Status report on the slim-National Haemophilia Database, version 3 (sNHD3)

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0. Executive Summary

0.1 Revisions of the database for analysis and implications for analysis: Two revisions to the database were made. The first was to revert HCV-status to what was known about the patient's HCV-exposures (i.e. to pooled plasma prior to 1988; to components prior to 1992) ***before*** HCV-testing. The analysis-plan was to define (as alternatives) an HCV-**diagnosis**-indicator/HCV-***negative***-indicator to be switched from the patient's HCV antibody test-date (as known to NHD). The analysis-plan was complicated by the extent to which HCV test-date was missing, namely for **84%** of persons tested. Since the **missing HCV-test-dates** for nearly 3,000 patients could not readily be acquired, we demonstrate the critical impact on key estimated covariate influences by assuming missing HCV-dates were alternatively 1 Jan 1992 (start of Epoch i) or 1 January 2010 (start of Epoch iii). The latter was justified by the fact that about one-fifth of known HCV-test-dates were in the 21st century.

A second revision was necessitated when, in answering queries about which patients were sent for record-linkage and, of those for whom personal identifying information (such as NHS number) was sent, what proportion were successfully linked, **residual duplicates** were discovered (mainly on account of duplicated NHS number), some of which concerned patients who had died (some necessitating a change to consensus cause of death), others of which had occurred when the patient's bleeding disorder diagnosis had changed (and a new record was instituted). Considerable work was undertaken at NHD to resolve these difficulties insofar as they affected (minimally as it happens) the well-defined subset of patients in our survival regression analyses.

Yet other patients – including a tranche in our well-defined subset for survival analysis - lacked an NHS-number, making both record-linkage and the eradication of residual duplicates less assured. This difficulty was addressed by conducting a sensitivity analysis (see **Appendix**) for the main findings – by omitting the tranche of patients with missing NHS number.

0.2 Well-defined subset for survival regression analysis in distinct epochs of follow-up: The well-defined subset comprised 6,282 patients who were first registered before 1992, first treated before 1992 (or date of first treatment was missing), alive at 1 January 1992, known sex and age at 1 January 1992 and who - according to NHD - had been HIV-infected, HCV-tested or exposed to pooled plasma prior to 1988 or to components prior to 1992. [Moderate/High confidence]

0.3 Survival analysis focused on distinct epochs: The four epochs were defined with the final two often combined, particularly for our secondary analysis of cause-specific deaths: that is

of liver-related or cardiovascular deaths which numbered **205**, **194** and **164** in the 1st, 2nd and combined last epochs.

Epoch 1: 1 January 1992 to 31 December 1999 (8 years with **830** deaths: **205** liver/cardiovascular)

Epoch 2: 1 January 1999 to 31 December 2009 (10 years with **583** deaths: **194** liver/cardiovascular);

Epoch 3: 1 January 2010 to 31 December 2013 (4 years with **242** deaths)

Epoch 4: 1 January 2014 to 31 December 2019 (6 years with **338** deaths); **OR**

Epoch 3+4:1 January 2010 to 31 December 2019 (10 years with **580** deaths: **164** liver/cardiovascular)

0.4 Key findings on all-cause mortality for the well-defined patient-subset: HIV diagnosis-date was missing for just three of the 966 HIV-infected patients in the above well-defined subset for analysis and 99% of HIV-diagnoses were made prior to 1992. All patients with bleeding disorder who were HIV-infected were assumed to be also HCV-infected.

The hazard ratio (**HR**) for **HIV/HCV co-infection** (relative to those HIV-uninfected) reduced from **12.2** (95% CI: 10.1 to 14.8) in Epoch 1 to **4.4**, **3.2** and **1.4** in Epochs 2, 3 and 4; and was **2.1** (95% CI: 1.5 to 2.8) in Epochs 3+4 combined. In Epoch 1, the HR for **HIV/HCV co-infection** was almost as high as HR of **14.8** for being aged 60+ at 31 December 1991 (95% CI: 11.7 to 18.6). [High confidence]

Highly Active Antiretroviral Treatment (HAART) accounts mainly for the above HIV-related sharp fall in HRs. Consequently, **HIV/HCV co-infected patients' HR** of **2.1** (95% CI: 1.5 to 2.8) in Epochs 3+4 combined can be interpreted as an upper bound for the **HR** in the same period for persons with bleeding disorder who were HCV-infected ***but not*** HIV-infected. [Moderate confidence]

When we differentiate HIV/HCV co-infected persons from patients who were **HCV-diagnosed** but are not HIV-infected (relative to those whose HCV-status is not known to NHD), the respective **HRs** in Epoch 3+4 are **2.2** (95% CI: 1.6 to 3.2) for **HIV/HCV co-infected** patients, **1.2** (95% CI: 0.9 to 1.5) for those who were **HCV-diagnosed** and **0.7** (95% CI: 0.5 to 0.9) for those who tested HCV antibody negative. [Low/Moderate confidence]

In the same regression analysis which also allowed for the joint influences of sex and age-band, together with bleeding disorder and its severity, the corresponding **HRs** in Epoch 3+4 for exposure to components before 1992 (relative to no such exposure) was **2.0** (95% CI: 1.6 to 2.5) and for exposure to pooled plasma prior to 1988 (relative to no such exposure) was **2.5** (95% CI: 1.9 to 3.2).

When covariate for exposure to components or pooled plasma were omitted, **HRs** in Epoch 3+4 increase slightly to **3.0** (95% CI: 2.1 to 4.2) for **HIV/HCV co-infected** patients, **1.6** (95% CI: 1.2 to 2.0) for those who were **HCV-diagnosed** and **0.7** (95% CI: 0.5 to 0.9) for those who tested HCV antibody negative. [Low/Moderate confidence].

0.5 Key findings on liver-related or cardiovascular death for the well-defined patient-subset: ***Cause-specific hazard ratio*** (**HR**) for **HIV/HCV co-infection** (relative to those uninfected) reduced from **5.5** (95% CI: 3.8 to 8.0) in Epoch 1 and **4.9** (95% CI: 3.2 to 7.5) in Epoch 2 to **1.7** (95% CI: 1.0 to 2.9) in Epochs 3+4 combined.

When we differentiate HIV/HCV co-infected persons from patients who were **HCV-diagnosed** but are not HIV-infected (relative to those whose HCV-status is not known to NHD), the respective ***cause-specific HRs*** in Epoch 3+4 are **2.6** (95% CI: 1.3 to 5.0) for **HIV/HCV co-infected** patients, **1.8** (95% CI: 1.1 to 2.8) for those who were **HCV-diagnosed** and **0.4** (95% CI: 0.2 to 0.8) for those who tested HCV antibody negative. [Low/Moderate confidence]

In the same regression analysis which also allowed for the influences of sex and age-band, together with bleeding disorder and its severity, the corresponding ***cause-specific HRs*** in Epoch 3+4 for exposure to components before 1992 (relative to no such exposure) was **1.9** (95% CI: 1.2 to 3.0) and for exposure to pooled plasma prior to 1988 (relative to no such exposure) was **2.4** (95% CI: 1.3 to 4.2).

0.6 Observations on Von Willebrand disease: Both in our primary analysis for all-cause mortality and in our secondary cause-specific analysis for liver-related or cardiovascular deaths, we observe in Epoch 3+4 significantly increased HRs (relative to baseline of Haemophilia A <= 5IU/dl) for von Willebrand patients of **1.6** (95% CI: 1.1 to 2.3) and **2.1** (95% CI: 1.1 to 4.0) respectively. We are aware of debate in the clinical literature on whether patients with Von Willebrand disease might be at altered-risk of liver-related and/or cardiovascular disease. Our findings may add usefully to the debate as the prognostic influences not only of sex and age-band have been accounted for but also exposure to components pre-1992 or pooled plasma pre-1988 together with HIV-infection and HCV-status as known to NHD.

0.7 Merits of further work: Use of sex and age-band appropriate expected deaths as offset in logistic or proportional hazards models has low priority for two reasons. First, the current regression models make comparison anyway across different bleeding disorders and severity; secondly, the substantially missing HCV-test-dates undermine credibility.

0.8 Recommendations: First, any patient with a bleeding disorder who was first treated prior to 1992 should seek to establish their HCV-status by asking their doctor to arrange for them to have an HCV-antibody test. Second, National Haemophilia Database, UKHCDO and the associated haemophilia centres need support to ascertain from centres the HCV-test-dates of patients in the above well-defined subset for analysis. Third, consideration could be given to making a public interest case for record-linkage between UKHSA's HCV-register and NHD to identify HCV-diagnoses in-common; those which UKHSA knows about which relate to persons with a bleeding disorder but NHD is unaware; and the reverse. Fourth, going forward, consideration might be given to establishing a new status-NHD on a similarly rigorous and UK-wide basis as NHS Blood and Transplant delivers for patients who require transplantation.

1. Background

The slim National Haemophilia Database (sNHD3) and associated code-book were updated after record-linkage in Northern Ireland, continued review of archives, further eradication of duplicates and reverted-categorization of patients whose HCV status had been altered to "presumed at HCV risk" on the basis of subsequent morbidity or mortality but who had been first registered prior to 1992 and whose date of first treatment was **either** prior to 1992 **or** missing.

The original sNHD, on which the Statistics Expert Group's report was based, pertained to 37,041 patients with 7,078 deaths prior to 2020. The updated sNHD3 pertains to 37,416 patients with 7,123 dates of death prior to 2020. The vast majority of new patients were registered with NHD after 2020 although born before 1992. The updated sNHD3 was made available to Dr Gittins on 17 November 2022.

Initial inspection of sNHD (and likewise sNHD3) identified anomalies in the International Disease Classification (version 10, ICD10) coding for cause of death and so, herein, we report only on the haemophilia doctors' consensus coding for cause of death.

Late registration of inquest-deaths in England, wales and Northern Ireland bedevils record-linkage studies which is why all analyses herein are to 31 December 2019 only. For example, Private Eye (page 40 in the week of 13 November 2022) referred to the recently concluded inquest into the **death on 21 December 2018** of an HCV-infected male (born in 1958, exposed to Factor V111 in 1976 and 1984, HCV-diagnosed in 1994). This man's death-date, ***which was nearly 4 years earlier than his inquest concluded***, was not located in sNHD3: **either** on account of the late registration of fact-of-death for inquest-deaths in England, Wales and Northern Ireland **or** due to infelicities in reporting or other reasons (NHD is a no-names confidential database).

Bleeding disorder (BD) and its severity impact on the likelihood of exposure to Hepatitis C virus (HCV) infection; may impact on whether sNHD3 has knowledge of the patient's HCV-test-history; and may affect the hazard of BD-linked causes of death. Patients who were HIV-infected during 1978-86 are assumed to be also HCV-infected. However, their (unknown) date of HCV infection may have preceded their date of HIV-infection.

We seek to analyse the records for patients who were born and NHD-registered before 1992 and for whom date of first treatment is either pre-1992 or is missing.

Primary de-selections: Year of birth was ***not earlier than 1992*** for 337 patients (down to 37,079); date of first registration was ***not pre-1992*** or was ***not valid (01/01/1900***) for 25,542 patients (down to 11,537); for 1,324 patients year of first treatment ***was not "before 1992 or missing"*** (down to 10,213). Twelve of 1,338 HIV infections are persons who did **not** meet these criteria.

Table 1.1 summarizes HCV-status, separately for male versus female patients, together with their survival status at 31 December 1991 and 31 December 2019. For males, in particular, the Statistics Expert Group's report (based on sNHD) explored BD and its severity by HCV-status and how the major categories for cause-of-death evolved according to calendar-period of death.

We note, however, that chronic HCV infection affects other organs besides the liver (such as kidneys, heart and brain) so that our **primary** focus for survival analysis will be **all-cause mortality** – overall and in distinct epochs of follow-up. Our **secondary** analysis targets circulatory and/or liver-related deaths (irrespective of whether HCV-infection is specifically mentioned).

Table 1.1 shows exceptionally, indeed suspiciously, low mortality by 31 December 1991 for those who were recorded as having been HCV antibody tested. The explanation is simple – **ascertainment bias**. Retrospective HCV antibody testing of stored blood samples appears to have been minimal so that persons with bleeding disorders would need to have survived until autumn 1991 to access HCV antibody testing. As we detail later, HCV test-dates are known to sNHD3 for only about one-sixth of the persons with bleeding disorders whose survival during 1992-2019 we wish to analyse; and are explored in some detail in **Section 2**.

Table 1.1 HCV-status, separately for male versus female patients, together with their survival status at 31 December 1991 and 31 December 2019 respectively. [1] components, [2] pooled plasma, *[3] Not known to be at-risk. Gender is missing for three patients.*

HCV-status	All eligible	MALES (% mortality)			FEMALES (% mortality)		
		Eligible	Dead by 31/12/1991	Dead by 31/12/2019	Eligible	Dead by 31/12/1991	Dead by 31/12/2019
HIV positive	**1326**	**1314**	**358**	**1002 (76%)**	**12**	**2**	**6 (50%)**
Tested HCV positive	**1977**	**1794**	**17**	**429 (24%)**	**183**	**0**	**30 (16%)**
Tested HCV negative	**1729** gender missed	**1231**	**0**	**100 (8%)**	**497**	**0**	**37 (7%)**
HCV = not known [1]	851 gender missed	563	131	311 (55%)	287	38	144 (50%)
HCV = not known [2]	1452	1301	464	892 (69%)	151	35	85 (56%)
Not known to be at-risk [3]	*696*	*488*	*195*	*472 (97%)*	*208*	*39*	*204 (98%)*
Sub-totals	8031 2 gender miss	6691	1165	3206	1338	114	506
Missing	**2182** gender missed	**1239**	**0**	**2**	**942**	**0**	**1**
Totals	10213 3 gender miss	7930	1165	3208	2280	114	507

Table 1.2 shows how deaths accumulated over calendar periods of follow-up. Six of 14 HIV-infected males who had died by 31 December 1984 had actually died pre-1984; none of the 12 HIV-infected females died before 1985.

Table 1.2 How deaths accumulated over calendar-periods of follow-up for eligible patients.

HCV-status	**MALE deaths by 31 December of**				**FEMALE deaths by 31 December of**			
	1984	2009	2013	2017	1984	2009	2013	2017
HIV positive	**14**	**944**	**976**	**992**	**0**	**6**	**6**	**6**
Tested HCV positive	**5**	**196**	**285**	**372**	**0**	**9**	**20**	**29**
Tested HCV negative	**0**	**23**	**47**	**75**	**0**	**6**	**14**	**27**
HCV = not known [1]	84	276	295	309	13	114	131	142
HCV = not known [2]	272	812	847	887	16	72	79	85
Not known to be at-risk [3]	*113*	*401*	*433*	*462*	*5*	*142*	*170*	*194*
TOTALS	**488**	**2652**	**2883**	**3097**	**34**	**349**	**420**	**483**

Table 1.3 for selected patients (ie Missing excluded) explores the associated bleeding disorder and its severity for the above male subgroups by HCV-status as we expect the proportion HIV-infected and tested HCV-positive to align with patients' likely need for blood products. The lower panel in **Table 1.3** reveals that survivorship is seemingly poor for patients with Any Acquired bleeding disorder and, sadly, is compromised early by HIV infection for those with severe Haemophilia A.

Table 1.3 males (ie Missing excluded) Bleeding disorder by severity and HCV-status {NB: Six of the HIV-infected females are patients with Von Willebrand disease, wherein HIV-infection rate appears to be the same for males and females.

HCV-status	HaemA <= 5 IU/dl	HaemA other	HaemB <= 5 IU/dl	HaemB other	Von Wille-brand	Any Acquired	Other	**Total**
HIV positive	1175 (89%)	103 (8%)	28	1	7 (0.5%)	0	0	**1314**
Tested HCV positive	**699 (39%)**	**576 (32%)**	**285**	**121**	**95 (5%)**	**0**	**18**	**1794**
Tested HCV negative	**323 (26%)**	**464 (38%)**	**77**	**72**	**237 (19%)**	**1**	**57**	**1231**
HCV = not known [1]	132 (23%)	214 (38%)	9	11	162 (29%)	8	27	**563**
HCV = not known [2]	558 (42%)	362 (28%)	160	114	65 (5%)	27	15	**1301**
Not known at-risk [3]	*62 (13%)*	*206 (42%)*	*19*	*22*	*81 (17%)*	*38*	*60*	*488*
Summed	**2949**	**1925**	**578**	**341**	**647**	**74**	**177**	**6691**
Deaths by:								
31 December 1991	675 (23%)	256 (13%)	70 (12%)	44 (13%)	61 (9.4%)	36 (49%)	23 (13%)	**1165 (17%)**
31 December 1999	1211 (41%)	437 (23%)	102 (18%)	73 (21%)	117 (18%)	63 (85%)	47 (27%)	**2050 (31%)**
31 December 2009	1424 (48%)	643 (33%)	161 (28%)	101 (30%)	186 (29%)	70 (95%)	67 (38%)	**2652 (40%)**
31 December 2013	1500 (51%)	728 (38%)	180 (31%)	115 (34%)	216 (33%)	72 (97%)	72 (41%)	**2883 (43%)**
31 December 2019	1607 (54%)	849 (44%)	214 (37%)	129 (38%)	253 (39%)	72 (97%)	82 (46%)	**3206 (48%)**

Table 1.3 females (ie Missing excluded) Bleeding disorder by severity and HCV-status {NB: Six of the HIV-infected females are patients with Von Willebrand disease, wherein the HIV-infection rate appears to be the same for males and females.}

HCV-status	HaemA <= 5 IU/dl	HaemA other	HaemB <= 5 IU/dl	HaemB other	Von Wille-brand	Any Acquired	Other	**Total**
HIV positive	**1**	**1**	**0**	**0**	**6 (50%)**	**1**	**3 (25%)**	**12**
Tested HCV positive	**0**	**0**	**1**	**0**	**104 (57%)**	**0**	**78 (43%)**	**183**
Tested HCV negative	**1**	**0**	**0**	**0**	**334 (67%)**	**1**	**161 (32%)**	**497**
HCV = not known [1]	1	0	0	0	198 (69%)	6	82 (29%)	287
HCV = not known [2]	1	2	1	1	55 (36%)	24 (16%)	67 (44%)	151
Not known at-risk [3]	*0*	*0*	*1*	*0*	*96 (46%)*	*32 (16%)*	*79 (38%)*	*208*
Summed	**4**	**3**	**3**	**1**	**793**	**64**	**470**	**1338**
Deaths by:								
31 December 1991	5				51 (6.4%)	28 (44%)	30 (6.4%)	**114 (8.5%)**
31 December 1999	7				98 (12%)	42 (66%)	69 (15%)	**216 (16%)**
31 December 2009	8				174 (22%)	51 (80%)	116 (25%)	**349 (26%)**
31 December 2013	8				220 (28%)	55 (86%)	137 (30%)	**420 (32%)**
31 December 2019	8				269 (35%)	57 (89%)	172 (37%)	**506 (38%)**

Subsequent formal survival analysis (**Section 3**) applies left-truncation to follow-up prior to 1 January 1992 and adjusts for gender and age-band in completed years at 31 December 1991; bleeding disorder and its severity; exposure to [1] components prior to 1992; exposure to [2] pooled plasma prior to 1988; **HIV-infection**; and – as time-dependent covariate – when information on HCV-status became known by NHD. Our formal survival analysis in **Section 3** considers the same epochs of follow-up as in the person-years descriptions given in the report by the Statistics Expert Group.

The epochs for which we summarize all-cause mortality and person-years of follow-up are:

i) from 1 January 1992 to 31 December 1999 (8 years);
ii) from 1 January 2000 to 31 December 2009 (10 years);
iii) from 1 January 2010 to 31 December 2013 (4 years); and
iv) from 1 January 2014 to 31 December 2019 (6 years).

Epochs iii) and iv) for all-cause mortality are combined in the main text (but shown separately in the **Appendix**) and for cause-specific mortality (cardiovascular and/or liver-related).

2. Descriptive statistics, prior to formal survival analysis from 1 January 1992, for reduced cohort of 6,739 persons **(ie missing excluded; known sex and age-band)**

For survival analysis, we reduced the initial cohort from 10,213 as follows: minus 4 participants with missing age, 3 with unknown gender (10,206); minus 2,178 due to missing data on HCV-status (8,028); minus 1,279 participants who died prior to 1992 (6,749).

Revisions: In response to queries about the performance of record-linkage, the data were further reduced due to the removal of 8 duplicates identified through matching of NHS numbers by UKHCDO: **leaving 6,741 individuals**. Further investigation of duplicated entries resulted in an updated versions of the data relating to the inclusion criteria and the HCV exposure variables. Thereby, two additional individuals were dropped due to date of first treatment being identified as in 1992 or later. The well-defined subset for analysis comprised **6,739 participants**.

Table 2.1 sets the scene - by gender, age-band at 31 December 1991, diagnostic group/severity and HIV/HCV-status - for the survival analyses to follow pertaining to the **6,739 persons with BD who were alive at 1 January 1992.**

Overall, 82% of the analysis cohort is male (5,520/**6,739**) but the percentage is highest for those HIV-infected (99%: 956/**966**), those who tested HCV antibody positive but were not HIV infected (90%: 1,793/**1,985**), and those whose HCV-status is not known but who were exposed to pooled plasma pre-1988 (88%: 815/**924**).

Older age at 31 December 1991 (60+ years), as the modal age-group, characterizes the three sub-cohorts whose HCV status is not known.

Two diagnostic categories alone account for at least 60% of any sub-cohort by HCV-status: for those HIV-infected, Haemophilia A accounts for 96%; and also for 63% of those who tested HCV antibody positive but are not HIV-infected. Haemophilia A Other and von Willebrand disease together account for 60% of those who tested HCV antibody negative; and of those whose HCV-status is not known but who were not known to have been exposed to HCV-risk; likewise for 71% of those whose HCV status is not known but who were exposed to at-risk components.

Table 2.1 Summary statistics by gender, age-band at 31 December 1991 and diagnosis/severity according to HIV/HCV status (without retrospection).

HIV/HCV-status	HIV positive	Tested HCV positive	Tested HCV negative	NK but Exposed to at-risk components	NK but Exposed to pooled plasma	NK HCV risk	**TOTAL**
Gender							
Male	**956**	**1793**	**1244**	422	**815**	290	5520
Column %	99%	90%	71%	64%	88%	63%	82%
Female	10	192	505	236	109	167	1219
TOTAL	**966**	**1985**	**1749**	**658**	**924**	**457**	**6739**
Age-band at 31 December 1991							
Under 10	6	66	366	12	16	8	474
10-19	178	370	319	53	77	14	1011
20-29	320	504	327	104	133	14	1402
30-39	249	438	280	117	167	32	1283
40-49	124	346	254	111	146	63	1044
50-59	64	159	137	79	120	84	643
60+ years	25	102	66	182	265	242	882
TOTAL	**966**	**1985**	**1749**	**658**	**924**	**457**	**6739**
Bleeding Disorder Diagnosis/Severity @ 1992 (modal age-band per BD/severity in red)							
HaemA <= 5IU/dl	851 (89%)	683 (34%)	324	81	307 (33%)	15	2261
HaemA Other	80 (8%)	585 (29%)	473 (27%)	169 (26%)	251 (27%)	128 (28%)	1686
HaemB <= 5IU/dl	21 (2%)	282	77	6	108	7	501
HaemB Other	1	129	72	7	83	9	301
Von Wille -brand	9	201	577 (33%)	299 (45%)	89	148 (32%)	1323
Any Acquired	1	0	2	7	19	45	74
Other	3	105	224	89	67	105	593
TOTAL	**966**	**1985**	**1749**	**658**	**924**	**457**	**6739**

Colour coding: **blue** typeface for highest and 2nd highest column-frequency, bar HIV-infected where **red** is outstanding top. Colour shading in top and bottom panels: turquoise shading for highest and 2nd highest column frequency, bar HIV-infected where grey is top.

For the above **6,739 patients with BD**, **Table 2.2** shows how the cohort was assembled in terms of year of 1st treatment, year of first exposure to pooled plasma product, year of 1st NHD-recorded HIV antibody positive and year of 1st NHD-recorded HCV test.

Table 2.2 shows **1969** (year of establishment of NHD) as year of 1st treatment for 13% of the cohort. Thereafter, rather than the annual number of 1st treated persons being constant, the number declines from 312 in **1970** to a nadir of 40 in **1973** but nears 800 in **1977** alone and for **1978 +1979**. Thereafter, the annual number 1st treated is roughly constant at around 250-300 until 1986, decreasing thereafter as the cohort abuts its cut-off date of 1 January 1992.

Year of 1st exposure to pooled plasma follows a broadly similar overall pattern but only 4% are recorded as having their 1st exposure to pooled plasma in **1969**. First exposures to pooled plasma continue in and beyond 1992. In summary, 77% of those with NHD-known date of 1st exposure to pooled plasma were exposed **prior to 1988** and a further 14% between during **1988-1991**.

Modal year of 1st NHD-recorded HIV antibody positive is **1985** with one-sixth of dates preceding **1984** (earliest 3 in **1979**) so that some retrospective HIV antibody testing of residual blood samples was clearly undertaken within the cohort to try to establish how early a patient's HIV-infection had occurred. In the analysis cohort, only seven persons were HIV-diagnosed **after 1991**.

Year of HCV test, as known to NHD, is substantially missing and, when present (602 HCV-test-dates; hence, 602 (16%) of 3,734 patients who were HCV antibody tested according to sNHD3), shows little evidence of retrospective HCV testing of stored residual blood samples to establish how early a patient's HCV-infection had occurred. Notice that only 18% of recorded-dates are **pre-1992**, two-thirds pre-1997 and 81% **before 2000** so that the HCV-tested cohort for analysis appears to be strongly survivor-selected. Our evidence is not only that a mere 18% of HCV test dates were pre-1992 (with 19% in 2000 or later) but also the evidence in **Table 1.1** that very few deaths (17/3,705) had occurred pre-1992 in those known to have been HCV antibody tested.

We do not, of course, know the distribution of HCV test-dates for the 84% for HCV-tested PwBDs in the analysis cohort whose HCV test-date was not recorded by sNHD3. To address this survivor-selection, we define two switch covariate [HCV antibody positive; HCV antibody negative] which are switched on at known HCV test-date but, when test-date is missing, we make one of three assumptions:

i) All HCV-tests whose date is unknown are assumed to have occurred pre-1992, in which we have [Low confidence]
ii) All HCV-tests whose date is unknown are assumed to have occurred pre-2000 in which we have [Low/Moderate confidence]
iii) All HCV-tests whose date is unknown are assumed to have occurred pre-2010 in which we have [Moderate confidence].

Even the above assumptions do not take into account that HCV test-seeking may be prompted by morbidity in our analysis cohort as the **NHD-recorded** evidence is not persuasive that patients were proactively counselled and offer HCV antibody testing close to when the UK blood supply was protected: that is, from September 1991.

Table 2.2 NHD-recorded years [**HIV test-date is missing for three persons who were HIV-infected]

Year	1st treatment		1st pooled plasma		1st HIV antibody positive		HCV test	
	Freq.	Cum%	**Freq.**	Cum%	**Freq.**	Cum%	**Freq.**	Cum%
1969	**801**	**13**	**201**	**4**				
1970	312	18	108	6				
1971	230	21	100	8				
1972	212	24	64	9				
1973	**40**	25	**63**	10				
1974	93	27	166	13				
1975	110	28	152	16				
1976	167	31	154	19			**1**	**<1**
1977	**797**	**43**	**734**	**32**				
1978	**447**	**50**	**427**	**40**				
1979	**342**	**56**	**299**	**45**	**3**	**<1**		
1980	**282**	**60**	**254**	**50**	**11**	**1**	**1**	**<1**
1981	**298**	**65**	**240**	**55**	**23**	**4**		
1982	279	69	233	59	**46**	**9**		
1983	319	74	226	63	**76**	**17**		
1984	314	79	190	67	**225**	**40**		
1985	259	83	209	70	**470**	**89**		
1986	257	87	183	74	**64**	**95**	**2**	**1**
1987	230	91	183	77	**18**	97.2		
1988	165	93	***218***	***81***	**10**	98.2	**1**	**1**
1989	143	96	***190***	***85***	**5**	98.8	**8**	**2**
1990	151	98	***186***	***88***	**4**	99.2	**43**	**9**
1991	132	100	***180***	**91**	**1**	99.3	**55**	**18**
1992			***63***	*93*	2	99.5	75	31
1993			***59***	*94*	2	99.7	64	42
1994			***57***	*95*	1	99.8	68	53
1995			***17***	*95*			51	61
1996			***16***	*95*			33	67
1997			***16***	*96*	1	99.9	30	72
1998			***25***	*96*			25	76
1999			***14***	*96*			**32**	**81**
2000			***14***	*97*	**1**	100	25	85
2001			***15***	*97*			25	90
2002			***13***	*97*			11	91
2003			***11***	*97*			14	94
2004			***12***	*98*			12	96
2005			***4***	*98*			2	96
2006			***11***	*98*			6	97
2007			***15***	*98*			3	98
2008			***17***	*98*			3	98
2009			***10***	*99*			8	99
2010+ (2010-19)			***83*** (75)	*100*			4	100
Recorded	**6380**		**5433**		**963****		**602**	
NA/missing	359		1306		5776		6137	
Total	**6739**		**6739**		**6739**		**6739**	

Table 2.3 gives the clinical consensus on deaths that occurred during 1992-2019 by HCV-status. HIV/AIDS or HIV-related lymphoma accounts for 373/648 deaths (58%) of deaths during 1992-2019 of HIV-infected persons with a bleeding disorder who were alive on 1 January 1992. Hepatocellular carcinoma (HCC) and HCV-related liver disease account for a further 122 deaths so that the patients' HIV/HCV co-infection accounted directly for at least 495/648 deaths (76%) during 1992-2019.

The major causes of the 2,403 deaths were cancer: other (384), HIV/AIDS or HIV lymphoma (373), bleeding-related (371), hepatocellular carcinoma (HCC) or HCV-related liver failure (326) and heart disease (307). Intracranial bleeding alone accounted for 240/371 (65%) of bleeding-related deaths. Suicide was uncommon (28/2,430 deaths: which is 1.2% of all deaths).

Table 2.3 Clinical consensus on cause of death by HCV status for deaths during **1992-2019**

Clinical Consensus on Underlying Cause of Death	HIV Infected	HCV Infected	At Risk Component	At Risk Pooled Plasma	HCV negative	Not Known	Total
1. Accidental death	1	5	2	4	0	5	17
2. Acquired bleeding	1	0	7	12	1	44	65
3. Bleeding - abdomen	5	1	0	1	1	1	9
4. Bleeding - chest	1	2	0	1	0	1	5
5. Bleeding – gastro	2	9	4	13	2	6	36
6. Bleeding – intracranial	54	43	33	78	7	25	240
7. Bleeding – other	4	2	2	5	1	2	16
9. Cancer – other	26	70	67	76	39	106	384
10. Creutzfeldt-Jakob	0	1	0	1	0	0	2
11. Frailty/ dementia	0	10	15	19	9	27	80
12. HIV / AIDS	342	0	0	0	0	0	342
13. HIV lymphoma	31	0	0	0	0	0	31
14. Heart disease	16	35	56	95	18	87	307
15. Hepatocellular cancer	12	86	4	17	0	3	122
16. Infection / multi	13	25	22	33	19	18	130
17. Liver failure	0	0	0	13	0	3	16
18. Liver failure – HCV	110	94	0	0	0	0	204
19. Liver failure – other	0	1	2	2	2	4	11
20. Not known	8	8	6	9	1	8	40
21. Other medical dis	9	36	36	50	25	51	207
22. Overdose	3	0	4	5	2	5	19
23. Post-op complication	1	3	0	5	1	0	10
24. Ruptured aneurysm	1	1	4	6	1	6	19
25. Stroke: thrombotic	0	8	8	10	5	18	49
26. Suicide	3	1	6	11	1	6	28
27. Trauma	5	3	4	9	5	9	35
28. Venous thrombosis	0	0	4	0	0	2	6
TOTALS	648	444	286	475	140	437	2430
SUB-TOTALS re BLEEDING (as %)	67 (10%)	57 (13%)	46 (16%)	110 (23%)	12 (9%)	79 (18%)	371 (15%)

3. Survival analysis to 31 December 2019 for *6,282*/6,739 persons with bleeding disorder who were alive at 1 January 1992 & *were HIV-infected or HCV-tested or had NHD-known exposure to HCV-at-risk components or pooled plasma concentrates.*

3.1 Orientation and limitations.

An initial word of caution is warranted as, seemingly, not all patients - for whom NHD was aware of death having occurred - were submitted for record-linkage, see **Table 3.1.1**. In addition, NHD did not receive information from NHS Digital (on a per-submitted-patient basis) about whether the patient's identifying information (as sent) was sufficient to meet NHS Digital's threshold for linkage. Instead, NHD received **only** information on date and cause of death for linkable patients who had died. The 96% of sent survivors who were apparently not-linked jarred with us to the extent that the variable clearly did not convey the information that we'd intended that it should.

Hence, the indicator on sNHD3 which was supposed to designate whether sufficient identifying information about a patient was submitted for (say) NHS Digital's threshold for probabilistic matching to be reached (ie linkable) may instead record only whether a death was identified for the patient in question. We have proceeded with analysis on the assumption that NHD generally held sufficient identifying information for linkage to have been achieved for a high proportion (over 85%) of submitted patient-identifiers. However, we were not able to perform due diligence for confirmation because the staff-member who liaised with national death registries is long-term sick.

We are therefore grateful to Ben Palmer with whom we were liaising as his further scrutiny in response to queries we had raised identified a related but different problem: namely, that the database from which sNHD2 was derived had not been thoroughly de-duplicated.

Table 3.1.1 How sent/linkage indicator was coded for **1,993 deaths in the analysis cohort** by whether death occurred during 1992-1999 or during 2000-2019

When death occurred	**Not sent** for linkage	***Sent for linkage***	**Not linked** but Sent	Sent & linked	All Deaths	**Not sent as % of** All Deaths	**Not linked *as % of Sent for linkage***
1992-2019	104	***1889***	254	1635	1993	**5.2%**	***13.4%***
1992-1999	81	***749***	19	730	830	**9.8%**	***2.5%***
By differencing							
2000-2019	23	***1140***	235	905	1163	**2.0%**	***20.6%***
Survivors	**Not sent** for linkage	***Sent for linkage***	**Not linked** but Sent	Sent & linked	All Survivors	**Not sent as % of** All Survivors	**Not linked *as % of Sent for linkage***
1992-2019	684	3605	3469	136	4289	**15.9%**	**96%**

As shown in **Table 3.1.2**, our selection-for-analysis criteria substantially mitigated the impact of duplication but, even in **Panels C** and **D** of **Table 3.1.2**, duplicates remained which needed to be resolved as a matter of urgency. All tables in the preceding From Section 2 onwards are based on sNHD3, the de-duplicated version of the database: as are all tables in **Section 3** excepting **Table 3.1.1** and **Table 3.1.2** which confirmed the need for further de-duplication. **Panel D** of **Table 3.1.2** indicates that record-linkage was without the benefit of NHS-number for 725 (11.5%) out of 6,287

patients. In the **Appendix** we explore the impact (no inferential changes) of excluding these patients for whom NHS-number was missing on our epoch-specific analyses of all-cause mortality.

Table 3.1.2 Tracing the extent of duplication to be resolved as selection-for-analysis criteria are applied.

Number of occurrences per NHS number	**Number of times a non-missing NHS number was duplicated in sNHD2**					Apparent count of patients	Implied count of patients
	Unique, ie zero	Duplicated once	Duplicated twice	Duplicated 3 times	Missing NHS		
Panel A: Before selection criteria are applied							
1	30,904					30,904	30,904
2		2,956				2,956	1,478
3			285			285	95
4				24		24	6
Missing					3,247	3,247	3,247
Panel A: TOTALS						37,416	***35,730***
Panel B selection: born and first treated before 1992 and date of first treatment is pre-1992 or Not Known							
1	7,508	***232***	***16***	***0***		7,756	7,756
2		38	***8***	0		46	23
Missing					2,411	2,411	2,411
Panel B: Apparent TOTALS but beware yellow as patients' past may have been lost						10,213	***10,190***
Panel C selection: Further de-selected if unknown sex or age-band or HCV-exposure status or if death-date is unknown or pre-1992							
1	5,810	***148***	***10***	***0***		5,968	5,968
2		14	***2***	0		16	8
Missing					765	765	765
Panel C: Apparent TOTALS but beware yellow as patients' past may have been lost Notice also that a further two patients were excluded due to revised information that their year of first treatment was not pre-1992.						6,749	***6,741***
Panel D selection: Further de-selected if HCV-exposure status was "not known to be at-risk"							
1	5,396	***146***	***10***	***0***		5,552	5,552
2		8	***2***	0		10	5
Missing					725	725	725
Panel D: Apparent TOTALS but beware yellow as patients' past may have been lost. Notice also that, as above, a further two patients were excluded due to revised information that their year of first treatment was not pre-1992.						6,287	**6,282**

A second note of caution is that the HCV-test-dates held by NHD for HCV antibody positive patients do not cluster close to 1991 - as they might be expected to do if HCV-testing had been offered promptly to, and accepted by, registered patients with bleeding disorders. The HCV-test-date that NHD holds may not, of course, be the earliest HCV-test date that centres or the patient knows about.

If NHD-date were the earliest**, **then there is an argument that patients who test HCV antibody positive should assume this designation from their HCV-test-date only. Most HCV-infections would have pre-dated 1992 and, had testing been conducted by 1 January 1992, then their duly-tested designation would have been established pre-1992. However, this approach breaches sound statistical principles about respecting **the importance of when a designation becomes applicable** [HCV-diagnosed; or confirmed HCV antibody negative] because, prior to the updated designation, the patient would have been managed and classified based only on his or her known exposure to HCV-at-risk plasma or components.

Since HCV-test-date is missing for 89% of the cohort whose survivorship we analyse during 1992-2019, we proceed as follows:

a) Fit covariate to designate **HIV-infected persons with bleeding disorder** but not explicitly for HCV-test status – enabling covariate adjusted appreciation of the survivorship of HIV-infected persons in distinct epochs of follow-up.
b) In addition, fit time-dependent SWITCH-indicators to designate when NHD recognises that a person with bleeding disorder has been diagnosed as HCV antibody positive **or** HCV antibody negative. However, to cope with substantially missing HCV test-dates, conduct sensitivity analysis which assumes that missing dates were all pre-1992 or their HCV antibody testing was delayed until 1 January 2010. [We did test an intermediate option, missing-dates switched at 1 January 2000, but this did not sufficiently recover the epoch-specific HRs for those HIV-infected which had been derived via the preceding a) analysis]

The main survival analyses relate to all-cause mortality because HCV-infection affects organ other than the liver. We conduct a secondary suite of analyses in which deaths which are not “liver-related or cardiovascular-related” are censored at the time of death from other causes. For this secondary analysis, we combined the third and fourth epochs of follow-up to increase the number of analysable events.

For both analyses - primary (all-cause mortality) and secondary (liver or cardiovascular-causes) - we anticipated that the influence of baseline covariates would evolve over time. For example, female advantage may be lost longer-term as death catches up with us all. The hazard-ratio (HR) associated with covariates whose impact is longer-term, rather than short-term, will tend to strengthen in later epochs. The HR for a combination of covariate-levels is got by multiplying together the HRs for each applicable covariate level – remembering that HR is 1 for each selected covariate-baseline as the jointly-estimated HRs per covariate-level are relative to each covariate’s baseline.

The lower age-band at 31 January 1991 has been set at under 20 years, the upper age-band at 60+ years so that, even 20-years later, the risk-set for this upper age-band remains sufficiently well represented. The format of all tables is the same: we indicate the number of persons in the risk-set at the start of the epoch of follow-up together with the number of events which occur within the epoch so that crude event-rates (number of events/number of persons at-risk) can be appraised. However, survival analysis takes proper account of the **number of person-years at risk** within an

epoch of follow-up and so compares hazard-rates which are akin to number of events per 1000 person-years at risk (as shown in the report by Statistics Expert Group but based on sNHD).

Proportional hazards regression analysis, however, adjusts for the joint influence of the set of covariates detailed in each table; and thereby allows us to estimate adjusted hazard-rates, each relative to its own covariate-baseline (HR = 1), which – when multiplied together – give the adjusted hazard-rate (relative of HR = 1 for a patient all of whose covariates are at baseline-levels) for any given patient of interest.

3.2 Descriptive focus on the 6,282 well-defined patients with some known exposure to at-risk components or at-risk pooled plasma.

By BD diagnosis/severity, **Table 3.2.1** summarizes mean and percentiles for a) year of 1st treatment and b) year of 1st exposure to pooled plasma product

Table 3.2.1 Summary statistics: year of 1st treatment and year of 1st exposure to pooled plasma

Diagnosis/severity	HaemA		HaemB		Von Wille-brand	Any Acquired	Other
	<=5 IU/dl	Other	<=5 IU/dl	other			
Year of 1st treatment (missing for 85 patients)							
# recorded data	2237	1542	491	289	1146	29	463
Mean	**1976.3**	**1978.5**	**1977.0**	**1979.4**	**1981.1**	**1985.1**	**1982.6**
Percentiles							
10th	1969	1970	1969	1972	1976	1980	1977
25th	1970	1973	1971	1975	1977	1981	1979
Median	**1977**	**1979**	**1977**	**1979**	**1981**	**1986**	**1983**
75th	1981	1983	1982	1983	1985	1987	1986
90th	**1986**	**1986**	**1986**	**1987**	**1988**	**1990**	**1989**
Year of 1st exposure to pooled plasma							
# recorded data	2164	1255	489	285	781	24	308
Mean	**1979.0**	**1982.4**	**1977.9**	**1980.0**	**1991.0**	**1985.5**	**1985.1**
Percentiles							
10th	1971	1977	1970	1973	1978	1980	1977
25th	1976	1978	1973	1976	1982	1981.5	1979
Median	**1978**	**1982**	**1977**	**1979**	**1990**	**1987**	**1984**
75th	1983	1986	1982	1984	1996	1987	1989
90th	**1987**	**1990**	**1987**	**1988**	**2008**	**1991**	**1993**

Table 3.2.2 gives the corresponding information by a) age at 1st treatment and b) age at 1st exposure to pooled plasma products: both considerable younger when severity is <= 5 IU/dl with median at 1st treatment of 10 years and 25% being first treated by two years of age.

Mean and median year of 1st treatment are closely similar within each BD diagnosis/severity whereas the mean age at 1st treatment and likewise mean age at 1st exposure to pooled plasma tend to be about 4 years older than the corresponding median (indicative to positively skewed

distributions), with the exception of three diagnostic categories: von Willebrand, Any Acquired BD and Other.

Table 3.2.2 Summary statist: age at 1st treatment and age at 1st exposure to pooled plasma products

Diagnosis/severity @1992	HaemA		HaemB		Von Wille-brand	Any Acquired	Other
	<=5 IU/dl	other	<=5 IU/dl	Other			
Age at 1st treatment							
# recorded data	2237	1542	491	289	1146	29	463
Mean	**14.1**	**23.7**	**15.8**	**22.5**	**25.0**	**57.7**	**27.5**
Percentiles							
10th	0	4	0	4	4	25	6
25th	2	9	2	9	10	53	14
Median	**10**	**20**	**10**	**18**	**22**	**65**	**26**
75th	22	35	25	32	37	67	38
90th	**36**	**51**	**40**	**52**	**52**	**71**	**51**
Age at 1st exposure to pooled plasma							
# recorded data	2164	1255	489	285	781	24	308
Mean	**16.6**	**27.2**	**16.6**	**23.0**	**35.0**	**56.1**	**30.3**
Percentiles							
10th	1	5	0	4	8	25	6
25th	4	12	3	9	19	48	19.5
Median	**12**	**24**	**11**	**19**	**32**	**64**	**30**
75th	25	39	26	33	48	67	40
90th	**40**	**56**	**42**	**52**	**65**	**71**	**55**

Finally, **Table 3.2.3** suggests that nine patients may have their HCV-exposure (to components or pooled plasma) mis-assigned to pooled plasma.

Table 3.2.3 Summary statistic according to HIV/HCV status for having been issued pooled plasma concentrates before 1988 or components before 1992.

HIV/HCV-status	HIV positive	Tested HCV positive	Tested HCV negative	NK but at-risk components	NK but pooled plasma	NK to be at HCV risk	TOTAL
Issued pooled plasma concentrates before 1988 ** (66% of those who were not exposed pre-1988 were never exposed)							
No Column %	21 2%	184 9%	1166 67%	658 100%	9 <1%	-	**2038
Yes	945	1801	583	0	915	-	4244
TOTAL	**966**	**1985**	**1749**	**658**	**924**	**-**	**6282**
Issued components before 1992							
No Column %	155 16%	669 34%	665 38%	9 1%	477 52%	-	1975
Yes	811	1316	1084	649	447	-	4307
TOTAL	**966**	**1985**	**1749**	**658**	**924**	**-**	**6282**

3.3 HIV-impact on survivorship during 1992-2019 after adjusting for baseline covariates

Comparing across Epochs in **Tables 3.3.1,** significantly lower hazard ratio (**HR**) for females is evident throughout. Hazard ratios increase with age-band and, for the second oldest age-bands are notably higher in Epochs 2 and 3+4 than in Epoch 1. Bleeding disorder and severity thereof are not hugely informative albeit some variation in HRs across epochs is noticeable. Exposure to components pre-1992 or to pooled plasma pre-1988 has a similar HR of **1.7** (95% CI: 1.2 to 2.3) in Epoch 1 which, for pooled plasma rises to **2.9** (95% CI: 2.2 to 3.7) by Epoch 3+4. Overwhelmingly influential is the hazard for HIV-infection, with associated HRs of **12.2** (95% CI: 10.1 to 14.8**)**, **4.4**, **3.2** and **1.4** in Epochs 1, 2, 3 and 4 (see **Appendix**); and of **2.1** (95% CI: 1.5 to 2.8) in Epochs 3+4 combined as shown in **Table 3.3.1**. Notice that, in Epoch 1, the HR for HIV-infection is almost as high as HR of **14.8** for being aged 60+ at 31 December 1991 (95% CI: 11.7 to 18.6).

Since all persons with bleeding disorder who were HIV-infected are expected also to have been HCV-infected, **Table 3.3.2** considers, per epoch, covariate influences on the risk of dying from liver-related or cardiovascular disease (LC deaths), in both of which chronic HCV may be implicated.

In this secondary analysis, survival is censored at the time of death from other causes (including and especially HIV disease) than those of specific interest (LC deaths). In this cause-specific analysis, we combine Epochs 3+4 and, as before, reduce the number of bleeding disorder/severity categories by combining Any Acquired BD/Other.

Comparing across Epochs in **Tables 3.3.2,** lower hazard ratio (**HR**) for females is again evident, significantly so in Epochs 1 and 3+4.

Hazard ratios for LC deaths increase with age-band but the LC-HR for the oldest age-band is significantly lower in Epoch 3+4 than in Epoch 1. A similar phenomenon, albeit not statistically significant is evident for those aged 50-59 years at 1 January 1992. Directly acting antiretroviral treatment or survivor selection of the oldest old or both may play a role.

Bleeding disorder and severity thereof are not hugely informative albeit some variation in HRs across epochs is noticeable. In particular, LC-HR in Epoch 3+4 was **1.8** (95% CI: 0.9 to 3.5) for Von Willebrand disease and **2.6** (95% CI: 1.2 to 5.9) for Any Acquired/Other diagnosis.

Exposure to pooled plasma pre-1988 had LC- HR which rose from **2.2** (95% CI: 1.3 to 3.7) in Epoch 1 to **3.9** (95% CI: 2.3 to 6.6) in Epoch 3+4.

Striking are the similar LC-HRs for HIV-infection of **5.5** (95% CI: 3.8 to 8.0) in Epoch 1 and **4.9** (95% CI: 3.2 to 7.5) in Epoch 2 which reduce very significantly to **1.7** (95% CI: 1.0 to 2.9) in Epochs 3+4.

Table 3.3.1 Primary analysis, all-cause mortality: HIV status

Proportional hazards regression analysis during

EPOCH 1 (1 January 1992 to 31 December 1999, number in risk-set **6,282** with **46,480** person-year)

EPOCH 2 (1 January 2000 to 31 December 2009, number in risk-set **5,452** with **51,386** person-years)

EPOCHS 3+ 4 (1 January 2010 to 31 December 2019, risk-set of **4,869** with **45,695** person-years)

COVARIATES	EPOCH 1: 830 deaths (1992-1999, 8 years)		EPOCH 2: 583 deaths (2000-2009, 10 years)		EPOCHS 3+4: 580 deaths (2010-2019, 10 years)	
	Hazard Ratio HR	95% CI for HR	**Hazard Ratio HR**	95% CI for HR	**Hazard Ratio HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.48**	0.32 to 0.72	**0.66**	0.47 to 0.94	**0.73**	0.53 to 1.01
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20	**0.93**	0.70 to 1.25	**0.75**	0.49 to 1.16	**0.50**	0.33 to 0.78
30-39	**1.47**	1.17 to 1.85	**1.91**	1.38 to 2.65	**1.70**	1.26 to 2.31
40-49	**2.25**	1.77 to 2.88	**3.50**	2.52 to 4.83	**3.66**	2.73 to 4.91
50-59	**3.8**	2.94 to 4.94	**7.7**	**5.5 to 10.7**	**9.1**	**6.7 to 12.3**
60+ years	**14.8**	**11.8 to 18.7**	**22.9**	**16.8 to 31.0**	**18.9**	**13.9 to 25.5**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**0.71**	0.57 to 0.88	**0.94**	0.75 to 1.19	**1.24**	0.99 to 1.56
Haemophilia B <= 5 IU/dl	**0.63**	0.43 to 0.91	**1.48**	1.07 to 2.04	**1.38**	0.98 to 1.95
Haemophilia B other	**1.14**	0.75 to 1.75	**1.30**	0.84 to 2.01	**1.35**	0.88 to 2.06
VonWillebrand disease	**1.03**	0.72 to 1.48	**1.30**	0.92 to 1.83	**1.53**	1.08 to 2.17
Any Acquired BD/Other	**1.29**	0.81 to 2.07	**1.37**	0.88 to 2.14	**1.33**	0.86 to 2.06
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.63**	1.31 to 2.03	**1.88**	1.49 to 2.39	**2.07**	1.65 to 2.60
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**1.68**	1.26 to 2.25	**1.73**	1.35 to 2.21	**2.89**	2.25 to 3.70
Yes, 1988-91	**1.00**	0.64 to 1.57	**1.17**	0.79 to 1.70	**1.70**	1.17 to 2.47
HIV-status (baseline = not known to be HIV-infected)						
HIV antibody positive	**12.2**	**10.1 to 14.8**	**4.4**	**3.4 to 5.7**	**2.07**	**1.51 to 2.82**

Table 3.3.2 Secondary analysis, cause-specific mortality: HIV-status

Covariate influences on HRs during

EPOCH 1 (1 January 1992 to 31 December 1999, 8 years: **205** liver or cardiovascular deaths);

EPOCH 2 (1 January 2000 to 31 December 2009, 10 years: **194** liver or cardiovascular deaths);

EPOCH 3+4 (1 January 2010 to 31 December 2019, 10 years: **164** liver or cardiovascular deaths).

COVARIATES	EPOCH 1: 205 LC deaths (1992-1999, 8 years)		EPOCH 2: 194 LC deaths (2000-2009, 10 years)		EPOCH 3+4: 164 LC deaths (2010-2019, 10 years)	
	Hazard Ratio HR	95% CI for HR	**Hazard Ratio HR**	95% CI for HR	**Hazard Ratio HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.33**	0.16 to 0.71	**0.67**	0.33 to 1.35	**0.33**	0.16 to 0.69
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	**0.90**	0.37 to 2.20	**0.19**	0.06 to 0.64	**0.49**	0.21 to 1.13
30-39	**2.59**	1.36 to 4.93	**2.20**	1.30 to 3.73	**1.67**	0.98 to 2.85
40-49	**5.7**	**3.1 to 10.6**	**3.8**	2.20 to 6.44	**3.8**	2.26 to 6.25
50-59	**11.6**	**6.2 to 21.6**	**8.0**	**4.6 to 13.8**	**6.9**	**4.0 to 12.0**
60+ years	**35.5**	**19.5 to 64.2**	**22.1**	**13.1 to 37.0**	**10.9**	**6.0 to 19.8**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**0.76**	0.52 to 1.11	**1.03**	0.70 to 1.52	**1.46**	0.97 to 2.20
Haemophilia B <= 5 IU/dl	**0.39**	0.18 to 0.85	**1.10**	0.61 to 1.99	**0.88**	0.44 to 1.76
Haemophilia B other	**0.79**	0.37 to 1.71	**1.17**	0.56 to 2.47	**1.56**	0.75 to 3.27
Von Willebrand disease	**1.26**	0.68 to 2.35	**1.03**	0.54 to 1.96	**1.80**	0.93 to 3.48
Any Acquired BD/Other	**1.30**	0.54 to 3.14	**0.72**	0.28 to 1.85	**2.62**	1.16 to 5.89
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.28**	0.84 to 1.92	**1.67**	1.11 to 2.52	**2.14**	1.37 to 3.34
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**2.20**	1.30 to 3.72	**2.14**	1.35 to 3.40	**3.90**	2.30 to 6.59
Yes, 1988-1991	**0.95**	0.38 to 2.37	**1.03**	0.46 to 2.31	**1.51**	0.63 to 3.65
HIV-status (baseline = not known to be HIV-infected)						
HIV antibody positive	**5.5**	**3.8 to 8.0**	**4.9**	**3.2 to 7.5**	**1.67**	**0.96 to 2.90**

3.4 HCV-impact on survivorship during 1992-2019 after adjusting for baseline covariates: HCV-status, with comparison of switch-scenarios for when HCV-status was ascertained

Importantly, when the HCV-switches are delayed to 1 January 2010 (rather than at 31 December 2000) for testees whose HCV test-date was not known to NHD, we recover essentially the same HR for Epoch 1 for those HIV/HCV co-infected as was estimated in **Section 3.3 – but not when all HCV-diagnoses were assumed known by 1 January 1992.** Hence, ***when*** the switch operators are implemented matters – as indeed we had expected would be the case. See **Appendix** for EPOCH 2's sensitivity also to the choice between 1992 and 2010 for when all undated HCV-test results are switched.

Table 3.4.1 Primary analysis, all-cause mortality: HCV-status, comparison of HCV-switch scenarios for covariate influences on **EPOCH 1 HRs** with all undated HCV-test results assumed known before 1 January 1992 versus only at 1 January 2010.

COVARIATES	**EPOCH 1, 830 deaths (1992-1999, 8 years)**				**EPOCH 3+4, 580 deaths (2010-2019, 10 years)**	
	Switch by 1 January 1992		*Switch by 1 January 2010*		***Identical by EPOCH 3***	
	HR	95% CI for HR	**HR**	95% CI for HR	**HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.55**	0.37 to 0.82	**0.48**	0.32 to 0.72	**0.72**	0.52 to 1.00
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	**1.04**	0.78 to 1.40	**0.94**	0.70 to 1.26	**0.53**	0.34 to 0.81
30-39	**1.45**	1.15 to 1.83	**1.47**	1.16 to 1.85	**1.70**	1.25 to 2.31
40-49	**2.20**	1.73 to 2.81	**2.25**	1.76 to 2.87	**3.71**	2.76 to 4.97
50-59	**3.56**	2.74 to 4.63	**3.82**	2.95 to 4.95	**9.5**	**7.0 to 12.8**
60+ years	**10.0**	**7.8 to 12.8**	**14.7**	**11.7 to 18.5**	**19.2**	**14.0 to 26.4**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**0.77**	0.63 to 0.97	**0.71**	0.57 to 0.88	**1.29**	1.02 to 1.62
Haemophilia B <= 5 IU/dl	**0.66**	0.45 to 0.96	**0.63**	0.44 to 0.92	**1.37**	0.97 to 1.92
Haemophilia B other	**1.21**	0.79 to 1.86	**1.16**	0.76 to 1.78	**1.44**	0.94 to 2.20
Von Willebrand disease	**0.97**	0.68 to 1.39	**1.02**	0.71 to 1.47	**1.62**	1.14 to 2.29
Any Acquired BD/Other	**1.15**	0.72 to 1.83	**1.28**	0.80 to 2.05	**1.40**	0.91 to 2.17
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.82**	1.45 to 2.27	**1.65**	1.33 to 2.06	**2.01**	1.60 to 2.53
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**1.95**	1.45 to 2.61	**1.72**	1.29 to 2.30	**2.48**	1.90 to 3.24
Yes, 1988-1991	**1.27**	0.81 to 1.99	**1.01**	0.64 to 1.57	**1.79**	1.22 to 2.63
HCV-status (baseline = HCV-status is Not Known at NHD)						
HIV antibody positive	**6.1**	**5.9 to 7.5**	**11.8**	**9.8 to 14.3**	**2.25**	**1.57 to 3.22**
HCV positive	**0.30**	**0.23 to 0.40**	**0.45**	**0.20 to 1.00**	**1.17**	**0.93 to 1.47**
HCV negative	**0.06**	**0.03 to 0.12**	**0.99**	**0.44 to 2.26**	**0.72**	**0.55 to 0.93**

Comparing across **Tables 3.4.2,** significantly lower hazard ratio for females weakens somewhat by the third decade of follow-up. Hazard ratios increase with age-band and, for the second oldest age-band, are notably higher in Epochs 2 and 3+4 than in Epoch 1. Bleeding disorder and severity thereof are not hugely informative albeit with some variation in HRs across epochs for Haemophilia A other and Haemophilia B <= 5 IU/dl: specifically, both have HRs significantly below 1 in Epoch 1 with advantage shifting to relative disadvantage in Epochs 2 and 3+4 for patients Haemophilia B <= 5 IU/dl. Relative disadvantage in Epoch 3+4 is also apparent for patients with Von Willebrand disease.

Exposure to components pre-1992 or to pooled plasma pre-1988 has a similar HRs of **1.7** (95% CI: 1.3 to 2.3) in Epoch 1 which, for pooled plasma, rises to **2.5** (95% CI: 1.9 to 3.2) by Epoch 3+4. New in **Table 3.4.2** is the estimated influence of having been diagnosed HCV antibody positive prior to Epoch 3+4 wherein the associated HR is **1.2** (95% CI: o.9 to 1.5).

Table 3.4.2 Primary analysis, all-cause mortality: HCV-status *with all undated HCV-test results assumed known at 1 January 2010.* Covariate influences on HRs in **EPOCHS 1, 2** and **3+4**

COVARIATES	EPOCH 1: 830 deaths (1992-1999, 8 years)		EPOCH 2: 583 deaths (2000-2009, 10 years)		EPOCH 3+4: 580 deaths (2010-2019, 10 years)	
	Switch at 1 January 2010		*Switch at 1 January 2010*		*Switched at 1 January 2010*	
	HR	95% CI for HR	**HR**	95% CI for HR	**HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.48**	0.32 to 0.72	**0.67**	0.47 to 0.94	**0.72**	0.52 to 1.00
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	**0.94**	0.70 to 1.26	**0.75**	0.48 to 1.15	**0.53**	0.34 to 0.81
30-39	**1.47**	1.16 to 1.85	**1.90**	1.37 to 2.64	**1.70**	1.25 to 2.31
40-49	**2.25**	1.76 to 2.87	**3.50**	2.52 to 4.83	**3.71**	2.76 to 4.97
50-59	**3.82**	2.95 to 4.95	**7.7**	**5.5 to 10.6**	**9.5**	**7.0 to 12.8**
60+ years	**14.7**	**11.7 to 18.5**	**22.7**	**16.7 to 30.8**	**19.2**	**14.0 to 26.4**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**0.71**	0.57 to 0.88	**0.94**	0.74 to 1.18	**1.29**	1.02 to 1.62
Haemophilia B <= 5 IU/dl	**0.63**	0.44 to 0.92	**1.47**	1.06 to 2.03	**1.37**	0.97 to 1.92
Haemophilia B other	**1.16**	0.76 to 1.78	**1.30**	0.84 to 2.01	**1.44**	0.94 to 2.20
Von Willebrand disease	**1.02**	0.71 to 1.47	**1.28**	0.90 to 1.81	**1.62**	1.14 to 2.29
Any Acquired BD/Other	**1.28**	0.80 to 2.05	**1.35**	0.87 to 2.11	**1.40**	0.91 to 2.17
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.65**	1.33 to 2.06	**1.91**	1.51 to 2.42	**2.01**	1.60 to 2.53
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**1.72**	1.29 to 2.30	**1.76**	1.37 to 2.25	**2.48**	1.90 to 3.24
Yes, 1988-1991	**1.01**	0.64 to 1.57	**1.16**	0.79 to 1.69	**1.79**	1.22 to 2.63
HCV-status (baseline = HCV-status is Not Known at NHD)						
HIV antibody positive	**11.8**	**9.8 to 14.3**	**4.3**	**3.3 to 5.6**	**2.25**	**1.57 to 3.22**
HCV positive	**0.45**	**0.20 to 1.00**	**0.75**	**0.49 to 1.14**	**1.17**	**0.93 to 1.47**
HCV negative	**0.99**	**0.44 to 2.26**	**1.06**	**0.64 to 1.76**	**0.72**	**0.55 to 0.93**

Finally, by LC-HRs comparing across epochs in **Tables 3.4.3,** we noted again significantly lower LC-HRs for females (Epoch 2 excepted); LC-HRs also increase with age but, for the two oldest age-bands, LC-HRs do not increase in later epochs. Bleeding disorder and severity thereof are not hugely informative albeit with some variation in HRs across epochs. Specifically, we note LC-HR in Epoch 3+4 of **2.1** (95% CI: 1.1 to 4.0) for patients with Von Willebrand disease.

Exposure to pooled plasma pre-1988 has a central LC-HR which is persistently above two but with wide 95% confidence intervals per epoch, for example **2.4** (95% CI: 1.3 to 4.2) in Epoch 3+4. New in **Table 3.4.3** is the estimated influence on LC-HR of having been diagnosed HCV antibody positive prior to Epoch 3+4 wherein the associated LC-HR is **1.8** (95% CI: 1.1 to 2.8).

Table 3.4.3 Secondary analysis, liver or cardiovascular (LC) deaths: HCV-status *with all undated HCV-test results assumed known at 1 January 2010.* Covariate effects on LC-HRs in distinct Epochs.

COVARIATES	EPOCH 1, 205 LC deaths (1992-1999, 8 years)		EPOCH 2, 194 LC deaths (2000-2009, 10 years)		EPOCH 3+4, 164 LC deaths (2010-2019, 10 years)	
	Switch by 1 January 2010		*Switch by 1 January 2010*		*Switch by 1 January 2010*	
	HR	95% CI for HR	**HR**	95% CI for HR	**HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.34**	0.16 to 0.71	**0.66**	0.33 to 1.35	**0.32**	0.15 to 0.66
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	**0.90**	0.37 to 2.20	**0.19**	0.06 to 0.66	**0.52**	0.23 to 1.19
30-39	**2.58**	1.36 to 4.92	**2.20**	1.30 to 3.74	**1.69**	0.99 to 2.89
40-49	**5.7**	**3.1 to 10.6**	**3.77**	2.20 to 6.47	**3.89**	2.34 to 6.47
50-59	**11.6**	**6.2 to 21.7**	**8.0**	**4.6 to 13.9**	**7.8**	**4.5 to 13.6**
60+ years	**35.0**	**19.3 to 63.6**	**22.3**	**13.3 to 37.5**	**12.8**	**6.9 to 23.7**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**0.75**	0.51 to 1.10	**1.05**	0.71 to 1.54	**1.56**	1.04 to 2.34
Haemophilia B <= 5 IU/dl	**0.39**	0.18 to 0.85	**1.10**	0.61 to 1.98	**0.84**	0.42 to 1.69
Haemophilia B other	**0.80**	0.37 to 1.73	**1.17**	0.55 to 2.47	**1.77**	0.84 to 3.76
Von Willebrand disease	**1.25**	0.67 to 2.32	**1.02**	0.54 to 1.95	**2.07**	1.07 to 4.00
Any Acquired BD/Other	**1.28**	0.53 to 3.08	**0.69**	0.27 to 1.80	**3.06**	1.35 to 6.93
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.28**	0.85 to 1.94	**1.74**	1.16 to 2.63	**1.94**	1.24 to 3.04
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**2.22**	1.31 to 3.76	**2.24**	1.40 to 3.57	**2.36**	1.33 to 4.18
Yes, 1988-1991	**0.94**	0.38 to 2.36	**1.06**	0.47 to 2.38	**1.73**	0.70 to 4.26
HCV-status (baseline = HCV-status is Not Known at NHD)						
HIV antibody positive	**5.4**	**3.7 to 7.8**	**4.7**	**3.0 to 7.1**	**2.55**	**1.30 to 5.05**
HCV positive	**0.58**	**0.18 to 1.82**	**0.69**	**0.33 to 1.43**	**1.79**	**1.13 to 2.84**
HCV negative	**1.53**	**0.48 to 4.91**	**0.42**	**0.10 to 1.69**	**0.40**	**0.21 to 0.79**

4. Discussion

The extent of missing HCV-test-dates is the major reason that our confidence in the results presented is at best Low/M

The various proportional hazards regression analyses in **Section 3**, each of which adjusts for gender, age-band at 1 January 1992, bleeding disorder and its severity, give rise to several estimated HRs in Epoch 3+4 that can variously claim to be the HR for all-cause mortality that best represents the hazard associated with HCV-infection (without HIV-infection) in persons with a bleeding disorder.

The various estimates are collated in **Table 4.1** together with brief comments on their provenance. Please recall that all estimates essentially arise from the same subset of patients and are thus highly inter-dependent.

Table 4.1 Appraisal of mono-HCV-infected HR in respect of all-cause mortality in Epoch 3+4 for persons with a bleeding disorder.

Analysis source	Hazard Ratio, **HR**	95% confidence interval	Commentary
HIV/HCV co-infected, HIV-status **Table 3.3.1**	**2.1**	1.5 to 2.9	Co-infection can be considered as an upper-bound for mono-HCV-infection
Exposure to pooled plasma pre-1988, HIV-status **Table 3.3.1**	**2.9**	2.2 to 3.7	Exposure to pooled plasma prior to 1988 or to components prior to 1991 applies for most HIV/HCV coinfections, see **Table 3.2.3**
Multiplying the above two HRs together	**6.0**	a to b	
HIV/HCV co-infected, HCV-status **Table 3.4.2**	**2.2**	1.6 to 3.2	Co-infection can be considered as an upper-bound for mono-HCV-infection
Exposure to pooled plasma pre-1988, HCV-status **Table 3.4.2**	**2.5**	1.9 to 3.2	Exposure to pooled plasma prior to 1988 or to components prior to 1991 applies for most HIV/HCV coinfections, see **Table 3.2.3**
Multiplying the above two HRs together	**5.6**	c to d	
HCV-diagnosed, HCV-status **Table 3.4.2**	**1.2**	1.0 to 1.5	
Exposure to pooled plasma pre-1988, HCV-status **Table 3.4.2**	**2.5**	1.9 to 3.2	Exposure to pooled plasma prior to 1988 or to components prior to 1991 applies for most diagnosed HCV infections, see **Table 3.2.3**
Multiplying the above two HRs together	**2.9**	e to f	
Exposure covariates not fitted, HCV-diagnosed **Appendix A4, HCV-status**	**1.6**	1.26 to 1.95	This last estimate is PH regression-analysis approximation to HCV case-control transfusion study except that here we do not know that all HCV-diagnosed were HCV-RNA positive

In summary, HR for all-cause mortality in Epoch 3+4 may be higher for mono HCV-infected patients with a bleeding disorder than for patients HCV-RNA-infected by transfusion (their estimated HR was 1.5) but, if so, only to a modest extent.

We have not attempted to estimate, via **Table 3.2.3** or otherwise, what proportion of patients who have not been HCV-tested (as far as NHD is aware) but were exposed to pooled plasma prior to 1988 or to components pre-1992 may indeed be HCV-infected. Such patients should be followed-up and offered an HCV antibody test as a matter of some urgency.

References

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See also Discussion.

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APPENDIX of ADDITIONAL TABLES on SURVIVAL ANALYSES in DISTINCT EPOCHS of FOLLOW-UP

A1. HIV-impact on survivorship during 1992-2019 after adjusting for baseline covariates

Separate survival analyses for all-cause mortality in EPOCH 3 and EPOCH 4: HIV-status

Comparison across **Table A1.1** and **Table A1.2** shows that the epoch-specific **HR** associated with **HIV/HCV coinfection** reduced from **12** (95% CI: 10 to 15) in **EPOCH 1** to **4.4** (95% CI: 3.7 to 5.4) in **EPOCH 2**, through **3.2** (95% CI: 2.1 to 5.0) in **EPOCH 3** to **1.4** (95% CI: 0.9 to 2.2) in **EPOCH 4**; or to **2.3** (95% CI: 1.6 to 3.2) as shown in **Table 3.3.1** for **EPOCHS 3+4** combined.

Table A1.1 Primary analysis, all-cause mortality: HIV status

Survival analysis during **EPOCH 1** (1 January 1992 to 31 December 1999, 8 years: initial risk-set **6,282** with **46,480.5** person-years; number of deaths is **830**) and **EPOCH 2** (1 January 2000 to 31 December 2009, 10 years: number in risk-set **5,452** with **51,385.5** person-years; number of deaths is **583**)

COVARIATES	EPOCH 1 (1992-1999, 8 years)				EPOCH 2 (2000-2009, 10 years)	
	# Initial Risk-set	# Events	Hazard Ratio HR	95% CI for HR	Hazard Ratio HR	95% CI for HR
Gender (baseline: male)						
Female	1052	47	**0.48**	0.32 to 0.72	**0.66**	0.47 to 0.94
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	1462	79	**0.93**	0.70 to 1.25	**0.75**	0.49 to 1.16
30-39	1251	150	**1.47**	1.17 to 1.85	**1.91**	1.38 to 2.65
40-49	981	127	**2.25**	1.77 to 2.88	**3.50**	2.52 to 4.83
50-59	559	102	**3.81**	2.94 to 4.94	**7.7**	**5.5 to 10.7**
60+ years	640	233	**14.8**	**11.8 to 18.7**	**22.9**	**16.8 to 31.0**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	1558	140	**0.71**	0.57 to 0.88	**0.94**	0.75 to 1.19
Haemophilia B <= 5 IU/dl	494	32	**0.63**	0.43 to 0.91	**1.48**	1.07 to 2.04
Haemophilia B other	292	26	**1.14**	0.75 to 1.75	**1.30**	0.84 to 2.01
Von Willebrand disease	1175	63	**1.03**	0.72 to 1.48	**1.30**	0.92 to 1.83
Any Acquired BD/Other	517	35	**1.29**	0.81 to 2.07	**1.37**	0.88 to 2.14
Exposure to components before 1992 (baseline = no						
Yes, pre-1992	4307	706	**1.63**	1.31 to 2.03	**1.88**	1.49 to 2.39
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	4244	730	**1.68**	1.26 to 2.25	**1.73**	1.35 to 2.21
Yes, 1988-1991	885	34	**1.00**	0.64 to 1.57	**1.17**	0.79 to 1.70
HIV-status (baseline = not known to be HIV-infected)						
HIV antibody positive	966	477	**12.2**	**10.1 to 14.8**	**4.4**	**3.4 to 5.7**

Table A1.2 Primary analysis, all-cause mortality: HIV-status

Survival analysis during **EPOCH 3** (1 January 2000 to 31 December 2013, 4 years: number in initial risk-set **4,869** with **18,994.5** person-years; number of deaths is **242**) and **EPOCH 4** (1 January 2014 to 31 December 2019, 6 years: number in risk-set **4,627** with **26,700.2** person-years ; number of deaths is **338**)

COVARIATES	EPOCH 3 (2010-2013, 6 years)				EPOCH 4 (2014-2019, 6 years)	
	# Initial Risk-set	# Events	**Hazard Ratio HR**	95% CI for HR	**Hazard Ratio HR**	95% CI for HR
Gender (baseline: male)						
Female	920	43	**0.82**	0.49 to 1.35	**0.67**	0.44 to 1.03
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	1349	9	**0.44**	0.20 to 0.97	**0.53**	0.32 to 0.90
30-39	1013	39	**2.03**	1.23 to 3.35	**1.53**	1.03 to 2.25
40-49	754	57	**4.70**	2.91 to 7.59	**3.10**	2.13 to 4.51
50-59	356	49	**9.7**	**5.9 to 15.9**	**8.8**	**6.0 to 12.8**
60+ years	210	62	**23.3**	**14.4 to 37.8**	**16.4**	**11.1 to 24.3**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	1264	71	**1.19**	0.83 to 1.72	**1.28**	0.95 to 1.71
Haemophilia B <= 5 IU/dl	409	18	**1.37**	0.80 to 2.37	**1.38**	0.90 to 2.13
Haemophilia B other	240	14	**1.50**	0.78 to 2.85	**1.25**	0.70 to 2.21
Von Willebrand disease	1015	51	**1.70**	0.99 to 2.92	**1.40**	0.88 to 2.21
Any Acquired BD/Other	435	17	**1.04**	0.50 to 2.13	**1.55**	0.90 to 2.67
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	3129	195	**2.05**	1.43 to 2.95	**2.08**	1.55 to 2.79
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	3074	183	**2.73**	1.86 to 4.02	**3.00**	2.17 to 4.15
Yes, 1988-1991	785	34	**1.91**	1.09 to 3.37	**1.54**	0.93 to 2.56
HIV-status (baseline = not known to be HIV-infected)						
HIV antibody positive	376	32	**3.23**	**2.06 to 5.04**	**1.43**	**0.91 to 2.23**

A2. HCV-impact on survivorship during 1992-2019 after adjusting for baseline covariates

Sensitivity of survival analyses for all-cause mortality in EPOCH 1 and EPOCH 2 to whether all undated HCV-test results are switched at 1 January 1992 or 1 January 2010: HCV-status

When all undated HCV-tests are switched at 1 January 1992, the HIV-related hazard-ratios in **Table A2.1** are seriously reduced: in **EPOCH 1** (from **12** in Table **A1.1** to **6** in **Table A2.1**) and in **EPOCH 2** (from **4.4** in **Table A1.1** to **1.9** in **Table A2.1**). Correct recovery is achieved when the switch-date is 1 January 2010. See also **Table A2.2** for our findings in **EPOCH 2**.

Table A2.1 (reproduced from **Section 3.3**) **Primary analysis, all-cause mortality: HCV-status**

Covariate influences on hazard ratios during **EPOCH 1** and in **EPOCH 3+4** with all undated HCV-test results assumed known before 1 January 1992 versus only at 1 January 2010.

COVARIATES	**EPOCH 1: 830 deaths (1992-1999, 8 years)**				**EPOCH 3+4: 580 deaths (2010-2019, 10 years)**	
	Switch by 1 January 1992		*Switch by 1 January 2010*		***Identical by EPOCH 3***	
	HR	95% CI for HR	**HR**	95% CI for HR	**HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.55**	0.37 to 0.82	**0.48**	0.32 to 0.72	**0.72**	0.52 to 1.00
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	**1.04**	0.78 to 1.40	**0.94**	0.70 to 1.26	**0.53**	0.34 to 0.81
30-39	**1.45**	1.15 to 1.83	**1.47**	1.16 to 1.85	**1.70**	1.25 to 2.31
40-49	**2.20**	1.73 to 2.81	**2.25**	1.76 to 2.87	**3.71**	2.76 to 4.97
50-59	**3.56**	2.74 to 4.63	**3.82**	2.95 to 4.95	**9.5**	**7.0 to 12.8**
60+ years	**10.0**	**7.8 to 12.8**	**14.7**	**11.7 to 18.5**	**19.2**	**14.0 to 26.4**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**0.77**	0.63 to 0.97	**0.71**	0.57 to 0.88	**1.29**	1.02 to 1.62
Haemophilia B <= 5 IU/dl	**0.66**	0.45 to 0.96	**0.63**	0.44 to 0.92	**1.37**	0.97 to 1.92
Haemophilia B other	**1.21**	0.79 to 1.86	**1.16**	0.76 to 1.78	**1.44**	0.94 to 2.20
Von Willebrand disease	**0.97**	0.68 to 1.39	**1.02**	0.71 to 1.47	**1.62**	1.14 to 2.29
Any Acquired BD/Other	**1.15**	0.72 to 1.83	**1.28**	0.80 to 2.05	**1.40**	0.91 to 2.17
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.82**	1.45 to 2.27	**1.65**	1.33 to 2.06	**2.01**	1.60 to 2.53
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**1.95**	1.45 to 2.61	**1.72**	1.29 to 2.30	**2.48**	1.90 to 3.24
Yes, 1988-1991	**1.27**	0.81 to 1.99	**1.01**	0.64 to 1.57	**1.79**	1.22 to 2.63
HCV-status (baseline = HCV-status is Not Known at NHD)						
HIV antibody positive	**6.1**	**5.9 to 7.5**	**11.8**	**9.8 to 14.3**	**2.25**	**1.57 to 3.22**
HCV positive	**0.30**	**0.23 to 0.40**	**0.45**	**0.20 to 1.00**	**1.17**	**0.93 to 1.47**
HCV negative	**0.06**	**0.03 to 0.12**	**0.99**	**0.44 to 2.26**	**0.72**	**0.55 to 0.93**

Table A2.2 Primary analysis, all-cause mortality: HCV-status

Covariate influences on hazard ratios during **EPOCH 2** and in **EPOCH 3+4** with all undated HCV-test results assumed known before 1 January 1992 versus only at 1 January 2010.

COVARIATES	EPOCH 2: 583 deaths (2000-2009, 10 years)				EPOCH 3+4: 580 death (2010-2019, 10 years)	
	Switch by 1 January 1992		*Switch by 1 January 2010*		***Identical by EPOCH 3***	
	HR	95% CI for HR	**HR**	95% CI for HR	**HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.77**	0.54 to 1.09	**0.67**	0.47 to 0.94	**0.72**	0.52 to 1.00
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	**0.91**	0.59 to 1.40	**0.75**	0.48 to 1.15	**0.53**	0.34 to 0.81
30-39	**1.81**	1.31 to 2.51	**1.90**	1.37 to 2.64	**1.70**	1.25 to 2.31
40-49	**3.31**	2.39 to 4.58	**3.50**	2.52 to 4.83	**3.71**	2.76 to 4.97
50-59	**6.5**	**4.7 to 9.1**	**7.7**	**5.5 to 10.6**	**9.5**	**7.0 to 12.8**
60+ years	**13.1**	**9.54 to 18.0**	**22.7**	**16.7 to 30.8**	**19.2**	**14.0 to 26.4**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**1.10**	0.87 to 1.40	**0.94**	0.74 to 1.18	**1.29**	1.02 to 1.62
Haemophilia B <= 5 IU/dl	**1.50**	1.08 to 2.06	**1.47**	1.06 to 2.03	**1.37**	0.97 to 1.92
Haemophilia B other	**1.45**	0.93 to 2.24	**1.30**	0.84 to 2.01	**1.44**	0.94 to 2.20
Von Willebrand disease	**1.27**	0.90 to 1.79	**1.28**	0.90 to 1.81	**1.62**	1.14 to 2.29
Any Acquired BD/Other	**1.26**	0.81 to 1.96	**1.35**	0.87 to 2.11	**1.40**	0.91 to 2.17
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**2.12**	1.67 to 2.70	**1.91**	1.51 to 2.42	**2.01**	1.60 to 2.53
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**2.03**	1.57 to 2.62	**1.76**	1.37 to 2.25	**2.48**	1.90 to 3.24
Yes, 1988-1991	**1.67**	1.15 to 2.48	**1.16**	0.79 to 1.69	**1.79**	1.22 to 2.63
HCV-status (baseline = HCV-status is Not Known at NHD)						
HIV antibody posive	**1.91**	**1.4 to 2.5**	**4.3**	**3.3 to 5.6**	**2.25**	**1.57 to 3.22**
HCV positive	**0.32**	**0.25 to 0.40**	**0.75**	**0.49 to 1.14**	**1.17**	**0.93 to 1.47**
HCV negative	**0.09**	**0.06 to 0.14**	**1.06**	**0.64 to 1.76**	**0.72**	**0.55 to 0.93**

Table A2.3 Secondary analysis, liver-related or cardiovascular mortality: HCV-status

For completeness, sensitivity of covariate influences on HRs for liver-related or cardiovascular (LC) deaths during **EPOCH 1** (**6,282** person at-risk) and in **EPOCH 3+4** (**4,879** persons at-risk) with all undated HCV-test results assumed known before 1 January 1992 versus at 1 January 2010.

COVARIATES	**EPOCH 1: 205 LC deaths (1992-1999, 8 years)**				**EPOCH 3+4: 164 LC deaths (2010-2019, 10 years)**	
	Switch by 1 January 1992		*Switch by 1 January 2010*		***Identical by EPOCH 3***	
	HR	95% CI for HR	**HR**	95% CI for HR	**HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.36**	0.17 to 0.77	**0.34**	0.16 to 0.71	**0.32**	0.15 to 0.66
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	**0.99**	0.40 to 2.39	**0.90**	0.37 to 2.20	**0.52**	0.22 to 1.19
30-39	**2.56**	1.35 to 4.88	**2.58**	1.36 to 4.92	**1.69**	0.99 to 2.88
40-49	**5.7**	**3.0 to 10.5**	**5.7**	**3.1 to 10.6**	**3.89**	2.34 to 6.47
50-59	**11.3**	**6.1 to 21.1**	**11.6**	**6.2 to 21.7**	**7.8**	**4.5 to 13.6**
60+ years	**29.2**	**15.8 to 53.8**	**35.0**	**19.3 to 63.6**	**12.7**	**6.8 to 23.7**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**0.82**	0.56 to 1.21	**0.75**	0.51 to 1.10	**1.56**	1.03 to 2.34
Haemophilia B <= 5 IU/dl	**0.39**	0.18 to 0.86	**0.39**	0.18 to 0.85	**0.84**	0.42 to 1.69
Haemophilia B other	**0.83**	0.38 to 1.80	**0.80**	0.37 to 1.73	**1.77**	0.84 to 3.76
Von Willebrand disease	**1.29**	0.69 to 2.39	**1.25**	0.67 to 2.32	**2.07**	1.07 to 4.00
Any Acquired BD/Other	**1.30**	0.54 to 3.14	**1.28**	0.53 to 3.08	**3.06**	1.35 to 6.93
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.32**	0.86 to 2.01	**1.28**	0.85 to 1.94	**1.94**	1.23 to 3.05
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**2.07**	1.20 to 3.56	**2.22**	1.31 to 3.76	**2.36**	1.34 to 4.18
Yes, 1988-1991	**1.08**	0.43 to 2.70	**0.94**	0.38 to 2.36	**1.73**	0.70 to 4.26
HCV-status (baseline = HCV-status is Not Known at NHD)						
HIV antibody positive	**4.2**	**2.8 to 6.5**	**5.4**	**3.7 to 7.8**	**2.56**	**1.30 to 5.05**
HCV positive	**0.74**	**0.49 to 1.11**	**0.58**	**0.18 to 1.82**	**1.79**	**1.13 to 2.84**
HCV negative	**0.12**	**0.04 to 0.37**	**1.53**	**0.48 to 4.91**	**0.40**	**0.21 to 0.79**

Table A2.4 Secondary analysis, liver-related or cardiovascular mortality: HCV-status

For completeness, covariate influences on hazard ratios for liver-related or cardiovascular (LC) deaths during **EPOCH 2** (**5,452** person at-risk) and in **EPOCH 3+4** (**4,879** persons at-risk) with all undated HCV-test results assumed known before 1 January 1992 or at 1 January 2010

COVARIATES	**EPOCH 2: 194 LC deaths (2000-2009, 10 years)**				**EPOCH 3+4: 164 LC deaths (2010-2019, 10 years)**	
	Switch by 1 January 1992		*Switch at 1 January 2010*		***Identical by EPOCH 3***	
	HR	95% CI for HR	**HR**	95% CI for HR	**HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.70**	0.34 to 1.41	**0.66**	0.33 to 1.35	**0.32**	0.15 to 0.66
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20 years	**0.22**	0.06 to 0.73	**0.19**	0.06 to 0.66	**0.52**	0.23 to 1.19
30-39	**2.17**	1.27 to 3.67	**2.20**	1.30 to 3.74	**1.69**	0.99 to 2.89
40-49	**3.79**	2.21 to 6.49	**3.77**	2.20 to 6.47	**3.89**	2.34 to 6.47
50-59	**8.2**	**4.8 to 14.3**	**8.0**	**4.6 to 13.9**	**7.8**	**4.5 to 13.6**
60+ years	**20.0**	**11.7 to 34.3**	**22.3**	**13.3 to 37.5**	**12.8**	**6.9 to 23.7**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**1.19**	0.81 to 1.73	**1.05**	0.71 to 1.54	**1.56**	1.04 to 2.34
Haemophilia B <= 5 IU/dl	**1.09**	0.60 to 1.96	**1.10**	0.61 to 1.98	**0.84**	0.42 to 1.69
Haemophilia B other	**1.28**	0.61 to 2.71	**1.17**	0.55 to 2.47	**1.77**	0.84 to 3.76
Von Willebrand disease	**1.15**	0.60 to 2.20	**1.02**	0.54 to 1.95	**2.07**	1.07 to 4.00
Any Acquired BD/Other	**0.77**	0.30 to 2.02	**0.69**	0.27 to 1.80	**3.06**	1.35 to 6.93
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.58**	1.04 to 2.40	**1.74**	1.16 to 2.63	**1.94**	1.24 to 3.04
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**1.61**	0.98 to 2.64	**2.24**	1.40 to 3.57	**2.36**	1.33 to 4.18
Yes, 1988-1991	**1.27**	0.56 to 2.87	**1.06**	0.47 to 2.38	**1.73**	0.70 to 4.26
HCV-status (baseline = HCV-status is Not Known at NHD)						
HIV antibody positive	**4.6**	**2.8 to 7.6**	**4.7**	**3.0 to 7.1**	**2.55**	**1.30 to 5.05**
HCV positive	**1.08**	**0.73 to 1.57**	**0.69**	**0.33 to 1.43**	**1.79**	**1.13 to 2.84**
HCV negative	**0.07**	**0.02 to 0.22**	**0.42**	**0.10 to 1.69**	**0.40**	**0.21 to 0.79**

A3. Excluding those with missing NHS number: no substantive inferential changes to primary analysis

Table A3.1 Primary analysis, all-cause mortality, HCV-status analysed during **EPOCH 1** (number in risk-set **5,556; 41,438** person-years); **EPOCH 2** (number in risk-set **4,881; 45,909** person-years) and **EPOCHS 3+ 4** combined (number in risk-set **4,332; 40,365** person-years)

COVARIATES	EPOCH 1: 675 deaths (1992-1999, 8 years)		EPOCH 2: 549 deaths (2000-2009, 10 years)		EPOCHS 3+4: 574 deaths (2010-2019, 10 years)	
	HR	95% CI for HR	**HR**	95% CI for HR	**HR**	95% CI for HR
Gender (baseline: male)						
Female	**0.43**	0.27 to 0.67	**0.63**	0.44 to 0.90	**0.64**	0.46 to 0.89
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20	**0.97**	0.70 to 1.35	**0.69**	0.44 to 1.08	**0.48**	0.31 to 0.74
30-39	**1.59**	1.22 to 2.06	**1.97**	1.41 to 2.75	**1.83**	1.35 to 2.50
40-49	**2.58**	1.97 to 3.38	**3.62**	2.60 to 5.04	**4.04**	3.00 to 5.44
50-59	**4.3**	3.20 to 5.76	**7.5**	**5.3 to 10.5**	**9.9**	**7.3 to 13.5**
60+ years	**16.8**	**13.0 to 21.8**	**26.8**	**19.6 to 36.6**	**30.0**	**22.0 to 40.8**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**0.64**	0.51 to 0.82	**0.79**	0.62 to 1.02	**1.00**	0.79 to 1.26
Haemophilia B <= 5 IU/dl	**0.53**	0.34 to 0.80	**1.29**	0.92 to 1.81	**1.29**	0.92 to 1.81
Haemophilia B other	**0.96**	0.59 to 1.57	**1.04**	0.66 to 1.64	**1.07**	0.70 to 1.64
VonWillebrand disease	**0.95**	0.63 to 1.43	**1.20**	0.84 to 1.72	**1.32**	0.92 to 1.88
Any Acquired BD/Other	**1.42**	0.85 to 2.39	**1.26**	0.79 to 2.01	**1.24**	0.79 to 1.93
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.49**	1.16 to 1.92	**1.58**	1.24 to 2.02	**1.73**	1.37 to 2.17
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**1.51**	1.08 to 2.10	**1.42**	1.09 to 1.86	**2.48**	1.91 to 3.21
Yes, 1988-91	**0.70**	0.41 to 1.20	**0.95**	0.64 to 1.41	**1.34**	0.92 to 1.96
HIV-status (baseline = not known to be HIV-infected)						
HIV antibody positive	**11.6**	**9.4 to 14.4**	**4.2**	**3.2 to 5.4**	**1.9**	**1.4 to 2.6**

Table A3.2 Primary analysis, all-cause mortality. Now includes HCV-status switched at 1 January 2010 **for those who were HCV-tested but test-date was missing.**

Analysis during EPOCH 1 (number in risk-set **5,556; 41,438** person-years), EPOCH 2 (risk-set **4,881; 45,909** person-years) and EPOCHS 3+ 4 combined (risk-set **4,332; 40,365** person-years).

COVARIATES	EPOCH 1 (1992-1999, 8 years) 675 deaths		EPOCH 2 (2000-2009, 10 years) 549 deaths		EPOCHS 3+4 (2010-2019, 10 years) 574 deaths	
	HR	95% CI for HR	HR	95% CI for HR	HR	95% CI for HR
Gender (baseline: male)						
Female	**0.43**	0.27 to 0.67	**0.63**	0.44 to 0.90	**0.69**	0.49 to 0.96
Age-band at 31 December 1991 (baseline: 20-29 years)						
Under 20	**0.97**	0.70 to 1.35	**0.69**	0.44 to 1.08	**0.50**	0.32 to 0.77
30-39	**1.59**	1.22 to 2.06	**1.97**	1.41 to 2.74	**1.81**	1.33 to 2.46
40-49	**2.57**	1.96 to 3.37	**3.62**	2.60 to 5.04	**4.06**	3.02 to 5.48
50-59	**4.3**	3.21 to 5.78	**7.5**	**5.3 to 10.5**	**9.8**	**7.2 to 13.3**
60+ years	**16.7**	**12.9 to 21.6**	**26.7**	**19.5 to 36.4**	**24.9**	**18.1 to 34.1**
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)						
Haemophilia A other	**0.64**	0.50 to 0.82	**0.78**	0.61 to 1.00	**1.02**	0.80 to 1.28
Haemophilia B <= 5 IU/dl	**0.53**	0.34 to 0.81	**1.28**	0.91 to 1.79	**1.24**	0.89 to 1.75
Haemophilia B other	**0.98**	0.60 to 1.59	**1.04**	0.66 to 1.64	**1.09**	0.71 to 1.68
VonWillebrand disease	**0.94**	0.62 to 1.41	**1.17**	0.82 to 1.67	**1.24**	0.87 to 1.77
Any Acquired BD/Other	**1.41**	0.84 to 2.36	**1.23**	0.77 to 1.96	**1.13**	0.72 to 1.77
Exposure to components before 1992 (baseline = no)						
Yes, pre-1992	**1.52**	1.18 to 1.96	**1.62**	1.26 to 2.07	**1.74**	1.38 to 2.18
Exposure to pooled plasma pre-1988 (baseline = no)						
Yes, pre-1988	**1.56**	1.12 to 2.17	**1.47**	1.12 to 1.91	**2.44**	1.85 to 3.23
Yes, 1988-91	**0.70**	0.41 to 1.20	0.95	0.64 to 1.40	**1.61**	1.10 to 2.36
HCV-status (baseline = HCV-status is Not Known at NHD)						
HIV antibody positive	**11.1**	**9.0 to 13.7**	**4.0**	**3.0 to 5.2**	**1.0**	**0.7 to 1.5**
HCV positive	**0.33**	**0.12 to 0.89**	**0.67**	**0.44 to 1.03**	**0.52**	**0.41 to 0.66**
HCV negative	**0.91**	**0.37 to 2.24**	**1.00**	**0.60 to 1.66**	**0.34**	**0.26 to 0.44**

A4. EPOCH 3+4 only: bleeding disorder/severity covariates fitted without exposure covariates; HRs for bleeding disorder/severity as a direct consequence

COVARIATES	EPOCHS 3+4: 580 death (2010-2019, 10 years); HIV-status		EPOCHS 3+4: 580 death (2010-2019, 10 years); HCV-status	
	Hazard Ratio, HR	95% CI for HR	**Hazard Ratio, HR**	95% CI for HR
Gender (baseline: male)				
Female	**0.69**	0.49 to 0.95	**0.67**	0.48 to 0.93
Age-band at 31 December 1991 (baseline: 20-29 years)				
Under 20	**0.51**	0.33 to 0.79	**0.54**	0.35 to 0.83
30-39	**1.74**	1.28 to 2.36	**1.74**	1.28 to 2.36
40-49	**3.57**	2.66 to 4.79	**3.69**	2.75 to 4.96
50-59	**8.3**	6.2 to 11.2	**9.1**	6.8 to 12.3
60+ years	**18.4**	13.6 to 24.9	**20.7**	15.1 to 28.4
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A <= 5 IU/dl)				
Haemophilia A other	**1.06**	0.85 to 1.33	**1.18**	0.93 to 1.48
Haemophilia B <= 5 IU/dl	**1.22**	0.88 to 1.70	**1.17**	0.84 to 1.63
Haemophilia B other	**1.13**	0.75 to 1.72	**1.21**	0.79 to 1.83
VonWillebrand disease	**1.17**	0.84 to 1.63	**1.44**	1.03 to 2.02
Any Acquired BD/Other	**1.17**	0.76 to 1.79	**1.33**	0.86 to 2.06
HIV-status (baseline = not known to be HIV-infected)				
HIV antibody positive	**2.32**	1.70 to 3.17		
HCV-status (baseline = HCV-status is Not Known at NHD)				
HIV antibody positive			**2.97**	2.09 to 4.22
HCV positive			**1.57**	1.26 to 1.95
HCV negative			**0.72**	0.55 to 0.93