score on most recent biopsy compared to 27% (n=12) of clotting factor participants and 16% (n=65) of anti-D participants (figure 11).

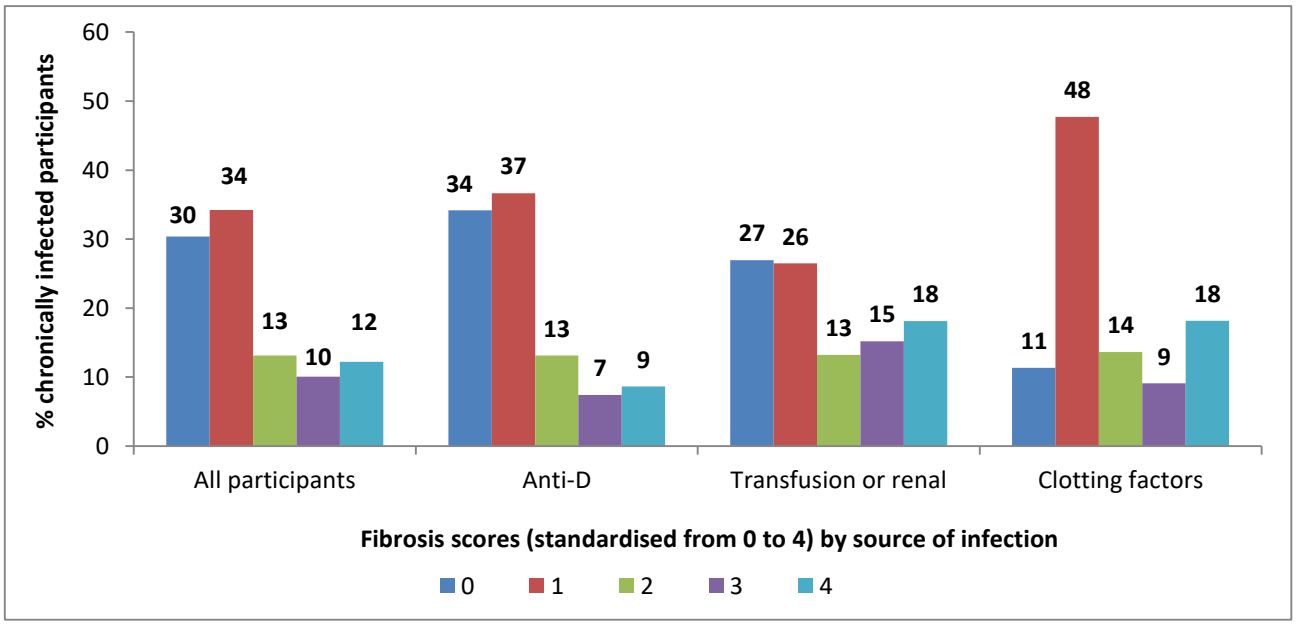


Figure 11. Fibrosis score* on last biopsy for chronically infected participants by source of infection (n=655)

*All 0-6 scores standardised to 0-4 (see Methods section 3.10 for description) to allow all biopsies to be analysed together. Note: the last biopsy was several years ago for many patients and biopsy results are particularly unrepresentative for clotting factor participants as only 42% ever had a liver biopsy with a fibrosis score.

4.6.3 Fibroscan results

Fibroscans are increasingly being used to monitor disease progression in the database cohort. Over half (52%, n=352) of living ever chronically infected database participants had a fibroscan test

since 2009 and almost two thirds of these patients had multiple fibroscans. When highest fibroscan results are assessed, 40% (n=141) had fibroscan results in the cirrhotic or pre-cirrhotic range (table 24), but this decreased to 30% (n=104) on assessment of most recent fibroscan result (table 25).

Table 24. Highest fibroscan results for ever chronically infected participants by source of infection (n=352)

Fibroscan results (kPa)	All participants		Anti-D		Transfusion or renal		Clotting factors	
	Num	%	Num	%	Num	%	Num	%
0-7.0	139	39.5	104	42.6	23	31.5	12	34.3
7.1-8.6	51	14.5	29	11.9	17	23.3	5	14.3
8.7-9.4	21	6.0	16	6.6	4	5.5	1	2.9
9.5-14.4	72	20.5	48	19.7	17	23.3	7	20.0
14.5+	69	19.6	47	19.3	12	16.4	10	28.6
	352	**100**	**244**	**100**	**73**	**100**	**35**	**100**

Table 25. Latest fibroscan results for ever chronically infected participants by source of infection (n=352)

Fibroscan results (kPa)	All participants		Anti-D		Transfusion or renal		Clotting factors	
	Num	%	Num	%	Num	%	Num	%
0-7.0	176	50.0	133	54.5	29	39.7	14	40.0
7.1-8.6	55	15.6	31	12.7	18	24.7	6	17.1
8.7-9.4	17	4.8	12	4.9	4	5.5	1	2.9
9.5-14.4	48	13.6	31	12.7	12	16.4	5	14.3
14.5+	56	15.9	37	15.2	10	13.7	9	25.7
	352	**100**	**244**	**100**	**73**	**100**	**35**	**100**

Changes in fibroscan results post treatment

Eighty participants who were successfully treated had pre- and post-treatment fibroscan results. Results improved for over half of those who achieved SVR on treatment (figure 12). The median fibroscan score before treatment was 10 (mean 11.8). This decreased to 7 after treatment (mean 9.4) (figure 12). However, for some the improvement was marginal and did not involve a change in fibrosis category when results standardised to a 0-4 scoring system were analysed; the fibrosis score decreased for 40% (n=32) of those who achieved SVR and stayed the same for around half (51%, n=41). The changes in fibroscan scores when standardised to 0 to 4 system (see Methods section 3.11) are shown in figure 13. Treatment was relatively recent for most patients with fibroscan results, so these changes are unlikely to be representative of longer-term post-treatment changes in fibrosis. The median duration between end of treatment and post treatment fibroscan was 10 months (range: 0-47 months). It is likely that some of the reductions in fibroscan

scores may in fact reflect decreased inflammation after successful treatment rather than improvements in fibrosis.[14,16] This is particularly true where large declines in fibroscan readings were seen quite soon after treatment.

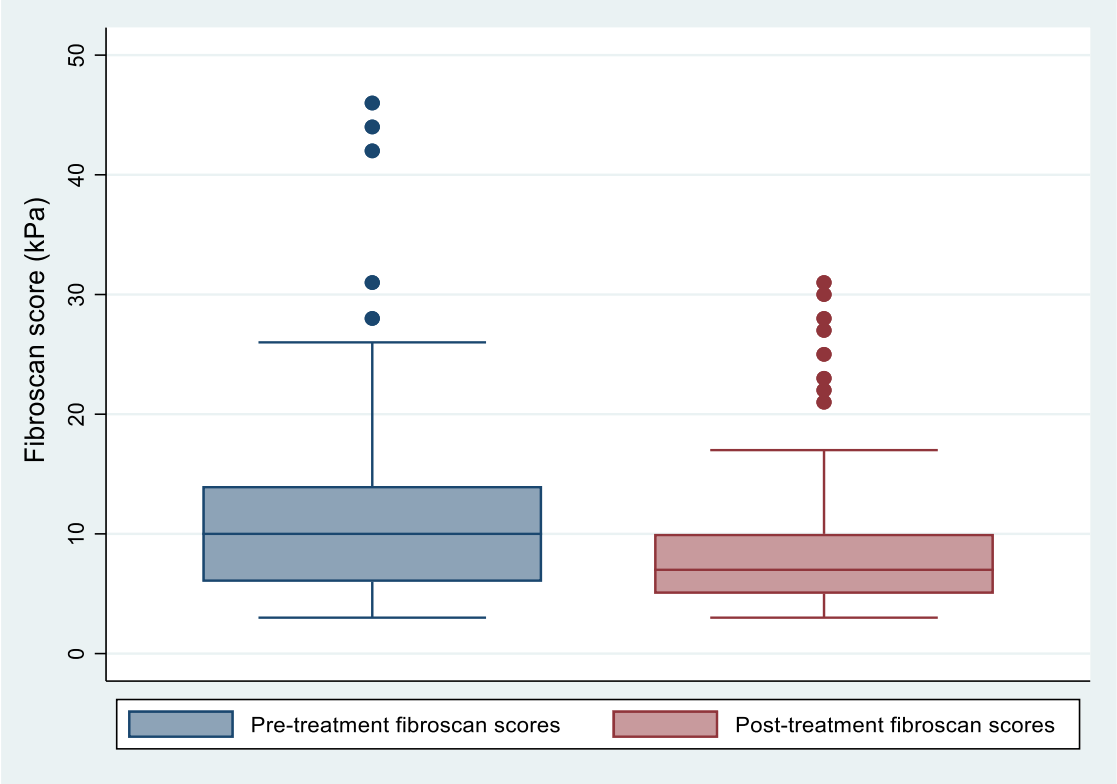


Figure 12. Median fibroscan scores pre- and post-treatment, for participants who achieved SVR and had pre- and post-treatment results (n=80)

Explanation of box and whisker plot: the line in the middle of the boxes is the median fibrosis score (middle number), 50% of fibroscan scores fall within the top and bottom of the boxes. The bottom whisker shows the lowest fibroscan results, the top whisker shows the highest fibroscan values excluding extreme outliers (dots)

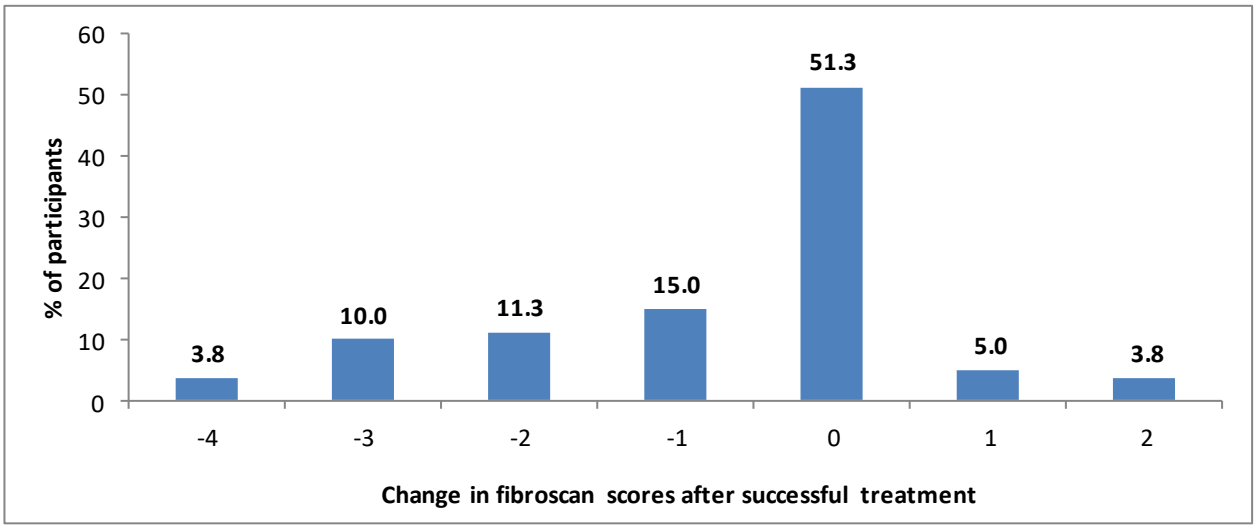


Figure 13. Change in standardised fibroscan results after treatment, for participants who achieved SVR and had pre- and post-treatment results (n=80)

Note: Scores standardized into to 0-4 categories (see chapter 3 and tables 28 and 29 for description)

4.7 Deceased participants

Three hundred and six participants (23%) had died by latest follow-up. Crude all-cause mortality rates were significantly higher (rate ratio 2.6, p<0.001) in participants who ever tested RNA positive (27% deceased, n=211, rate 8.2 per 1,000 person years of follow up) compared to those who never tested RNA positive (10% deceased, n=45, 3.1 per 1,000 person years of follow up).

All-cause mortality

On Poisson multivariate regression analysis, all-cause mortality rates (i.e. deaths from any cause) remained significantly higher in participants who had ever tested RNA positive (rate ratio 1.9, p<0.001), and were also higher in those ever reported to have high alcohol intake (rate ratio 2.7, p<0.001), those who were older at infection (35+ years compared to less than 35 years) (rate ratio 2.9, p<0.001) and in males (rate ratio 1.9, p<0.001). When source of infection was substituted for sex in the model, blood transfusion/renal participants and clotting factor participants had significantly higher all-cause mortality rates than anti-D participants. However, it should be noted that hepatology clinic attendance was better for chronically infected participants and some patients who had not attended their hepatology unit in recent years may have died and not been identified as deceased, leading to potential bias in the assessment of all-cause mortality.

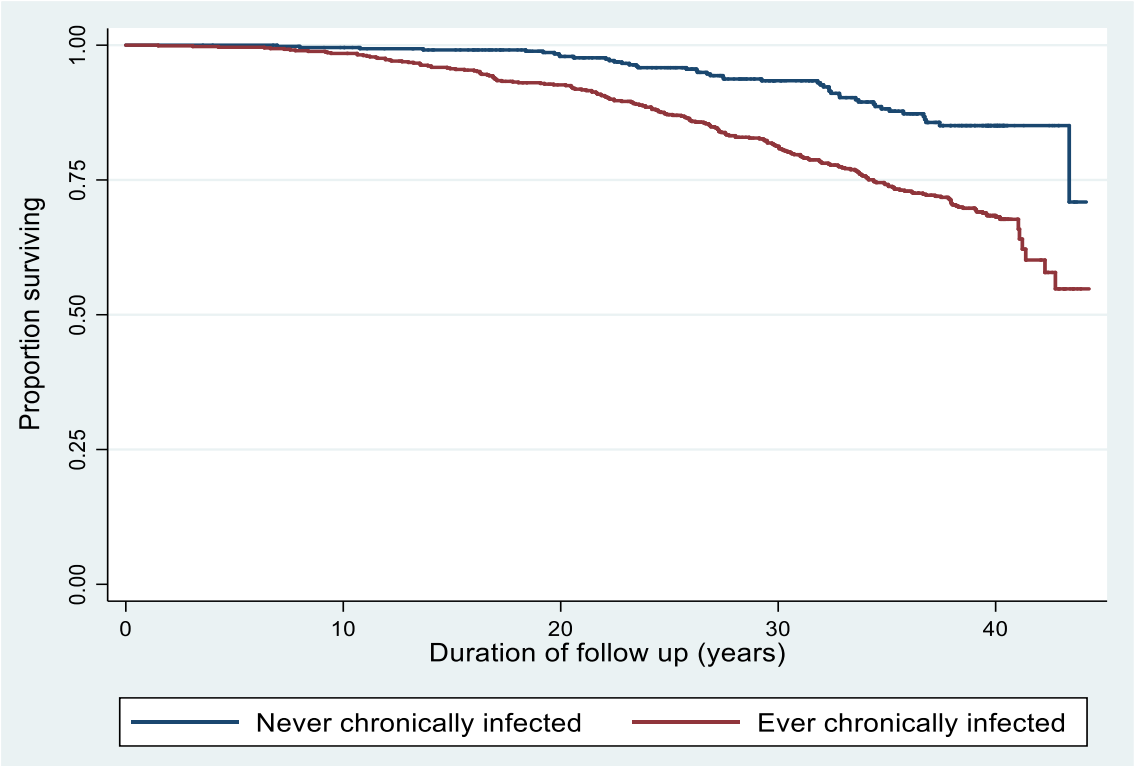


Figure 14. Proportion of participants who had not died over the follow-up period by RNA status – Kaplan Meier estimates

Liver-related mortality

Death certificates were available for 273 of the 306 database participants who had died (89%). Death was directly caused by liver disease for 86 (see methods section 3.8 regarding coding of deaths). The causes of death for these participants were:

- chronic viral hepatitis C (n=39)
- liver cell carcinoma (HCC) (n=29)
- liver failure (n=6)
- cirrhosis of the liver (n=5)
- unspecified liver cancer (n=2)
- intrahepatic bile duct carcinoma (n=1)
- liver transplant failure and rejection (n=1)
- B-cell lymphoma (n=1)
- chronic viral hepatitis B (n=1)
- toxoplasma hepatitis (n=1)

Of the 86 participants who died from liver-related causes, 71 were chronically HCV infected at the time of their death, 5 had been chronically infected in the past, but had cleared the virus, two were never chronically infected and eight had no RNA results in their charts. Table 26 shows further details for the 76 patients who were ever chronically HCV infected and died from liver-related causes.

Table 26. Death from liver-related disease in ever chronically infected database participants (with univariate chi-square tests for differences in prevalence of liver-related death across different categories of host and virus variables)

Ever chronically infected database participants	Number who died directly from liver-related disease	% who died directly from liver-related disease	p-value	Median age at death (years)	Median duration RNA positivity at death (years)
All	76	9.6		60	28
Sex			0.001		
Females	43	7.5		63	30
Males	33	15.2		55	25
Source of infection			<0.001		
Anti-D	21	5.0		62	32
Transfusion or renal	40	15.3		64.5	24.5
Clotting factors	14	13.5		50.5	27
Highest recorded alcohol intake			<0.001		
Non drinker	15	8.9		68	24
Within recommended limits	23	5.2		57	30
Moderately high	6	9.7		57	32
High	25	34.7		59	27
Age at infection			0.007		
<25 years	24	8.9		50	31
25-34 years	23	7.0		59	31
35+ years	29	15.3		71	24
HCV genotype			0.282		
Genotype 1	56	9.6		61.5	30
Genotype 2	6	15.8		68.5	23.5
Genotype 3	10	7.3		55.5	24.5

Crude liver related mortality rates were significantly higher (rate ratio 20.4, p<0.001) in participants who ever tested RNA positive (10% deceased, n=76, rate 2.8 per 1,000 person years of follow up) compared to those who never tested RNA positive (0.4% deceased, n=2, 0.1 per 1,000 person years of follow up) (figure 15).

Information on alcohol consumption was available for 91% (n=69) of the chronically infected participants whose death was caused by liver disease. Thirty six percent (n=25) had indicators of high levels of alcohol consumption at some stage in their medical charts, but this does not necessarily indicate prolonged periods of high alcohol consumption.

On Poisson multivariate regression analysis, liver related mortality rates remained significantly higher in participants who had ever tested RNA positive (rate ratio 12.6, p<0.001), and were also higher in those ever reported to have high alcohol intake (rate ratio 5.6, p<0.001), those who were

older at infection (35+ years compared to less than 35 years) (rate ratio 2.4, p<0.001) and in males (rate ratio 1.7, p=0.026). When source of infection was substituted for sex in the model, blood transfusion/renal participants had significantly higher liver related mortality rates than anti-D participants (rate ratio 2.5, p=0.001).

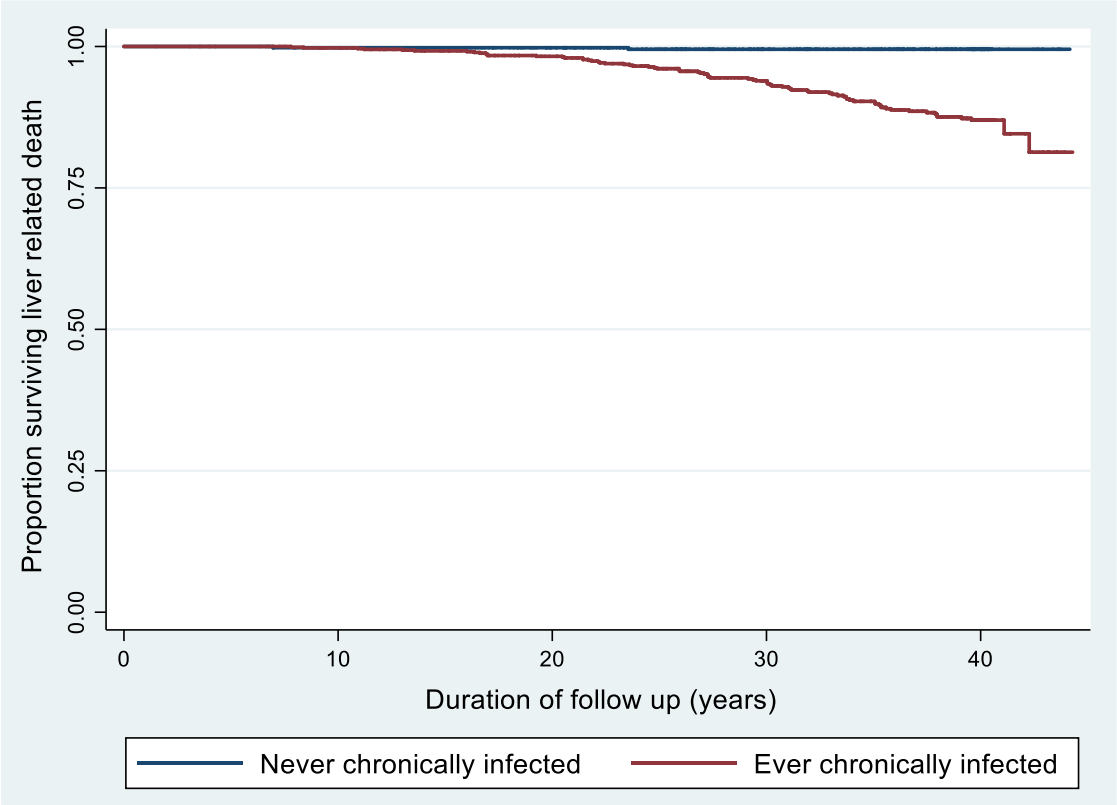


Figure 15. Proportion of participants who had not died from liver-related causes over the follow-up period by RNA status – Kaplan Meier estimates

Non-liver related mortality

Death was not directly related to liver disease for 187 of the database participants who had died by latest follow up (68% of those for whom death certificates were available) (see methods section 3.8 regarding coding of deaths). No RNA results were recorded for 28 of these participants.

Comparing non-liver related mortality rates in participants who were ever chronically infected with hepatitis C and those who were never chronically infected provides an indication of whether hepatitis C infection had an impact on non-liver related mortality. Sixteen percent (n=126, crude mortality rate: 4.7 per 1,000 person years) of database participants who were ever chronically HCV infected had died from non-liver related causes by the end of latest follow up compared to 7% (n=33, crude mortality rate: 2.3 per 1,000 person years) of never chronically infected patients

(crude rate ratio 2.0 p<0.001). However, on Poisson multivariate regression analysis, non-liver related mortality rates (i.e. deaths from any cause except liver disease) did not vary significantly by RNA status (rate ratio 1.4, p=0.08) after adjusting for alcohol intake, sex and age at infection.

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

HCV disease progresses particularly after two to four decades of infection.[6] The median duration of RNA positivity for database participants who became chronically infected was 32 years at the end of latest follow up. This was the sixth round of data collection and increases can be seen in the prevalence of liver-related health outcomes since baseline data were collected (figure 16).

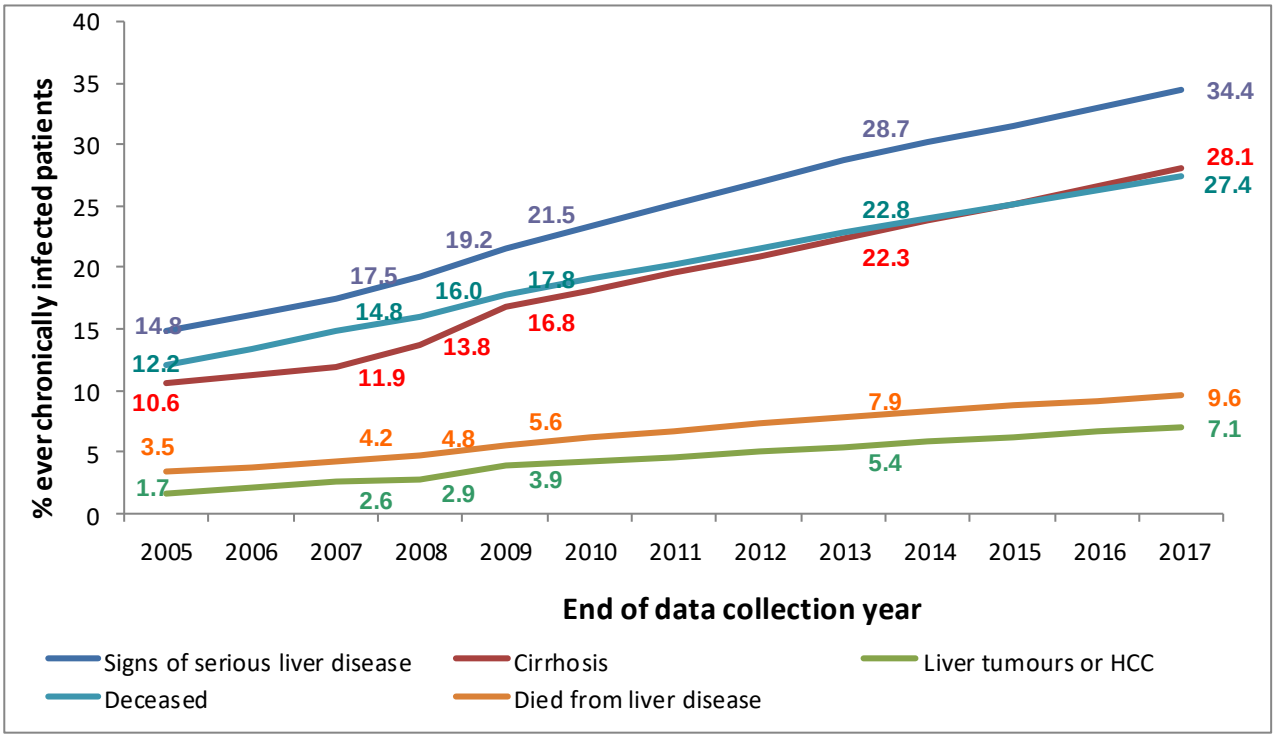


Figure 16. Changes in the prevalence of all cause mortality and liver-related outcomes for chronically infected participants since baseline data were collected for the database

4.9 Antiviral treatment for hepatitis C

Seventy one percent (n=573) of ever chronically infected participants had 796 courses of antiviral treatment by latest follow-up. This was a very significant increase in treatment compared to the previous round of data collection when less than half of chronically infected patients had been treated. A treatment outcome was available for 572, of whom 85% (n=486) had achieved a sustained virological response (SVR). Participants who stopped treatment early are included when calculating SVR.

The SVR rate improved dramatically since the previous round of data collection (figure 17). The first all-oral, interferon-free, direct acting antiviral drug (DAA) regimens were approved in Ireland in December 2014 and there are now several DAA combinations in use. Of the 262 database participants treated with DAAs by the end of latest follow up, outcome was available for 261, and 258 had achieved an SVR (table 27). This is an SVR rate of 99%. Of the three patients who failed to achieve SVR on DAA treatment, two were treated for less than one month and one was treated for 3 months. All stopped treatment for medical reasons. SVR rates for patients treated using DAAs, by type of drug regimen and duration of treatment, are shown in figure 18. DAA treatment outcomes did not vary by genotype, HIV status, sex, source of infection, age or level of fibrosis (table 27). Tolerance of antiviral treatment was also very high with only 1% of patients treated with DAAs stopping treatment early due to side effects compared to 19% of those who had been treated with interferon/pegylated interferon and ribavirin.

Treatment uptake and response on last course of treatment is shown in table 28 and figure 19. This includes patients who have died without being successfully treated and would not have had the opportunity to avail of treatment using the new DAA drug regimens. Treatment response for treatment naïve patients, by drug regimen and genotype, is shown in figure 20.

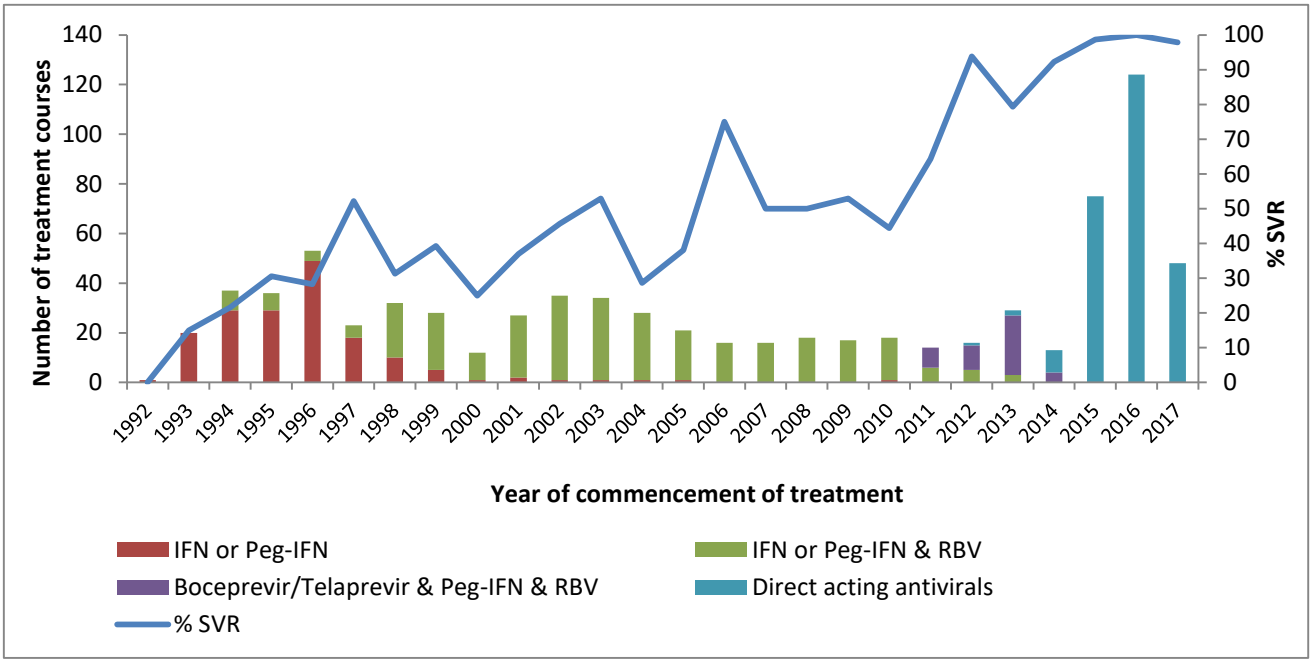


Figure 17. Number of treatment courses by type of treatment and percentage SVR, 1992-2017

Note: Outcome is awaited for 1 participant (not included when calculating SVR). Many patients (29%) were treated more than once.

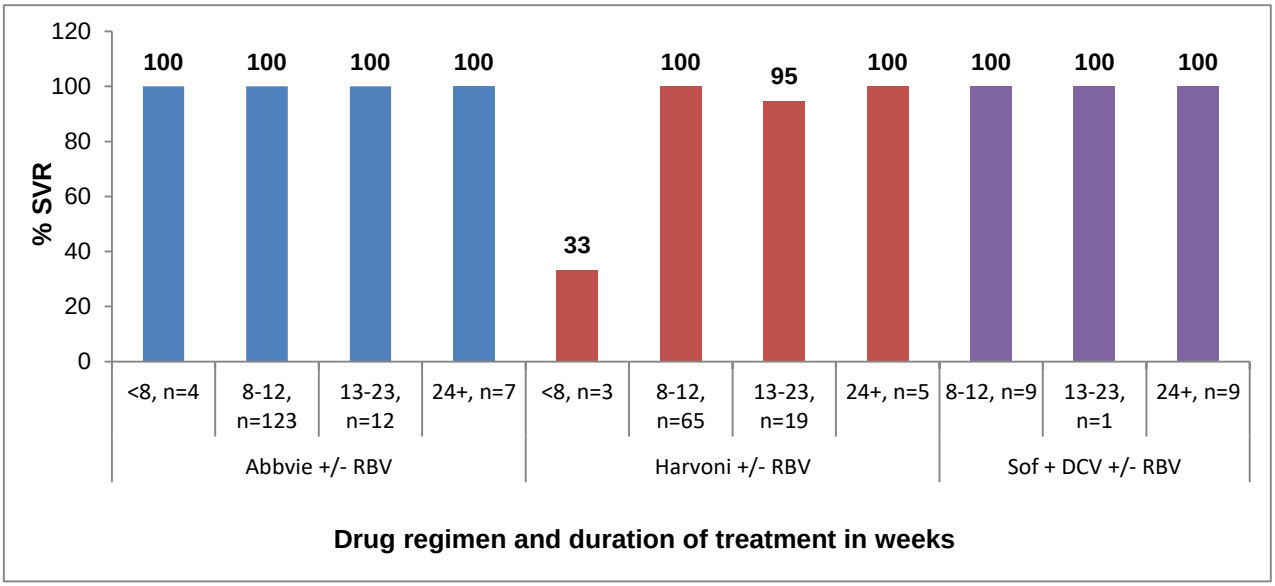


Figure 18. Percentage SVR for patients treated with DAAs, by type of drug regimen and duration of therapy

Note: Treatment outcome awaited for one patient and 4 patients were treated with other DAA drug regimens – all achieved SVR. These 5 patients are not included in figure 18

Drug regimens: Abbvie = Viekira (paritaprevir/ritonavir, ombitasvir and dasabuvir), Harvoni = ledipasvir + sofosbuvir SOF = sofosbuvir, DCV = daclatasvir, RBV = ribavirin

Table 27. Number and percentage of participants, who were alive and chronically infected when DAAs were approved in Ireland, and number and percentage who were treated with DAAs, by demographic and virus characteristics

Characteristic	Patients alive and chronically infected when DAAs approved	Treated with DAAs	% Treated with DAAs	Number with outcome	Number SVR	% SVR
All	372	262	70.4	261	258	98.9
Sex						
Female	313	222	70.9	221	219	99.1
Male	59	40	67.8	40	39	97.5
Source of infection						
Anti-D	254	194	76.4	193	192	99.5
Blood clotting factors	23	20	87.0	20	19	95
Blood transfusion/renal	94	48	51.1	48	47	97.9
High fibrosis score on biopsy or fibroscan						
No	200	136	68.0	136	136	100
Yes	154	124	80.5	123	120	97.6
Genotype						
1	333	242	72.7	241	238	98.8
2	9	5	55.6	5	5	100
3	29	14	48.3	14	14	100
Age at latest follow up						
0 to 49 years	25	16	64.0	16	16	100
50 to 64 years	115	86	74.8	86	84	97.7
65+ years	232	160	69.0	159	158	99.4
Reasons for not being treated						
Refused treatment	31					
Last attended unit >5 years ago	26					
Last attended unit in 2013 or 2014	11					
Died since DAAs approved in Ireland	15					
Other medical problems or advanced age	9					
Moved abroad	5					
Treatment planned at time of data collection	1					
Unknown	12					

Note: Treatment outcome awaited for 1 participant, omitted when calculating SVR. One participant with genotype 4 was omitted from the genotype breakdown in this table. Fibrosis scores from biopsies or fibroscans were not available for 18 participants. One participant infected through another source was not included in the source of infection breakdown in this table.

Table 28. Number and percentage of ever chronically infected participants treated with any drug regimen, number and percentage SVR, by demographic and virus characteristics

Characteristic	Number of participants treated - any drug regimen	% treated - any drug regimen	Number SVR	% SVR on last treatment
All	573	70.9	486	85
Sex				
Female	432	73.6	374	86.8
Male	141	63.8	112	79.4
Source of infection				
Anti-D	331	77.5	298	90.3
Blood clotting factors	168	61.8	123	73.2
Blood transfusion/renal	72	68.6	63	87.5
High fibrosis score on biopsy or fibroscan				
No	302	74.2	278	92.1
Yes	241	84.9	186	77.5
Genotype				
1	425	71.1	363	85.6
2	29	76.3	23	79.3
3	109	76.2	92	84.4
Age at latest follow up				
0 to 49 years	86	65.7	72	83.7
50 to 64 years	233	77.2	191	82.0
65+ years	254	67.7	223	88.1

Note: Treatment outcome awaited for 1 participant, omitted when calculating SVR. Genotype not available for 7 participants who were treated. Three participants with genotypes 4 or 5 who were treated were omitted from the genotype breakdown in this table. Fibrosis scores from biopsies or fibroscans were not available for 30 of the participants who were treated. Two of the treated patients who were infected through other means are not shown under source of infection this table.

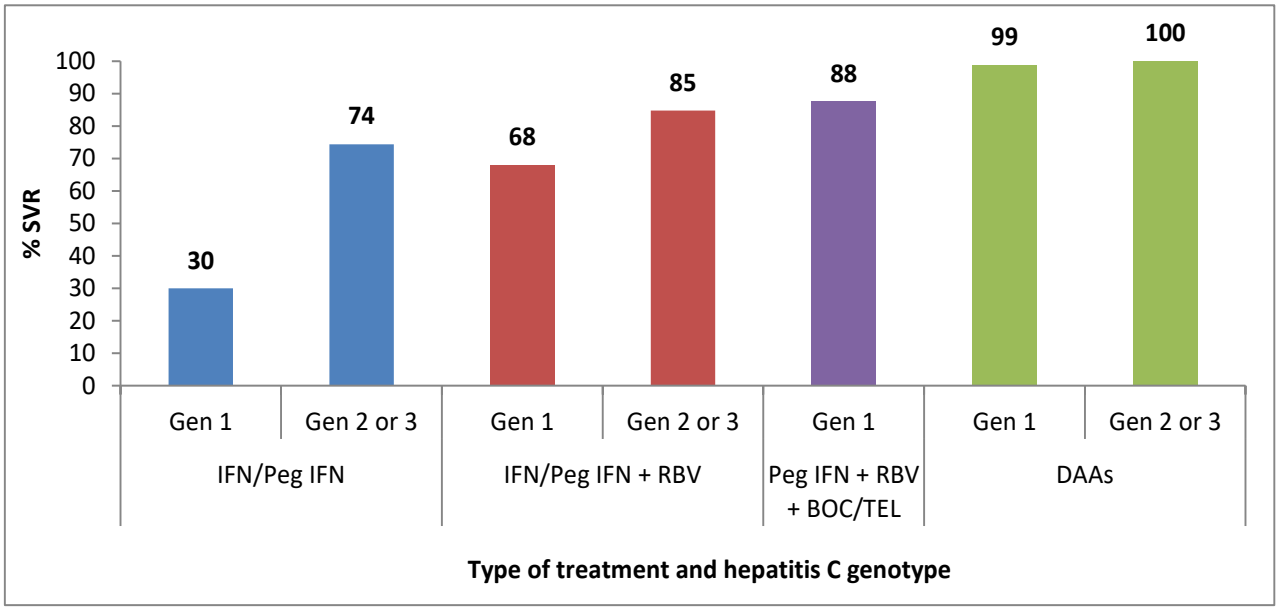


Figure 19. Percentage SVR for patients when last treated (some treatment naïve and some previously treated), by type of drug regimen and hepatitis C genotype

Note: A small number of patients with other genotypes or who were treated with other drug regimens are omitted from figure 19. Boc=Boceprevir, Tel=Telaprevir, Peg IFN=Pegylated interferon, RBV=Ribavirin

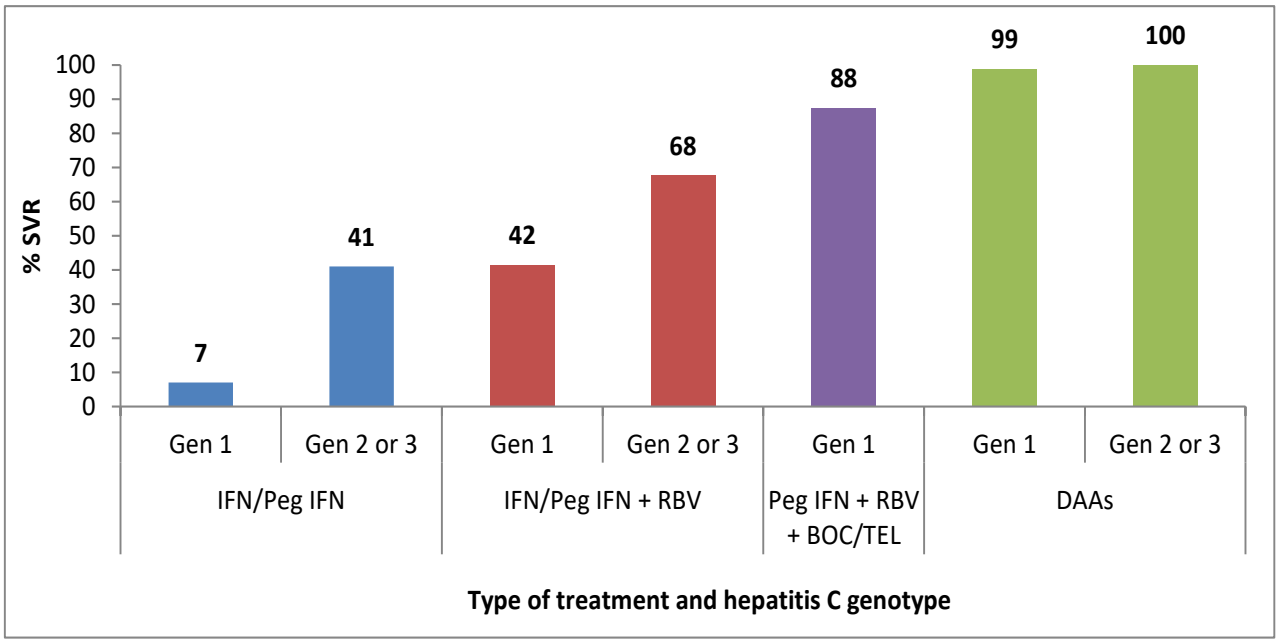


Figure 20. Percentage SVR for patients when first treated (treatment naïve), by type of drug regimen and hepatitis C genotype

Note: A small number of patients with other genotypes or who were treated with other drug regimens area omitted from figure 20

4.10 Liver transplants

Twenty five ever chronically infected database participants had received twenty eight liver transplants by the end of 2017. The median age at transplant was 54 years (range: 29-66 years) and the median duration of HCV infection at transplant was 29 years (range: 1-40 years). Seven transplant recipients (28%) had evidence of high alcohol consumption at some stage.

One transplant recipient was successfully treated prior to transplant. The remaining patients were RNA positive when transplanted and all of those tested post-transplant remained RNA positive. Post-transplant biopsy or other staging results were available for sixteen liver transplant recipients. Within five years of transplant, two had developed HCC, six had developed cirrhosis, two had moderate or advanced fibrosis, three had mild fibrosis and two had no fibrosis. One further transplant recipient developed cirrhosis and HCC many years after transplant.

Sixteen of the liver transplant patients had died by the end of latest follow up. Eight died from liver-related causes, six died from non-liver-related causes and no death certificate was available for the two remaining patients. The median time between transplant and death for these patients was 6 years. All of the remaining nine patients have since been successfully treated (one was the patient who was treated pre-transplant).

4.11 Medical conditions (relevant conditions only)

Medical conditions recorded in participants' hospital records were recorded in 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 were treated privately or if the condition was not discussed with the consultant hepatologist. However, if the condition was serious or known to be associated with HCV infection we think it is more likely to have been reported and recorded.

Without a comparison group, it is difficult to determine if the prevalence of these conditions 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 HCV 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 recorded.

Table 29 shows common medical conditions that differ significantly by HCV RNA status, and other medical conditions of interest (i.e. mentioned in published studies as associated with HCV or raised by patient support groups). The table indicates where there is a statistically significant ($p<0.05$) difference in the prevalence of the condition between participants who were ever chronically infected and those who were not. Differences should be interpreted with caution as follow-up was better for chronically infected participants, and this may have led to a bias in the reporting and recording of medical conditions. It should also be noted that the number of patients with some of these conditions was small.

Table 29. Medical conditions recorded in charts of participants

Conditions that differed significantly by RNA status, and other conditions of interest*, excluding conditions known to pre-date hepatitis C infection

Disease or condition	Chronically infected		Never chronically infected		Statistically significant difference - Fisher's exact test
	Num	%	Num	%	p-value
Hypertension	329	40.7	138	29.7	**<0.001**
Depression	272	33.7	104	22.4	**<0.001**
Fibromyalgia†	114	14.1	47	10.1	**0.044**
Diabetes	93	11.5	29	6.2	**0.007**
Osteoporosis	83	10.3	23	5.0	**0.001**
Dermatitis and eczema	69	8.5	24	5.2	**0.026**
Anxiety	50	6.2	15	3.2	**0.024**
Gastro-oesophageal reflux disease	46	5.7	11	2.4	**0.005**
Glomerulonephritis	8	1.0	0	0	**0.031**
Ovarian cancer (females only)	6	1.0	0	0	**0.043**
Fatigue & lethargy	260	32.2	141	30	0.531
Arthralgia/joint pain	194	24.0	118	25.4	0.589
Osteoarthritis	110	13.6	55	11.8	0.387
Arthritis, unspecified	32	4.0	17	3.7	0.880
Rheumatoid Arthritis	15	1.9	8	1.7	1.000
Hysterectomy (females only)	118	20.1	73	17.1	0.255
Osteopenia	90	11.1	48	10.3	0.708
Dry/gritty/sore eyes	57	7.1	23	5.0	0.151
Sicca/Sjorgen syndrome	19	2.4	10	2.2	1.000
Parkinson's Disease	9	1.1	4	0.9	0.778
Cryoglobulinaemia	7	0.9	1	0.2	0.271
Multiple Sclerosis	2	0.3	4	0.9	0.199
Non-Hodgkin's lymphoma	3	0.4	1	0.2	1

* Data for some conditions, mentioned in the 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. †There was a more significant difference by RNA status in females – 18.4% in ever chronically infected patients compared to 11% in never chronically infected patients, p=0.001

Depression

The factors independently associated with depression were assessed using multivariable binomial regression. Depression was significantly more likely to be recorded in the medical charts of ever chronically infected database participants, females, those aged 50-64 years and those with a history of high alcohol consumption.

Osteoporosis

Osteoporosis was significantly more likely to be recorded for older, ever chronically infected females. Data on the prevalence of osteoporosis in the general population are available from the Irish longitudinal study on ageing (TILDA), which includes data on over 8,000 people. In this study, 17% of female study participants aged 50-64 years, 28% of females aged 65-74 years and 35% of females aged 75+ years had osteoporosis.[36] This is actually higher than the prevalence observed in the ever chronically infected female hepatitis C database participants in the same age groups (7%, 16% and 24%). However, there may be a blurring of the lines between a diagnosis of osteoporosis and osteopenia. The prevalence of either osteoporosis or osteopenia in ever chronically infected female database participants was 21% in 50-64 year olds, 32% in 65-74 year olds and 41% in those aged over 74 years. The prevalence of either condition in never chronically infected females was similar to that in the TILDA study.

Diabetes mellitus

Diabetes was recorded in the medical charts of 9% (n=124) of database participants (table 30). Database participants who were chronically HCV infected were significantly more likely to have diabetes recorded in their medical records than those who never developed chronic infection (12% compared to 6%, crude risk ratio 1.85, 95% CI 1.2 – 2.8, p-value 0.003). However, the duration of follow up was shorter for participants who did not become chronically HCV infected and this may have led to underreporting of diabetes in this group of participants.

It was also difficult to control for the impact of BMI on diabetes as BMI data were available for just under half of participants and BMI was more likely to be recorded for chronically infected patients. Considering only patients with BMI data, there was no association between RNA status (ever chronically HCV infected compared to never chronically infected) and risk of diabetes. The only factor that was significantly associated with diabetes, after adjusting for age, sex and RNA status was obesity.

Data on the prevalence of diabetes in the general population were also available from the TILDA study. In this study, 7% of study participants aged 50-64 years and 12% of those aged 65-74 years had diabetes.[36] This is lower than observed in the ever chronically infected hepatitis C database participants in the same age groups (13% & 14%), but slightly higher than the prevalence found in the database participants who did not develop chronic infection (4% & 10%).

Table 30. Prevalence of diabetes mellitus in ever and never chronically infected participants by BMI, sex, source of infection, age at end of follow up and HCV genotype

	All participants		Ever chronically infected		Never chronically infected	
	Num	%	Num	%	Num	%
All participants (n=1322)	**124**	**9.4**	**93**	**11.5**	**29**	**6.2**
BMI category (n=629)						
Underweight or normal	14	6.3	13	8.7	1	1.4
Overweight	27	12.1	21	13.7	6	8.5
Obese	38	20.7	24	19.8	14	22.2
No BMI data	45	6.5	35	9.1	8	3.1
Sex (n=1322)						
Females	93	9.1	65	11.1	26	6.1
Males	31	10.5	28	12.7	3	7.7
Source of infection (n=1322)						
Anti-D	72	8.9	49	11.5	22	5.9
Transfusion or renal	44	13	37	13.6	6	9.2
Clotting factors	8	4.9	7	6.7	1	4.4
Age at end of latest follow up (n=1322)						
<50 years	6	2.3	5	3.8	0	0
50-64 years	47	9.4	39	12.9	8	4.3
65+ years	71	12.6	49	13.1	21	11.4

Note: Two database participants with diabetes did not have RNA results recorded (included in the "all" category)

Hypertension

The prevalence of hypertension was higher in ever chronically infected database participants (41%) compared to those who never became chronically infected (30%). However, because hypertension may be more likely to be diagnosed in patients who engage more with healthcare and follow up was better for ever chronically infected participants, this finding should be interpreted with caution. Older age was also associated with a higher prevalence of hypertension. Just over a third (34%) of ever chronically infected database participants aged 50-64 years had hypertension recorded in their medical records compared to 52% of those aged 65-74 years. These prevalences are higher than those reported in the TILDA study for the same age groups: 29% of

those aged 50-64 years and 41% of those aged 65-74 years.[36] The equivalent figures for never chronically infected database participants were 21% and 48%, which were more in line with the findings from the TILDA study.

Chapter 5. Focus on three individual patient groups

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

5.1 Summary and comparison of outcomes in the three groups

Database participants who became chronically infected with HCV through anti-D had the lowest prevalence of serious liver disease despite having the longest median duration of RNA positivity at the end of latest follow-up. Twenty eight percent (n=121) had clinical signs of serious liver disease, including 25% (n=105) with cirrhosis, after a median duration of hepatitis C RNA positivity of 38 years (tables 3 & 31, figure 21).

In comparison, 40% (n=109) of transfusion/renal participants had clinical signs of serious liver disease, including 34% (n=92) with cirrhosis, after a median duration of HCV RNA positivity of 24 years (tables 9 & 32, figure 21). The prevalence of signs of serious liver disease was also very high in those who became chronically infected through receipt of clotting factors, with 45% (n=47) having clinical signs of serious liver disease and 28% (n=29) diagnosed with cirrhosis after a median duration of RNA positivity of 30 years (tables 11 & 33, figure 21).

There are several potential explanations for these differences in liver-related outcomes. Firstly, we would expect co-morbidities to be higher in transfusion/renal participants in general, as many were infected with HCV as a result of treatment for serious medical conditions such as cancer. Transfusion/renal participants were also slightly older overall when infected with HCV, with a median age at infection of 32 years for ever chronically infected participants, compared to 28 years for anti-D participants and 14 years for participants infected through clotting factors. More than 40% of participants infected through receipt of clotting factors were coinfected with HIV and this is likely to have impacted disease progression in this group. Sex, or other characteristics associated with sex, may also be a factor as chronically infected female database participants had a lower prevalence of serious signs of liver disease than male participants despite having longer durations of RNA positivity overall. Alcohol intake also varied by sex (figure 5) and hence by source of infection, with 13% of chronically infected transfusion/renal participants and 16% of chronically

infected clotting factor participants consuming high levels of alcohol at some stage, compared to 6% of anti-D participants (tables 31, 32, 33).

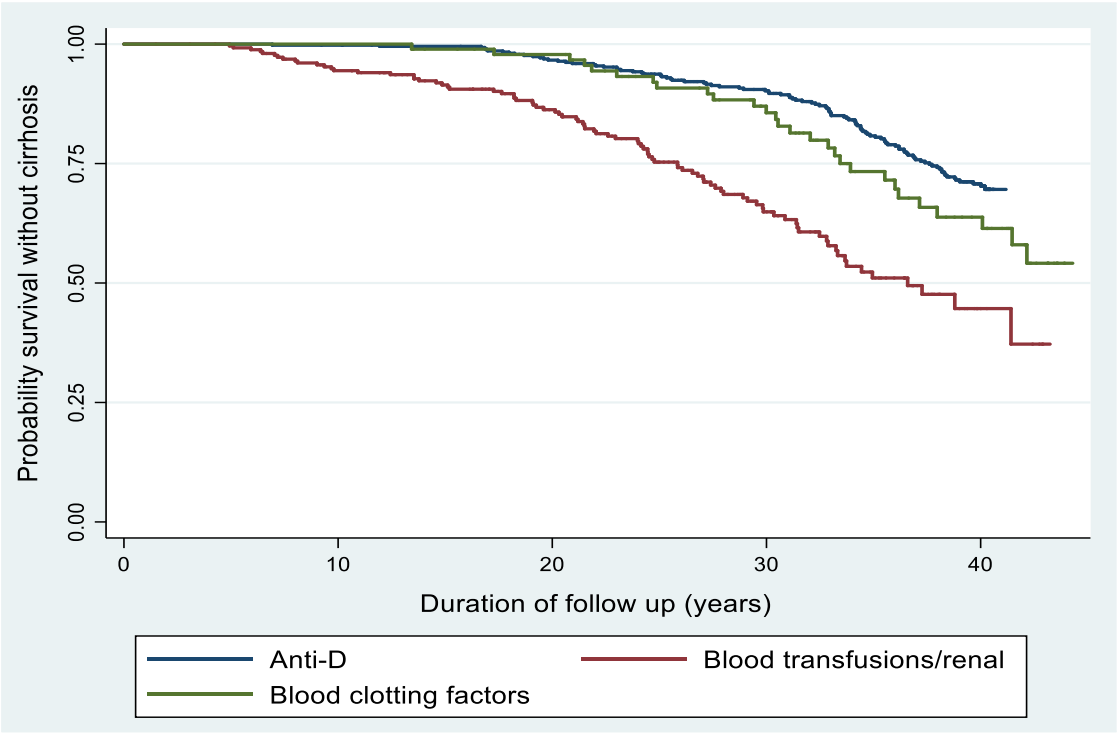


Figure 21. Proportion of ever chronically infected participants who have not developed cirrhosis over the follow-up period by source of infection – Kaplan Meier estimates

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

The anti-D group is entirely composed of females who were infected during or after pregnancy[37] (median age at infection: 28 years). Infection due to contaminated anti-D has been traced to batches of anti-D from two infected donors.[37] Batches from the first donor were contaminated with genotype 1b HCV and were distributed between 1977 and 1979. Eighty four percent (n=683) of anti-D participants were infected during this period. Batches from the second donor were infected with genotype 3a 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 anti-D participants was outside the two outbreak periods and the source of their infection is unclear. Just over half of anti-D participants ever tested HCV RNA positive (53%, n=427). Demographic characteristics for participants infected through anti-D are shown in table 31. Data on outcomes and RNA status are shown in the summary tables section at the start of this report (tables 3-8). Treatment outcome data are shown in tables 27 and 28.

Despite having the longest median duration of RNA positivity, database participants infected through anti-D had the lowest prevalence of serious liver-related outcomes. This is likely to be attributable, in part, to the fact that this group was composed of young females who were likely to have been in relatively good health when infected with HCV. Reported alcohol consumption was also lower for the anti-D group. For many years, the prevalence of severe liver related outcomes was particularly low in this group. However, treatment uptake was also historically lower in the anti-D patient group and the percentage of patients with cirrhosis increased markedly after 30 years of infection.

Table 31. Summary of demographic and virus characteristics for all anti-D database participants by RNA status (n=811)

Anti-D all	All		Ever chronically infected		Alive & currently chronically infected		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%
All anti-D participants	**811**		**427**		**54**		**374**	
Sex (n=811)								
Females	811	100	427	100	54	100	374	100
Males	0	0	0	0	0	0	0	0
Age at infection (n=811)								
Median (range)	**28**	**16-44**	**28**	**17-44**	**30**	**19-44**	**28**	**16-43**
<20	46	5.7	23	5.4	2	3.7	23	6.2
20-29	456	56.2	235	55.0	25	46.3	213	57.0
30-39	289	35.6	161	37.7	23	42.6	126	33.7
40+	20	2.5	8	1.9	4	7.4	12	3.2
Age at end of follow up (n=811)								
Median (range)	**64**	**26-84**	**66**	**31-84**	**68**	**41-84**	**62**	**26-84**
0-49	94	11.6	28	6.6	3	5.6	61	16.3
50-64	340	41.9	168	39.3	17	31.5	167	44.7
65+	377	46.5	231	54.1	34	63.0	146	39.0
Time since infection (n=811)								
Median	**38**	**4-55**	**40**	**9-55**	**40**	**9-55**	**35**	**4-52**
<25 years	111	13.7	30	7.0	2	3.7	76	20.3
25-34 years	197	24.3	87	20.4	12	22.2	106	28.3
35+ years	503	62.0	310	72.6	40	74.1	192	51.3
Duration RNA positivity (n=427)								
Median			**38**	**1-55**	**40**	**9-55**	n/a	
<25 years			71	16.6	2	3.7		
25-34 years			95	22.3	12	22.2		
35+ years			261	61.1	40	74.1		
Highest alcohol intake (n=777)								
Non drinker	169	21.8	78	18.8	14	27.5	90	25.4
Within recommended limits	536	69.0	288	69.2	33	64.7	245	69.0
Moderately high	39	5.0	25	6.0	3	5.9	14	3.9
High	33	4.3	25	6.0	1	2.0	6	1.7
HCV genotype (n=424)								
Genotype 1			381	89.9	52	96.3	n/a	
Genotype 2			2	0.5	0	0.0		
Genotype 3			41	10	2	4		
Body mass index (n=443)								
Normal or underweight	160	36.1	96	35.6	11	31.4	64	37.0
Overweight	153	34.5	94	34.8	14	40.0	59	34.1
Obese	130	29.4	80	29.6	10	28.6	50	28.9

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

n/a: not applicable

With notable disease progression and the availability of new, highly effective DAA drugs, treatment uptake and SVR rate increased significantly in the most recent four years of follow up for the anti-D patient group. Only 43% had ever been treated at the end of 2013 and just over half of these patients had achieved SVR. By the end of 2017, 78% (n=331) of ever chronically infected anti-D participants had been treated and 90% (n=298) had achieved SVR. Almost 200 anti-D participants were treated using DAA drug regimens since the last round of follow up with almost all achieving SVR (194 treated, 192 SVR, 1 treatment failure and 1 outcome awaited (still on treatment at the time of data collection).

Mortality

Seventeen percent (n=71) of ever chronically infected anti-D patients were deceased by latest follow up. Thirty percent (n=21) had died directly from liver-related causes and 59% (n=42) had died from non-liver related causes, mostly cancer (n=18), cardiac (n=7) or pulmonary disease (n=6). A death certificate was not available for the remaining 11% (n=8). Some of those who did not die directly from liver-related causes, or for whom a death certificate was not available, had evidence of advanced liver disease. Of all ever chronically infected deceased anti-D participants, 54% (n=38) had signs of serious liver disease, including 45% with cirrhosis (n=32) and 10% (n=7) with HCC, at the time of their death.

Current HCV status

Of the 356 ever chronically infected anti-D participants who were alive at the end of latest follow up, 54 remained chronically infected. A small number had not been treated due to other significant medical issues, but over 70% had either refused treatment or had not attended hepatology services since the approval of DAA drugs in Ireland. At the time of data collection, the hepatology units were attempting to re-engage with chronically infected patients who had not attended recently or had previously refused treatment, and It is likely that a significant proportion of the remaining patients have since been successfully treated.

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

Participants infected through blood transfusions or treatment for renal disease were the most heterogeneous patient group in terms of age and sex (table 32). This cohort had the highest median age at infection (32), but this ranged from 0 to 77 years. Fifty nine percent of chronically infected participants were female and forty one percent were male, making this the only group with sizeable proportions of each sex. Using the assumptions outlined in Methods section 3.3, most of the blood transfusion/renal participants were infected in the late 1970s and 1980s. Database participants infected through blood transfusions or treatment for renal disease had a high rate of HCV chronicity at diagnosis. RNA results were missing for two, but where results were available, 81% (n=272) were chronically infected and 19% (n=65) had cleared the HCV virus by the time they were diagnosed (table 10). Among ever chronically infected participants, the transfusion/renal group had the shortest duration of RNA positivity at latest follow-up (median 24 years). Demographic characteristics for participants infected through blood transfusions or treatment for renal disease are shown in table 32. Data on outcomes and RNA status are shown in the summary tables section at the start of this report (tables 9 and 10). Treatment outcome data are shown in tables 27 and 28.

Mortality

Forty one percent (n=112) of chronically infected participants infected through blood transfusion or treatment for renal disease were deceased by latest follow up. Thirty six percent (n=40) had died from liver-related causes and 55% (n=62) from non-liver related causes, mostly cardiac disease (n=17), kidney disease (n=14), cancer (n=13) or pulmonary disease (n=4). Death certificates were not available for the remaining 9% (n=10). Some of the patients who did not die directly from liver-related causes, or for whom a death certificate was not available, had evidence of advanced liver disease. Of deceased ever chronically infected transfusion/renal participants, 54% (n=60) had signs of serious liver disease, including 45% (n=50) with cirrhosis and 24% (n=27) with HCC, at the time of their death.

Current HCV status

One hundred and sixty ever chronically infected transfusion/renal participants were alive at the end of latest follow up. Of these, 81% (n=129) had been treated, with 91% (n=118) achieving SVR.

Of those treated with DAA drugs (n=47), all achieved SVR (1 additional patient who did not achieve SVR had subsequently died, giving a 98% overall success rate with DAA treatment). Three additional patients were RNA negative with no recorded treatment (presumed late spontaneous resolution) and thirty nine remained chronically infected. Forty one percent (n=16) of those recorded as remaining chronically infected had not attended hepatology services for over five years (some of these patients are likely to be deceased), 18% (n=7) had not attended since the approval of DAA drugs, eight patients had refused treatment, one was considering treatment, two were living abroad, two were not treated due to other medical conditions/advanced age and the reason for not being treated was not recorded for the remaining three patients.

Table 32. Summary of demographic and virus characteristics for transfusion or renal database participants by RNA status

Transfusion or renal	All		Ever chronically infected		Alive & currently chronically infected		Never chronically infected	
	Num	%	Num	%	Num	%	Num	%
All transfusion/renal participants	**339**		**272**		**39**		**65**	
Sex (n=339)								
Females	199	58.7	150	55.2	26	66.7	48	73.9
Males	140	41.3	122	44.9	13	33.3	17	26.2
Age at infection (n=339)								
Median	**32**	**0-77**	**32**	**0-77**	**37**	**0-66**	**34**	**0-63**
<20	52	15.3	45	16.5	10		7	10.8
20-29	83	24.5	63	23.2	18		20	30.8
30-39	89	26.3	71	26.1	36		17	26.2
40+	115	33.9	93	34.2	36		21	32.3
Age at end of follow up (n=339)								
Median	**64**	**16-91**	**64**	**16-91**	**73**	**24-90**	**65**	**16-91**
0-49	67	19.8	52	19.1	3	7.7	15	23.1
50-64	106	31.3	89	32.7	9	23.1	17	26.2
65+	166	49.0	131	48.2	27	69.2	33	50.8
Time since infection (n=339)								
Median	**28**	**1-55**	**29**	**1-55**	**36**	**7-52**	**26**	**7-44**
<25 years	123	36.3	95	34.9	9	23.1	27	41.5
25-34 years	122	36.0	97	35.7	9	23.1	25	38.5
35+ years	94	27.7	80	29.4	21	53.9	13	20.0
Duration RNA positivity (n=272)								
Median	**24**	**1-52**	**24**	**1-52**	**36**	**7-52**	n/a	
<25 years	140	51.5	140	51.5	9	23.1		
25-34 years	78	28.7	78	28.7	9	23.1		
35+ years	54	19.9	54	19.9	21	53.9		
Highest alcohol intake (n=306)								
Non drinker	97	31.7	79	31.6	16	44.4	17	30.9
Within recommended limits	143	46.7	117	46.8	15	41.7	26	47.3
Moderately high	27	8.8	21	8.4	1	2.8	6	10.9
High	39	12.8	33	13.2	4	11.1	6	10.9
HCV genotype (n=263)								
Genotype 1			153	58.2	26	66.7	n/a	
Genotype 2			27	10.3	4	10.3		
Genotype 3			82	31.2	9	23.1		
Genotype 5			1	0.4	39	100.0		
Body mass index (n=141)								
Normal or underweight	49	34.8	44	37.3	9	64.3	5	21.8
Overweight	52	36.9	43	36.4	3	21.4	9	39.1
Obese	40	28.4	31	26.3	2	14.3	9	39.1

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

n/a: not applicable

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

Database participants infected through blood clotting factors were predominantly male (93%, n=154) (table 33). Using the assumptions outlined in Methods section 3.3, 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 became chronically infected. By latest follow-up, the median age for clotting factor participants who ever became chronically infected was 50 years and the median duration of RNA positivity was 30 years. Forty two percent (n=69) of all clotting factor participants were co-infected with HIV. Demographic characteristics for participants infected with HCV through blood clotting factors are shown in table 33. Data on outcomes and RNA status are shown in the summary tables section at the start of the report (tables 11 and 12). Treatment outcome data are shown in tables 27 and 28.

Of the 165 database participants infected through blood clotting factors, 64% (n=105) were chronically infected with HCV at diagnosis and 22% (n=37) had no RNA results in their charts. These patients had all died prior to RNA testing, but it is likely that some were chronically infected with HCV as 14% (n=5) already had documented clinical signs of liver disease. The remaining 14% (n=23) of clotting factor patients had RNA results in their charts but had never tested HCV RNA positive. These participants showed no signs of serious liver-related disease by latest follow-up (table 12).

Table 33. Summary of demographic and virus characteristics for clotting factor database participants by RNA status

Clotting factors	All		Ever chronically infected		Alive & currently chronically infected		Never chronically infected	
			Num	%	Num	%	Num	%
All clotting factor participants	**165**		**105**		**4**		**23**	
Sex (n=165)								
Females	11	6.7	7	6.7	0	0.0	2	8.7
Males	154	93.3	98	93.3	4	100	21	91.3
HIV status (n=165)								
HIV negative	96	58.2	69	65.7	4	100	21	91.3
HIV positive	69	41.8	36	34.3	0	0.0	2	8.7
Age at infection (n=165)								
Median	**13**	**0-59**	**14**	**0-53**	**16.5**	**7-42**	**11**	**0-38**
<20	111	67.3	71	67.6	3	75.0	16	69.6
20-29	29	17.6	20	19.1	0	0.0	4	17.4
30-39	16	9.7	9	8.6	0	0.0	3	13.0
40+	9	5.5	5	4.8	1	25.0	0	0.0
Age at end of follow up (n=165)								
Median	**47**	**12-85**	**50**	**18-85**	**53**	**44-85**	**43**	**26-71**
0-49	94	57.0	50	47.6	2	50.0	15	65.2
50-64	54	32.7	44	41.9	1	25.0	4	17.4
65+	17	10.3	11	10.5	1	25.0	4	17.4
Time since infection (n=165)								
Median	**32**	**8-52**	**37**	**14-52**	**40**	**28-42**	**32**	**19-44**
<25 years	53	32.1	16	15.2	0	0.0	4	17.4
25-34 years	45	27.3	29	27.6	1	25.0	12	52.2
35+ years	67	40.6	60	57.1	3	75.0	7	30.4
Duration RNA positivity (n=105)								
Median	**30**	**4-50**	**30**	**4-50**	**40**	**28-42**	n/a	
<25 years	27	25.7	27	25.7	0	0.0		
25-34 years	41	39.1	41	39.1	1	25.0		
35+ years	37	35.2	37	35.2	3	75.0		
Highest alcohol intake (n=123)								
Non drinker	23	18.7	17	18.7	0	0.0	2	10.0
Within recommended limits	54	43.9	40	44.0	2	50.0	9	45.0
Moderately high	25	20.3	19	20.9	1	25.0	5	25.0
High	21	17.1	15	16.5	1	25.0	4	20.0
HCV genotype (n=92)								
Genotype 1			60	65.2	2	50.0	n/a	
Genotype 2			9	9.8	0	0.0		
Genotype 3			20	21.7	2	50.0		
Genotype 4			2	2.2	0	0.0		
Genotype 5			1	1.1	0	0.0		
Body mass index (n=42)								
Normal or underweight	11	26.2	9	25.7	2	66.7	2	33.3
Overweight	18	42.9	16	45.7	1	33.3	2	33.3
Obese	13	31.0	10	28.6	0	0.0	2	33.3

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

n/a: not applicable

HIV co-infection and outcomes

Thirty four percent (n=36) of the HCV chronically infected participants, 84% (n=31) of those with no HCV RNA results and two participants who never tested HCV RNA positive were HIV positive. It is difficult to ascertain the true effects of HIV co-infection on HCV disease progression as 68% (n=47) of the co-infected participants were deceased and most died in the 1990s. However, 64% (n=23) of those who were HIV positive and ever chronically infected with hepatitis C had clinical signs of serious liver disease compared to 35% (n=24) of those who were HIV negative. In a binomial regression model the factors significantly associated with signs of serious liver disease in chronically infected clotting factor participants were HIV positivity (risk ratio 1.6, p=0.016), high alcohol intake (risk ratio 2, p<0.001) and longer duration of RNA positivity (30 years or longer compared to less than 30 years) (risk ratio 1.9, p=0.005).

The rate of cirrhosis was also higher in HIV co-infected participants, but this difference was not statistically significant (HIV positive: 31% had cirrhosis, rate of 8.6 per 1,000 person years at risk, HIV negative: 26% had cirrhosis, rate of 7.7 per 1,000 person years at risk, rate ratio 1.1, p=0.75). In a Poisson regression model looking at factors associated with rate of cirrhosis in HCV chronically infected clotting factor patients (including age at end of follow up, sex, alcohol consumption and HIV status), ever having high alcohol consumption was the only factor statistically significantly associated with a higher rate of cirrhosis. However, it should be noted that cirrhosis may have been historically under reported in this patient group as they were less likely to have had biopsies and had fewer biopsies compared to the other patient groups.

Mortality

Overall, 47% (n=77) of clotting factor participants had died by latest follow-up (table 11). Forty seven were HIV positive (68% of all HIV positive patients) and thirty were HIV negative (31% of all HIV negative patients).

No HCV RNA results

Thirty seven of the deceased participants had no hepatitis C RNA results in their medical records. These patients all died before 1998 and 84% (n=31) were HIV positive. The cause of death was reported as HIV/immunodeficiency for sixteen, liver-related causes for seven (two were not related to hepatitis C), haemophilia for six, other non-liver related causes for three, unspecified infection for two and the death certificate was not available for the remaining three patients.

Death due to HIV infection may be underestimated as there was significant stigma associated with HIV infection and HIV may have been omitted as a cause of death from some death notifications.

Ever chronically infected with HCV

Of the 105 clotting factor participants who were ever confirmed to be chronically infected with hepatitis C, 34% (n=36) were HIV positive and 66% (n=69) were HIV negative. Thirty five percent (n=37) were deceased by latest follow up, 38% (n=14) of whom had died from liver-related causes. Some of the patients who did not die directly from liver-related causes, or for whom a death certificate was not available, had evidence of advanced liver disease. Of deceased ever chronically infected clotting factor participants, 68% (n=25) had signs of serious liver disease, including 46% (n=17) with cirrhosis and 22% (n=8) with HCC, at the time of their death.

All cause mortality was higher for chronically HCV infected patients who were also HIV positive, but this difference was not statistically significant. Forty four percent (n=16) of chronically HCV infected HIV positive patients had died by the end of latest follow up (6 from liver related causes, 5 from HIV/immunodeficiency, 3 from haemophilia, 1 from other non-liver related causes and the death certificate was not available for 1). This compares to 30% mortality (n=21) in HIV negative chronically infected patients (8 of whom died from liver related causes, 2 from haemophilia and 11 from other non-liver related causes). The all cause mortality rates were 12.1 deaths per 1,000 person years at risk for the HIV positive patients and 8.0 deaths per 1,000 person years at risk for the HIV negative patients, rate ratio: 1.5, p=0.104. Similarly, liver-related mortality was higher for HIV positive patients, but the difference by HIV status was not statistically significant: 4.6 liver-related deaths per 1,000 person years at risk for HIV positive chronically infected patients compared to 3.3 for HIV negative patients (rate ratio: 1.4, p=0.528).

Three participants who had hepatitis C RNA results in their medical records, but had never tested RNA positive had also died, but none from liver or HIV related conditions.

Current HCV status

Sixty nine percent (n=72) of participants chronically infected through blood clotting factors had received antiviral treatment for HCV by latest follow-up and 88% (n=63) had achieved SVR. Excluding deceased patients, 91% (n=62) had been treated with 98% (n=61) achieving SVR. Treatment uptake and success rate did not vary significantly by HIV status. All living HIV positive

database participants (n=20) have been successfully treated for HCV and only four HIV negative participants remained chronically infected when last followed up (one was treated, but treatment was stopped early for medical reasons, one refused treatment and two were not treated due to other medical conditions).

Chapter 6. Conclusion

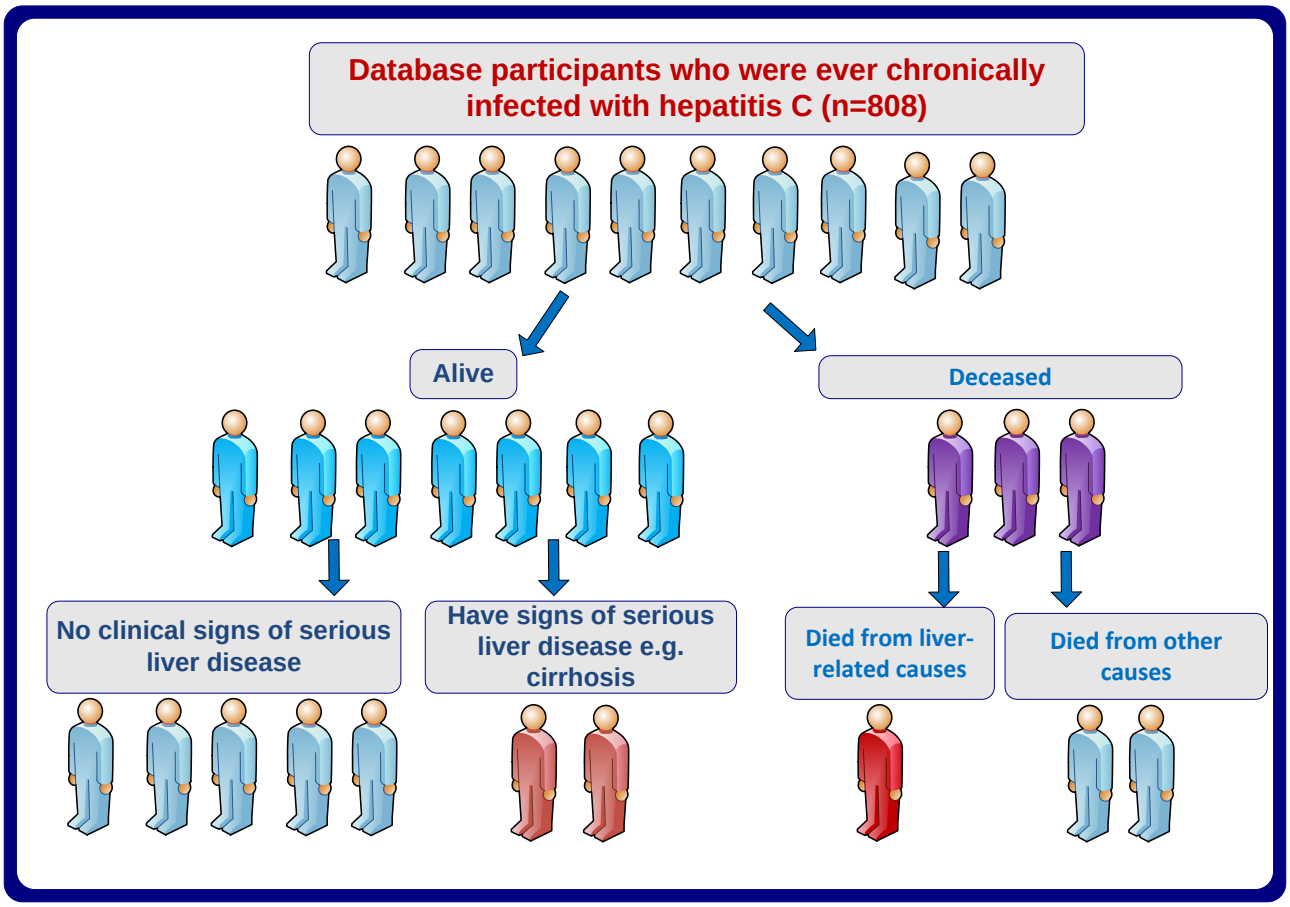


Figure 25. Summary of hepatitis C infection and disease progression in all ever chronically infected database participants

This report describes the health status of 1,322 people infected with hepatitis C through the administration of blood or blood products in Ireland as of the end of 2017. The database participation rate was high, at 77%, and has allowed us to follow the effects of HCV on the health of patients as this population has aged and the duration of HCV infection has increased. The average duration of active infection (RNA positivity) was 32 years at the end of follow up. Among those who developed chronic infection, just over one third had developed signs of serious liver disease (34%) including cirrhosis (28%) and liver cancer (7%) and 10% had died from liver-related causes (figure 25). Participants who did not develop chronic HCV infection rarely show signs of advanced liver disease.

The factors found to be associated with liver disease progression in the database participants with chronic infection have been well described in the literature: high alcohol intake, longer duration of

infection, male sex and older age.[1,6,10] There is clear evidence from published international sources that heavy alcohol use accelerates fibrosis progression and increases the risk of cirrhosis, HCC and end stage liver disease.[38-40] Aside from chronic infection, the most important factor associated with liver disease progression in the database population was alcohol.

In previous reports on the database cohort, genotype 3 was found to be independently associated with having more severe liver disease. This effect was not observed in this round of follow up. Results published in the international literature have conflicted in relation to the impact of HCV genotypes on fibrosis progression and on the development of cirrhosis and HCC.[41-43]

The differences in outcomes by source of infection have also lessened in recent years. Disease progression was initially slower in the anti-D patient group, but a combination of low treatment uptake and longer duration of infection has meant that adverse liver outcomes increased significantly in this group, particularly after 30 years of infection. One quarter of the anti-D group had developed cirrhosis by latest follow up. This was not significantly lower than in participants infected through blood clotting factors (28%). Database participants infected through blood transfusions or treatment for renal disease had higher prevalences of liver disease, with over a third being diagnosed with cirrhosis despite having the shortest duration of RNA positivity at 24 years.

BMI was not found to be a key factor in disease progression in the database population. However, BMI data were available for just over half of chronically infected participants and may not have been representative of the group as a whole.

The most significant change since the previous round of data collection has been the dramatic success of the DAA drugs - 99% of database patients treated with DAA drug regimens achieved SVR. Of the total database population, only 98 people were recorded as still living with chronic HCV infection at the end of the most recent data collection period. Some had refused treatment, others were no longer attending hepatology services and some had not been treated due to other health issues. It is likely that a proportion of these patients are effectively lost to follow up and may have moved abroad or died. At the time of data collection, efforts were being made to encourage patients who were still living with chronic infection in Ireland, and not regularly

attending their hepatology unit, to re-engage in care so that they could be assessed and offered treatment.

Of the 587 ever HCV chronically infected database participants remaining alive at the time of latest data collection, 83% had been successfully treated. However, ongoing monitoring will still be required for successfully treated patients who had signs of liver disease at the time of treatment as they remain at risk of further liver disease progression. Twenty two percent of successfully treated living participants had cirrhosis recorded in their medical records and 3% had HCC.

Epilogue

This report is the final report of the Hepatitis C Database. Since 2004, the HSE Health Protection Surveillance Centre (HPSC), in association with eight specialist hepatology units, has reported on the natural history of infection, the outcomes of treatment, and other relevant information for planning of services, using information gathered periodically over this time. As of 2017, the last data collection period, more than 35 years have elapsed since infection occurred in the majority of those included in the database.

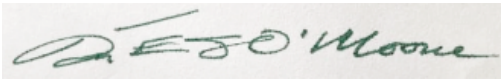
I would like to sincerely thank all those involved in this work, particularly those people infected with hepatitis C virus (HCV) through the administration of blood or blood products. This work was only made possible firstly due to the support of patients who gave their consent to be included in the database, and secondly due to the work of the patient support groups who encouraged participation. I sincerely thank them for their participation and support during this time which has deeply informed our understanding of the course and impact of hepatitis C virus infection over time. This insight has shaped our understanding and enabled us as a scientific and medical community to develop new treatment programmes to support the needs of those infected.

Thanks to the development of new therapeutic interventions over the past few years, specifically direct acting antiviral medicines (DAAs), the vast majority of people infected with HCV can now be treated to cure, with evidence of sustained virological response (SVR). This means that the virus is no longer present in the body, cannot cause harm to those previously infected, and cannot be transmitted to others. The HSE National Hepatitis C Treatment Programme offers this highly effective treatment free of charge to all people known to be living with HCV in Ireland. This report has shown that 99% of those infected through the administration of blood or blood products and who were treated with these drugs, cleared the infection. This is both a great outcome for those people infected and a great milestone in public health in Ireland.

Sadly, among those who developed chronic infection, as of 2017, one third had developed signs of serious liver disease such as cirrhosis and liver cancer, some of whom have died. Following up these patients for more than 35 years after infection has shown that those who did not develop chronic HCV infection do not subsequently show signs of serious liver-related disease.

I am glad to say that transfusion-related HCV infection, and infection from contamination of blood products, no longer occur since the introduction of routine screening of blood for HCV antibodies in the 1990s. With the advent of highly effective drug treatments, work is underway to make HCV infection a very rare disease in Ireland as per the World Health Assembly targets for 2030.

Going forward, surveillance and monitoring of hepatitis C will remain a Public Health priority with continued efforts in public education, testing and provision of accessible treatment, especially to those vulnerable and under-served people at risk of infection and at risk of transmitting infection to others. There is more work to be done in addressing health inequalities in our population in relation to exposure to infection, access to testing, access to treatment, support with treatment to achieving cure, and also on issues such as reinfection (which may be a concern for those who remain at risk of infection following cure due to behaviours such as injecting drug use). We need to amplify the message that Hepatitis C is a curable infection; that we can treat it and we can eliminate it as a public health problem in Ireland by 2030. But this will take ongoing work, including research to inform knowledge on designing and delivering testing and treatment programmes that meet the needs of all. It is hoped that the successful response to treatment in those with transfusion-related hepatitis C will contribute to encouraging others who remain at risk of infection to avail of free testing and treatment.



Dr Éamonn O'Moore, Director of National Health Protection, National Health Protection Office

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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 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.

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

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

Fibroscan
A FibroScan is a specialized ultrasound machine for your liver. It measures fibrosis (scarring) and steatosis (fatty change) in your 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 determining which antiviral drugs to use to treat hepatitis C.

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.

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.

Recombinant immunoblot assay (RIBA)
An additional test for hepatitis C specific antigens in a patient's blood. RIBA tests are usually performed after a positive EIA result and are used to confirm the presence of antibodies to the

hepatitis C virus. A positive RIBA result is generally considered confirmation that a patient has been infected with hepatitis C but cannot differentiate between past infection and current infection.

Renal
The term renal refers to the kidney.

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

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

Splenomegaly
Enlarged spleen.

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

Statistical terms

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).

Multivariable regression (e.g. logistic, binomial, Poisson and Cox regression)
Multivariable 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 multivariable regression model, each factor in the model is adjusted for the effect of the other factors on the outcome.

Odds ratio (OR)

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. An OR of more than 1 indicates that the rate is higher in one group compared to the other. This is assessed in conjunction with a p-value (<0.05 is usually taken as indicating a statistically significant difference between the groups) and 95% confidence intervals.

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.

Risk ratio (RR)

The risk ratio is a measure of the risk of an event occurring in one group divided by the risk of it occurring in another group. A risk ratio of 1 indicates that the event is equally likely in both groups. A risk ratio of more than 1 indicates that the risk is higher in one group compared to the other. This is assessed in conjunction with a p-value (<0.05 is usually taken as indicating a statistically significant difference between the groups) and 95% confidence intervals.

Hazard rate

The hazard rate for survival time data is the probability of "failure" (outcome of interest: death, liver-related death, cirrhosis, HCC) at a given point in time conditional on having survived to up to that time.

Hazard ratio (HR)

Ratio of hazard rate in one group compared to that in another e.g. ever chronically infected patients compared to never chronically infected, males compared to females. A HR of 1 indicates that the event is equally likely in both groups. A HR of more than 1 indicates that the hazard rate is higher in one group compared to the other. This is assessed in conjunction with a p-value (<0.05 is usually taken as indicating a statistically significant difference between the groups) and 95% confidence intervals.

Abbreviations

AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase (a liver enzyme)
Anti-HCV	Antibody to hepatitis C virus
BOC	Boceprevir
DAA	Direct acting antiviral drugs
EIA	Enzyme immunoassay, a screening test for hepatitis C
HAA	Health (Amendment) Act
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPSC	Health Protection Surveillance Centre, formerly known as the National Disease Surveillance Centre
HSE	Health Service Executive
IBTS	Irish Blood Transfusion Service, formerly known as the Blood Transfusion Service Board
PCR	Polymerase chain reaction
RBV	Ribavirin
RIBA	Recombinant immunoblot assay, a more specific hepatitis C test
RNA	Ribonucleic acid
SVR	Sustained virological response
TVR	Telaprevir
WHO	World Health Organization

Appendix A

Members of the National Hepatitis C Database Steering Committee (as of 2018)

Dr Lelia Thornton, National Hepatitis C Database Project Coordinator, Health Protection Surveillance Centre (up to August 2018)
Ms Michele Tait, Programme Manager of the National Hepatitis C Treatment Programme (up to 2018), HSE Hepatitis C National Coordinator **(**Chair up to mid-2018)
Ms Ger Kane, HSE Hepatitis C National Coordinator (Chair from mid-2018)
Ms Kay Maher, Department of Health
Dr Barbara Coughlan, University College Dublin
Ms Susan Gaughran, Transfusion Positive
Ms Debbie Greene, Irish Haemophilia Society
Ms Maura Long, Transfusion Positive
Ms Carol McNulty, St Vincent's University Hospital
Mr Mark Murphy, Irish Kidney Association
Ms Niamh Murphy, Health Protection Surveillance Centre
Prof. Suzanne Norris, St James's Hospital

Appendix B

Members of the National Hepatitis C Database Scientific and Technical Group (as of 2018)

Professor Billy Bourke, Our Lady's Children's Hospital, Crumlin, Dublin
Professor Garry Courtney, St Luke's Hospital, Kilkenny
Professor Orla Crosbie, Cork University Hospital, Cork
Professor John Hegarty, St Vincent's University Hospital, Dublin
Professor John Lee, University College Hospital, Galway
Ms Carol McNulty, St Vincent's University Hospital, Dublin
Ms Niamh Murphy, Health Protection Surveillance Centre
Professor Frank Murray, Beaumont Hospital, Dublin
Dr Niamh Nolan, St Vincent's University Hospital, Dublin
Professor Suzanne Norris, St James's Hospital, Dublin
Professor Cliona O'Farrelly, Trinity College Dublin
Dr Stephen Stewart, Mater Misericordiae University Hospital
Dr Lelia Thornton, Health Protection Surveillance Centre

Appendix C: Data collection form for fifth round of follow-up

Recommended next follow up

- ☐ 6 month HCC surveillance
- ☐ 1 year
- ☐ > 1 year & < 2 years
- ☐ 2 years
- ☐ > 2 years
- ☐ Discharged
- ☐ Not stated

Section 4. Comments/notes

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

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

HCV
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 5

1. Database ID _____

2. Form completed by _____ **3. Date form completed** |_|_|_|_|_|_|

4. 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)

5. Has this patient attended this hepatology Unit since last form completed?

Yes ☐ No ☐

Database ID ______________

Section 1. Patient Details

Sex **Male** ☐ **Female** ☐ **Height** ________ **Weight** ________ **BMI** ________

Alcohol intake at last visit (*units/week*) Non-Drinker ☐ Number of units ______________

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

If yes: date of death (dd/mm/yy): __/__/__ **Cause of death** ______________

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

If yes, please specify ______________

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

If yes, please specify ______________

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

If yes, please specify ______________

Section 2. Clinical Status

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

Yes ☐ No ☐

If yes, please specify below

- ☐ Ascites
- ☐ Varices/Bleeding Varices
- ☐ Cirrhosis
- ☐ Liver tumour/HCC
- ☐ Encephalopathy
- ☐ Other (please specify) ______________

Extrahepatic manifestations of HCV infection (diagnosed since last form completed)

Yes ☐ No ☐

If yes, please specify below

- ☐ Cryoglobulinaemia
- ☐ Glomerulonephritis
- ☐ Porphyria
- ☐ Cutaneous vasculitis
- ☐ Other (please specify) ______________
- ☐ Neuropathy
- ☐ Lymphoma
- ☐ Sicca / Sjögren syndrome
- ☐ Diabetes

Section 3. Clinical Management

Date of most recent visit for HCV related care (dd/mm/yy) __/__/__

				Date (*dd/mm/yy*)
Liver related	**CT** ☐	**MRI** ☐	**US** ☐	__/__/__
result				
Liver related	**CT** ☐	**MRI** ☐	**US** ☐	__/__/__
result				
Liver related	**CT** ☐	**MRI** ☐	**US** ☐	__/__/__
result				

Fibroscan results

Date						
__/__/__	**Kpa**	______	**Success rate %**	______	**IQR**	______
__/__/__	**Kpa**	______	**Success rate %**	______	**IQR**	______
__/__/__	**Kpa**	______	**Success rate %**	______	**IQR**	______
__/__/__	**Kpa**	______	**Success rate %**	______	**IQR**	______

Database ID ______________

Liver transplant recipient (since last form completed) Yes ☐ No ☐

If yes, Date (dd/mm/yy): __/__/__ Are they currently on the waiting list? Yes ☐ No ☐

Section 4. Test Results

HCV PCR (ALL since last form completed)

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

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

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

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

Date: Started	Finished	Regime: Name/preparation	Dose	Schedule
__/__/__	__/__/__			
__/__/__	__/__/__			
__/__/__	__/__/__			

1: Early discontinuation -patient led
2: Early discontinuation -Clinician led
3. *Relapse (undetectable at EOT, detectable at either 12 weeks or 24 weeks)
4: **SVR at 12 or 24/48 weeks
5: Lost to follow up
6: No response
7: Still on treatment

Overall response to treatment ☐

*Detectable at either 12 weeks or 24 weeks depending on treatment regime
** SVR at 12 weeks for DAA and 24/48 weeks for interferon based therapy

Treatment stopped early (due to side effects)

____

____

____

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

Transfusion Positive
Fitzwilliam Business Centre, 26 Upper Pembroke Street, Dublin 2. Tel: 01 234 3740. Email: transfusionpositive@eircom.net, website: www.transfusionpositive.ie

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

Irish Kidney Association
Donor House, Block 43a Park West, Dublin 12. Tel: 01 620 5306. E-mail: info@ika.ie, website: www.ika.ie

Anti D Women's Group
Carmichael Centre, The Lodge, North Brunswick Street, Dublin 7. Tel: 01 873 4359. Email: antidwomen@gmail.com

Ladies C Anti D Support Group
Agher, Summerhill, Co. Meath A83 WP29. Tel: 086 1639004. Email: chris.bruton1@gmail.com

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

Children's Health Ireland (CHI) at Crumlin (formerly 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 Hospital Galway
Hepatology Unit, Newcastle Road, Galway. Tel: 091 544 370/091 524 222

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

Liaison Officers

HSE Hepatitis C National Office

Ms Ger Kane, National coordinator hepatitis C services, HSE Mill Lane, Palmerstown, Dublin 20. Tel: 01 620 1750/01 620 1712, email: ger.kane@hse.ie

CHO 1: Leitrim/Sligo/Donegal

Ms Paula Forrest, Homecare Services, 1st floor County Clinic, St Conal's Hospital, Letterkenny, Co. Donegal. Tel: 074 910 9129/087 1359275 email: paula.forrest@hse.ie

CHO2: Galway/Mayo/Roscommon

Mr. Richard Broderick, Primary Care Unit, HSE Merlin Park, Galway. Tel: (091) 775 416, email: richard.broderick@hse.ie

CHO3: Clare/Limerick/Tipperary North

Ms Louise Carey, Primary Care Services, Ballycummin Avenue, Raheen Business Park, Raheen, Limerick, V94 D1W9. Tel: 061 483442/087 9668471, email: LouiseP.Carey@hse.ie

CHO 4: Cork/Kerry

Norah Heffernan, Primary Care Unit, HSE-South, Floor 3, Block 15, St. Finbarr's Hospital, Douglas Road, Cork. T12 XH60. Tel: 021 492 3833/087 1609785, email: norah.heffernan@hse.ie

CHO5: Carlow/Kilkenny/Tipperary South/Waterford/Wexford

Linda Knox, Primary Care Unit, HSE, Lacken, Dublin Road, Kilkenny. Tel 056 778 4101 email: linda.knox@hse.ie

CHO 6: Dublin South West/ Dublin West

To be appointed, Hep C Liaison Officer, HSE Stewart's Hospital, Mill Lane, Palmerstown, Dublin 20. Tel: 01 77 8518, email Ger.kane@hse.ie

CHO 7: Dublin South East/Dun Laoghaire/Bray/Wicklow and Dublin South/ Kildare & West Wicklow

To be appointed, Hep C Liaison Officer, HSE Stewart's Hospital, Mill Lane, Palmerstown, Dublin 20. Tel: 01 77 8518, email Ger.kane@hse.ie

CHO8: Laois, Longford, Offaly/Westmeath

Ms Elaine Barry Flynn, Primary Care Unit, HSE, St Loman's, Springfield, Mullingar, Co Westmeath. Tel: 044 938 4429, email: elainem.barry@hse.ie

CHO 9: Dublin North West/ Dublin North/ Dublin North Central and Cavan, Louth , Meath & Monaghan

Mr Larry Bathe, Primary Care Unit, Railway Street, HSE, Railway Street, Navan, Co Meath. Tel: 046 9076451, email: larry.bathe@hse.ie

Relevant National Agencies

Health Protection Surveillance Centre,
25-27 Middle Gardiner St, Dublin 1. Tel: 01 876 5300. 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: ger.kane@hse.ie