The impact of HIV on mortality rates in the complete UK haemophilia population

UK Haemophilia Centre Doctors' Organisation

Objective: To estimate the effect of HIV-1 infection on subsequent mortality in a complete population.

Design: Prospective cohort study.

Subjects: A total of 7250 haemophilic males were registered in the UK Haemophilia Centre Doctors' Organisation database, 1977 - '1998, Most were infected with hepatitis C virus. In the early 19805, 1246 were infected with HIV-1 from contaminated clotting factor concentrate, The main outcome measure was the date of death.

Results: During 1977-'1984 annual mortality in severely haemophilic males was 0.9%. For those with HIV, annual mortality increased progressively from 1985 reaching over 10% during 1993-1996 before falling to 5% in '1997-1999, whereas without HIV it remained approximately 0.9% throughoutI9B5-1999. For moderately/mildly haemophilic males the annual mortality was 0.4% during 1977-1984. Without HIV it remained approximately 0.4% throughout 1985-'1999, but with HIV it was similar to that in severe haemophilia with HIV. Survival was strongly related to age at HIV infection. The large temporal changes in mortality with HIV were largely accounted for by HIV-related conditions. Without HIV annual liver disease mortality remained below 0.2% throughout 1985-1999, but with HIV it was 0.2% during 1985-1990, 0.8% during 1991-1996, and 0.8% during 1997-1999.

Conclusion: These data provide a direct estimate of the effect of HIV-1 infection on subsequent mortality in a population with a high prevalence of hepatitis C. From approximately 3 years after HIV infection, large, progressive increases in mortality were seen, From 1997, after the introduction of effective treatment, substantial reductions occurred, although mortality from liver disease remained high,

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Keywords: Cohort study, haemophilia, hepatitis C virus, highly active antiretroviral therapy, HIV, liver disease, mortality

Introduction

In most Hl Vvinfected groups it is impossible to estimate directly the effect of infection on subsequent mortality because information is lacking on the mortality rates that would have occurred in its absence. People with haemophilia are a notable exception. In the early 1980s. they were exposed to HIV-l infection through treatment with plasma-derived clotting factor concentrates. New infections ceased in the mid-1980s when donor screening and viral inactivation procedures during concentrate manufacture were introduced. By then, however, many patients had been infected. Mortality and disease incidence in the complete UK haemophilia population before and after infection with HIV have previously been reported 11-4j. This paper

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updates that evidence and reports on mortality rates since the introduction of effective treatment for HIV with highly active anriretroviral therapy (HAART) in mid-1996, Before the rnid-1980s, haemophilia treatment also carried a near certain risk of hepatitis C virus (HCV) infection, and the majority of this population, including almost all those with severe haemophilia, were infected [5-81. Data on mortality from liver disease are therefore also presented.

Methods

The UK Haemophilia Centre Doctors' Organisation (UKHCDO) has maintained a nationwide register of individuals diagnosed with haemophilia A (factor VIII deficiency) or B (factor IX deficiency) since!976 [9]. The register is updated continuously using data 011 newly diagnosed individuals and deaths received from individual haemophilia centres, In addition, the vital status on 1 January 2000 of registered individuals was checked with the UK Office for National Statistics.

HIV-1 testing became available late in 1984, and virtually all haemophilia patients who had received potentially infected blood products were tested very shortly afterwards. Information on HIV test results and AIDS diagnoses has been collated [1-3,10,111, Previously stored blood samples for some individuals enabled an estimation of the seroconversion date for all those infected. For over 80% the estimate was during 1981-1983, with the median December 1982. The definition of AIDS was always that currently in use in the UK [121.

Individual information on HCV status is not available. Information on treatment with high HCV risk products is, however, held in the database, and studies in small groups have shown that close to 100% of those treated before 1985 were infected with HCV, with a single exposure to large-pool concentrate usually causing infection [5- 7,13J.

For each individual, the person-years at risk were calculated from the date of registration on the database until the date of death or emigration or, for those still alive and in the UK, 1 January 2000. For the few whose vital status on 1 January 2000 could not be established, their contribution to the person-years was taken to end on the last date when they were known to be alive. Annual death rates, directly standardized for age [14] using the distribution of person-years in the HIV-infected individuals in age groups less than 20, 20-29, 30-39, 40-49 and over 50 years, were calculated for all causes and for individual causes by calendar year, haemophilia severity and, from 1985, HIV status. Death certificates were obtained for individuals who had died, and the underlying cause was coded to the 9th revision of the International Classification of Diseases [15], except if the underlying cause was described as haemophilia as a result of some other, more specific cause (e.g. AIDS, hepatitis), then the more specific cause was taken whenever appropriate. All deaths certified as being caused by AIDS or an AIDS-defining condition. or occurring in individuals reported as having developed an AIDS-ddining condition shortly before death; were classified as HIV related.

For the Hl'V-infected group, survival from 1 January 1985 to 1 January 1987, 1 January 1989, .. " 1 January 1997, and I January 2000 was calculated separately for those aged 1-14, 15-34. 35-54 and over 55 years at infection using the equation:

$$S(t) = \exp\left\{ - \sum_i \alpha O_i / Y_i^+ \right\} \qquad (1)$$

where $S(t)$ is the probability of surviving to time t: ni, O_i^+, and Y_i^+ are the numbers of calendar years, observed deaths and person-years, respectively, in the ;th calendar period, and summation is over calendar periods to time t. The survival that HIV-infected individuals would have experienced without infection was also calculated by replacing O_i^+ in equation (1) by

$$E_i^+ = \sum_j Y_{ij}^+ O_j^- / Y_j^-,$$

where O_j^- and Y_j^- are the numbers of observed deaths and person-years in HIV-uninfectcd individuals with severe haemophilia in the jth 5-year attained-age group during j985–1999, Y_{ij}^+ is the number of person-years in the jth attained-age group in HIV-infected individuals in calendar period i, and summation is over all attained-age groups. Relative .survival [16] was calculated by considering the excess number of deaths in HIV-infected compared with uninfected individuals, i.e. by replacing O_i^+ in equation (1) by $(ot - E_i^+)$. Calculations were completed using the computer package Stata [171.

Results

Of the 7250 haemophilic men and boys living in the UK during 1977-1998 and registered on the UKHCDO database. 2262 had severe (clotting factor concentration < 1 IU/dl), and 4988 had moderate/mild haemophilia. Among those with severe haemophilia, 952 were infected with HIV (53% of those alive on 1 January 1985). whereas 294 individuals with moderate/

mild haemophilia were infected (7% of those alive on 1 January 1985). The lower proportion among those with moderate/mild haemophilia reflects the lower treatment frequency in this group. Among EIV-infccted individuals, 65.8% of those with severe and 59.9% of those with moderate/mild haemophilia had died by 1 January 2000, whereas for EIV-uninfected individuals the proportions who had died were much lower, at 18.3% for those with severe and 13.0% for those with moderate/mild haemophilia (Table 1).

During 1977-1984, mortality in individuals with severe haemophilia remained constant at 0.9% (Table 2). Among HIV-uninfected individuals, mortality remained at this level during 1985-1999. In contrast, among HIV-infecred individuals, mortality increased progressively to 2.5, 4.3, 5.8, 8.1, and 12.7% in the years 1985–1986, 1987-1988, 1989-1990, 1991-1992, and 1993-1994, respectively (Fig. 1). In 1995-1996 annual mortality was 11.3%, before falling to 5.3% in 1997-1999, after the introduction ofHAART. For individuals with moderate/mild haemophilia, annual mortality during 1977-1984 was 0.4%. This is half the corresponding value in individuals with severe haemophilia, and the difference is principally caused by the lower mortality from causes involving bleeding. For individuals with moderate/mild haemophilia without HIV, annual mortality remained at 0.4% throughout 1985-1999. For individuals with moderate/mild haemophilia with HIV, annual mortality increased progressively, to 2.5, 2.6. 5.9, 8.1, 11.5, and 13.1% in years 1985-1986, 1987-1988, 1989-1990, 1991-1992, 1993-1994, and 1995-1996, before falling to 2.9% in 1997-1999.

The UKHCDO database indicated that all but 10 of the 1-I1V-infecrcd individuals had received high HCV risk products, as had 895 of the HIV-uninfectcd individuals with severe haemophilia (92% of those born before 1985), and 2497 of the HIV-uninfecced individuals with moderate/mild haemophilia (64% of those born before 1985). Enquiries at haemophilia centres showed that UKHCDO treatment records were not comprehensive, and that all 10 of the remaining EIV-infected individuals and rnany others with severe haemophilia were also likely to have received high HCV risk products. When the analyses in Table 2 were repeated excluding those with no recorded exposure to high HeV risk products, the results were essentially unchanged: annual mortality in those with severe haemophilia was 0.9% (0.5-1.2), 0.9% (0.6-1.3), 1.0% (0.6-1.4), and 0.9% (0.6-1.3) during 1977-1978, 1979-1980, 1981-1982 and 1983-1984, whereas for those with severe haemophilia without HIV annual mortality during 1985–1986, 1987-1988, 1989-1990, 1991-1992, 1993-1994, 1995–1996 and 1997-1999 was 0.9% (0.5-1.2), 0.9% (0.5-1.4), 0.9% (0.4-1.4), 0.6% (0.2-0.9), 0.9% (0.5-1.4), 1.2% (0.7-1.7), and 0.7% (0.4-1.1), respectively. For moderate/mild haemophilia the corresponding values during 1977-1978, 1979-1980, 1981-1982, 1983-1984, 1985-1986, 1987-1988, 1989-1990, 1991-1992, 1993-1994, 1995-1996 and 1997-1999 were 0.5% (0.3-0.7), 0.5% (0.3-0.6), 0.4% (0.2-0.5). 0.5% (0.4-0.7), 0.4% (0.2-0.5), 0.4% (0.2-0.5), 0.5% (0.3-0.7), 0.4% (0.3-0.6), 0.5% (0.3-0.6), 0.4% (0.3-0.6), and 0.4% (0.3-0.5), respectively.

A strong gradient in mortality was observed with age at HIV infection: for those infected at ages 1-14 years, 57%, of those alive on 1 January 1985 survived to 1 January 2000, whereas for those infected at ages 15-34, 35-54 and over 55 years, 38, 12, and 2%, respectively, survived to 1 January 2000 (Fig. 2). Some age gradient would be expected without HIV: mortality among the HIV-uninfected individuals suggests that, without HIV, survival in the I-IIV-infected group to 1 January 2000 in the four age-at-infection groups would have been 98, 92, 69, and 39%, respectively. When mortality in the HIV-infccted individuals was corrected for deaths

Table 1. Numbers of males in the UK with haemophilia A or 8 and registered in the UK Haemophilia Centre Doctors' Organization national database 1977-1998, together with vital status on 1 January 2000.

	Severe haemophilia"		Moderate or mild haemophilia"		
	Infected with HIV·I		infected with HIV·I		
	Yes[c]	No	Yes';	No	Total
Alive and resident in UK	318 (33.4)c1	1013 (77.3)	116 (39.5)	3882 (82.7)	5329 (73.5)
Dead	626 (65.8)	240 (18.3)	176 (59.'))	608 (13.0)	1650 (22.8)
Emigrated	5 (0.5)	14 (1.1)	I (0.3)	53 (1.1)	73 (1.0)
Lost to follow-up	3 (0.3)	430.3)	1 (0.3)	151 (3.2)	198 (2.7)
Total"	952 (100.0)	1310(100.0)	294 (100.0)	4694 (100.0)	7250 (100.0)

"Concentration of cloning factor in the blood less than 1 IU/dl. "Includes 123 individuals with unknown severity, two of whom were infected with HIV-I. "Includes 12 individuals (nine severe, three moderate/mild) who died before I January 1985 whose HIV status was established using stored blood samples and two individuals (one severe, one moderate/mild) who died in 1984 for whom no HIV test was carried out but who, from their symptoms, are likely to have been infected with HIV. dColumn percentages in brackets. "Excluding individuals treated in the UI< who usually live overseas.

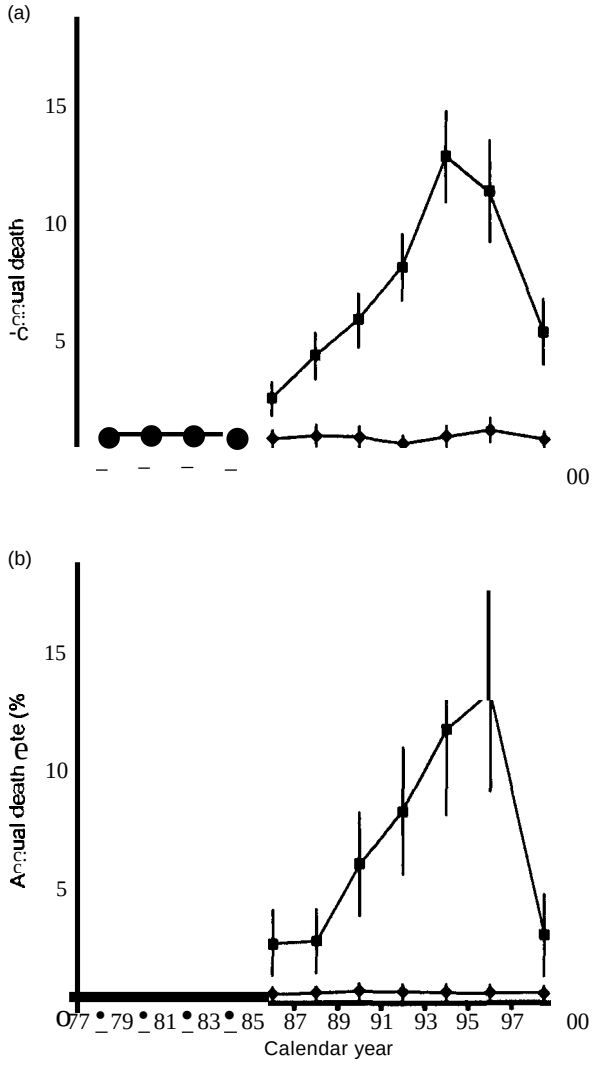

Fig. 1. Annual death rate (%), standardized for age, in haemophilic males in the UK by severity of haemophilia, calendar year and, from 1985, HIV status. (a) Severe haemophilia; (b) moderate or mild haemophilia. Vertical lines are 95% confidence intervals - • 1977-'1984: all; • 1985-1999: HIV positive; • 1985-1999: HIV negative.

that would have been expected without HIV, a strong age gradient remained: relative survival to 1 January 2000 in those aged 1-14. 15-34, 35-54 and over 55 years at HIV infection was 59, 41, 18 and 4%. respecti vely.

Of the 788 deaths in HIV-infected individuals during 1985-1999, 610 were HIV related, and annual mortality from EIV-related causes rose from 3.0% during 1985-1990 to 8.4% during 1991-1996 and then fell to 2.9% during 1997-1999. For all causes of death the temporal pattern was similar with annual mortality at 4.0, 10.3 and 4.7% in 1985-1990, 1991-1996 and 1997-1999 (Table 3). Considering the 178 deaths not classified as HI V related, annual mortality rose from 1.0% in 1985-1990 to 1.9% in 1991-1996, then fell slightly, to 1.8%, in 1997-1999. These values arc considerably higher than those for HIV-uninfected individuals, in whom annual mortality from all causes (standardized for age and haemophilia severity) was 0.8% (0.6, 1.0), 0.8% (0.6, 1.0), and 0.7% (0.5, 1.0) during 1985-1990, 1991-1996, and 1997-1999, respectively.

Among HIV-infected individuals, 59 of the 178 deaths not classified as HIV related were from liver disease, including seven liver cancers, and annual mortality from liver disease was 0.2% in 1985-1990, rising to 0.8% in 1991-1996 and remaining at 0.8% in 1997-1999. Among the deaths classified as HIV related, a further 27 were certified as being caused by liver disease: when these were included annual liver disease mortality was 0.2% (0.1, 0.3),1.2% (0.9,1.5), and 1.2% (0.6, 1.7) in 1985-1990, 1991–1996, and 1997-1999, respectively, In contrast, among HIVvuninfectcd individuals annual liver disease mortality was (1.09% (0.05, 0.13) during 1985-1999, and 0.05% (0.01, 0.08), 0.11% (0.04, 0.18), and 0.14% (0.04, 0.23) during 1985-1990, 1991-1996, and 1997-1999, respectively, The exclusion of patients with no recorded high HeV risk exposure had little effect in the HIV-uninfected group: annual liver disease mortality in this restricted group during 1985-1999 was 0.10% (0.06-0.14), whereas values during the years 1985-1990, 1991-1996, and 1976-1999 were 0.05% (0.01-0.09), 0.12% (0.05-0.19) and 0.13% (0.04-0.23), respectively.

For deaths classified neither as EIV related nor from liver disease, annual mortality in HIV-infected individuals varied little during 1985-1999, taking values 0.9, 1.1 and 1.0% during 1985-1990, 1991-1996 and 1997-1999, respectively (Table 3), whereas for 1-I1V-uninfected individuals the corresponding values were appreciably lower, at 0.7% (0.6, 0.8) during 1985-1999, and 0.7% (0.5, 0.9), 0.7% (0.5, 0.9), and 0.6% (0.3,0.8) during 1985-1990, 1991-1996, and 1997-1999, respectively, For the 119 deaths in HIV-infected individuals, all available information regarding cause was inspected. No common pattern was apparent, although several suggested immunodeficiency (see previous analyses of these data [1,2]). There was no evidence that death was caused by a toxic effect of HAART in the information regarding the 14 deaths occurring during 1997-1999.

Discussion

The infection of 1246 UK haemophilic males with I-IJV-1 during the early 1980s offers unusual insight

Table2. Annual death rates (%) in males with haemophilia in the UK, 1977-1999.

	Infected with HIV-I		
Calendar year	Yes	No	All individuals
Severe haemophilia			
1977-1978			0.9 (0.5-1.3)"
1979-1980			0.9 (0.6-1.3)
1981-1982			1.0 (0.6-1.3)
1983-1984			0.9 (0.6-1.3)
1985–1986	2.5 (1.8-3.3)	0.8 (0.5-1.2)	1.8 (1.3-2.2)
1987-1988	4.313.3-5.3)	1.010.5-1.4)	2.8 (2.2-3.4)
1989-1990	5.8 (4.7-6.9)	0.9 (0.4-1.3)	3.3 (2.7-3.9)
1991-1992	8.1 (6.6-9.5)	0.6 (0.3-1.0)	4.113.4-4.9)
'1993-1994	12.7(10.8-14.6)	0.9 (0.5-1.4)	6.0 (5.1-6.9)
1995–1996	11.3 (9.2-13.4)	1.2 (0.7-1.7)	5.1 (4.2-6.0)
1997-1999	5.3 (3.9-6.7)	0.8(0.5-1.1)	2.2 (1.7-2.7)
Moderate or mild haemophilia			
1977-1978			0.5 (0.3-0.7)
1979-1980			0.4 (0.3-0.6)
1981–1982			0.4 (0.3-0.5)
1983-1984			0.5 (0.4-0.7)
1985-1986	2.5 (1.1-4.0)	0.4 (0.2-0.5)	*0.5 W.3-0.7)*
1987–1988	2.6 (1.2-4.0)	0.4 (0.3-0.6)	0.6 (0.4-0.B)
1989-1990	5.9 (3.7-8.0)	0.5 (0.3-0.7)	0.8 (0.6-1.1)
1991-1992	8. t (5.4-10.8)	0.5 (0..1-0.6)	1.0 (0.8-1 ..1)
1993-1994	11.5 (7.9-15.1)	0.4 (0.3-0.5)	1.0 (0.7–1.2)
1995-1996	13.1 (8.9-17.3)	0.4 10.3-0.51	0.9 (0.7-1.1)
1997-1999	2.9 (1.2-4.6)	0.4 (0..1-0.5)	0.5 (0.4-0.6)

[a]Age-standardized annual death rates per 100 person-years at risk and 95% confidence intervals.

into the impact of this virus on mortality. The reasons for this are: the chance of infection depended only on how much clotting factor concentrate an individual needed j18J, and which particular batches he received; the infections took place during a short time period and within a dearly defined total population that had a wide age-range; a reliable test for HIV antibodies had become available shortly after the infections occurred; the testing of those potentially infected was essentially complete: the previously stored blood samples enabled the sercconversion date to be estimated, and it has been possible to calculate mortality separately for HI V-infected individuals and others.

There arc, inevitably, a number of limitations to this study. One is that the vital status on I January 2000 of 73 individuals who emigrated and 198 individuals lost to follow-up is unknown. If their subsequent mortality has been similar to the mortality among those with complete follow-up, the study results would be unchanged. However, if their mortality differs, some bias may have occurred. For HIV-infected individuals, only 10 are involved. With such a small number, the study results would scarcely be affected even if they had substantially increased or decreased mortality compared with all HIV-infcctcd individuals. Among the HIV-uninfecrcd individuals the numbers emigrating are also small in relation to the total and therefore, once again, the differences between their mortality and that of those who did not emigrate would make little difference. The number of HIV-uninfected individuals lost to follow-up is larger. If they had lower mortality than those with complete follow-up, then the study results would not change. Some bias might occur if they had substantially higher mortality, but this is unlikely because individuals in poor health are unlikely to lose contact with their haemophilia centre.

In the entire UK haemophilia population, annual mortality was constant during 1977-1984, at approxirnately 0.9% in severe haemophilia, and 0.4% in moderate/mild haemophilia. From 1985, mortality in those not infected with HIV remained essentially unchanged but, among the infected individuals, mortality rose progressively by large amounts. Among those infected, the timing of the increase was identical in the two severity groups, and in each calendar period mortality rates were similar in size in the two groups, despite the different proportions infected and their different mortality rates in the absence of infection (Fig. 1). Survival was poorer in HIV-infected individuals than in uninfected individuals at all ages (Fig. 2). However, a much larger proportion of individuals remained alive by the end of the follow-up period for those who were younger when infected, even after correcting for the mortality expected in the absence of H.IV. Such an age gradient would be anticipated from the greater number of thymic cells in younger individuals, giving a greater possibility for the ongoing replenishment of the CD4 T-cell population [19J.

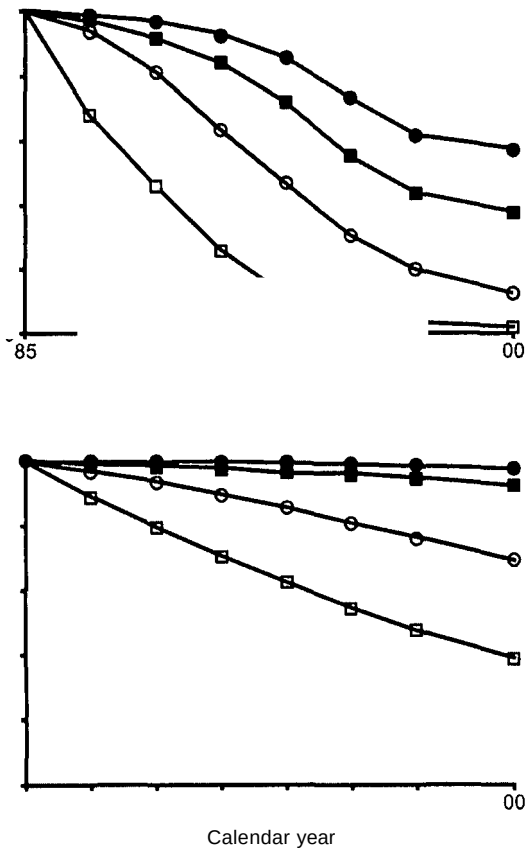

Fig. 2. (a) Survival in HIV-infected haemophilic males in the UK by calendar year for individuals infected at ages 1-14, 15-34, 35-54 and over 55 years; (b) expected survival based on mortality rates in those who were not infected. The numbers of individuals alive on 1 January 1985 who were infected with HIV at ages 1-14 (e), 15-34 (■), 35-54 (0), and over 55 years (0) were 312, 606, 255 and 59, respectively.

This haemophilia population has a high prevalence of HCV infection, and another limitation of this study is that individuals cannot formally be classified by HeV status. Sensitive tests to detect antibodies to HCY antigens became available only in the 1990s, and serum samples for this large population were not stored systematically. There is thus no possibility of ascertaining the HCV status for many who died before this. A surrogate marker of HCV infection is, however, available, which suggests that ncarly100% of the HIV-infected individuals and almost all others with severe haemophilia and born before 1985 were infected with HCV 15,61. Among those with moderate/mild haemophilia and without HIV, some individuals have never needed treatment with blood products and probably remain free of HCV. Nevertheless, when those without documented high HCV risk exposure are excluded, the study results scarcely change.

The impact of eo-infection with HCY on mortality in HIV infection is hard to estimate precisely, Before I()97 it was probably proportionately small, because during this period liver disease was the certified cause of death for only 9% of the deaths in HIV-infectcd individuals. Studies comparing HIV-infected individuals in different exposure categories, some of whom would have had much lower HCV prevalence, have also found no appreciable effect of exposure category on survival before the HAART era 120].

During 1997-1999, mortality fell sharply in HIY-infected individuals, both in severe and in moderate/mild haemophilia (Fig. 1). A similar fall, occuning shortly after the introduction of HAART, has been reported in other groups 121-23], and clearly demonstrates the impact of HAART. However, at the end of the present follow-up period, mortality in HIY-infected individuals still remained substantially higher than in HIV-uninfected individuals. Both the large increase in mortality up to 1996 and the subsequent fall were chiefly caused by changes in mortality from HIV-related causes (Table 3). However, when mortality from other causes was examined separately, a substantial increase over time remained, with the value during 1991–1996 almost double that for 1985-1990 and no appreciable decline in 1997-1999. The increase was entirely caused by an increase in liver disease, which during 1997-1999 was the certified cause of death for over 25% of deaths in Hl Vvinfected individuals. This tallies with findings in other studies of HIV/HCV eo-infection in which liver disease has also emerged as a leading cause of death in recent years [13,24,25]. The treatment of HCY infection with a combination of IFN-α and ribavirin became widespread in the UK during 2000 [26]. Therefore its impact on liver disease in this population is, as yet, unknown.

For deaths that were classified neither as HIY related nor from liver disease, mortality remained virtually constant during 1985-1999, albeit at a higher level than that of HIV-uninfcctcd individuals. It seems likely that at least some of these deaths were attributable to HIV, although there was no indication that the individuals concerned had developed an AIDS-defining condition. HAART has been associated with several categories of major toxic effects 127], but there was no evidence of any deaths occurring as a result of HAART in this population.

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Table 3. Annual death rates (%) during 1985-1999 in males with haemophilia in the UK who were infected with HIV.1, by calendar period and cause of death.

	Calendar period			
Cause of death	1985-1990	1991-1996	1997-1999	Total 198.5-1999
All causes				
No. of deaths	257	462	69	788
Death rate[a]	4.00.5,4.5)	10.3 (9.4, 11.2)	4.7 (3.6, 5.9)	6.3 (5.9, 6.8)
Htv-related"				
No. of deaths	190	378	42	610"
Death rate	3.0 (2.6, 3.4)	8.4 (7.6, 9.2)	2.9 (2.0, 3.9)	4,9 (4.5, 5.3)
All other causes				
No. of deaths	67	84	27	178
Death rate	1.0 (0.8,1.3)	1.9 (1.5, 2.3)	1.8(1.1,2.4)	1.4 (1.2, 1.61
Liver disease				
No. of deaths	10	36	13	59[d]
Death rate	0.2 (0.1,0.3)	0.8 (0..5,I.OI	0.8 (0.4, 1.3)	0.5 (0.4, 0.6)
Others				
No. of deaths	57	48	14	119
Death rate	0.9 (0.7, 1.1)	1.1 (0.8, 1.4)	1.0 (0.5,1.4)	1.0 (0.8,1.1)

[a]Age-standardized annual death rate per 100 person-years at risk (95% confidence interval). "Deaths certified as caused by AIDS or an AIDS-defining condition, or occurring in individuals who had been reported as having developed an AIDS-defining condition shortly before death. (Includes 27 deaths in which liver disease was reported as the underlying cause: four in 1985-1990;18 in 1991-1996; five in 1997-1999. One of these, who died in 1996, had liver cancer. When these 27 deaths are included, the annual death rate (%) from liver disease in HIV-infected patients was 0.7 (0.1, 0.8) during 1985-1999 and 0.2 (0.1,0.3), 1.2 (0.9, "1.5), andI.2 (0.6, '1.7) during 198.5-"1990. 199'1-1996, and 1997-1999, respectively. "tncludes seven liver cancers: one in 1985-1990, four in 1991-1996. and two in 1997-1999.

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Data collection was carried out by Rosemary Spooner, Sau Wan Kan, Paul Giangrande and Sarah Darby. The statistical analysis was designed by Sarah Darby and carried out by Sarah Darby and Sau Wan Kan, All members of the Analysis and Writing Committee participated in the preparation of the report.

UK haemophilia centres contributing data to this study

Aberdeen: Grampian Area Haemophilia Centre, Aberdeen Royal Infirmary. *As/!ford:* Haematology Laboratory, Ashford Hospital. *Bangor:* Haemophilia Centre, Ysbyry Gwynedd. *Barnstaplc:* Department of Haematology. North Devon District Hospital. *Basingstolec:* The North Hampshire Haemophilia Centre, North Hampshire Hospital. *Bath:* Department of Haematology, Royal United Hospital (North). *Bedford:* Department of Haematology, Bedford Hospital Trust. *Belfast:* N.1. Haemophilia Comprehensive Care Centre, Belfast City Hospital; Royal Belfast Hospital for Sick Children. *Birminguam:* Haemophilia Unit. Queen Elizabeth I-Iospital; Department of Haematology, The Birmingham Children's Hospital NHS Trust. *Blackburn:* Department of Haematology. Blnckburn Royal Infirmary. *Bournc-moutn/Poole:* Department of Haematology, Poole General Hospital. *Br(u!ford:* Bradford Haemophilia Centre; Department of Paediatrics, I3radford Royal Infirmary. *Brighton:* Department of Haematology, Royal Sussex County Hospital. *Bristol:* Avon Haematology Unit, Bristol Oncology Centre; Department of Oncology/ BMT, Royal Hospital for Sick Children. *Bury St Edniuuds:* The West Suffolk Hospital, *Cambetlcy:* Department of Pathology, Frirnley Park Hospital. *Cambridge:* Department of Clinical Haematology, Addenbrooke's Hospital. *Canterhu ry:* Haemophilia Centre, Kent and Canterbury Hospital. *Cardiff:* Departmcnt of Haematology, University Hospital of Wales. *Carlisle:* Department of Pathology, Cumberland Infirmary. *Carslialton:* Department of Haernarology, St Helier Hospital. *Cheunsford:* Department of Haematology, Broornfield Hospital. *Chertsev:* Department of Pathology, St Peter's Hospital. *Chichester:* Haematology Laboratory, St Richard's Hospital. *Colchester:* Department of Haematology, District General Hospital. *Coventry:* Department of Haematology, Walsgrave Hospital NHS Trust. *Derby:* Derbyshire Royal Infirmary. *Dordiester:* Department of Haematology, West Dorset Hospital. *Dundee:* Haemophilia Unit, Ninewells Hospital. *Eastbournc:* Department of Haematology, District General Hospital. *Edinburgh:* Haemophilia Centre, Royal Infirmary; Department of Haematology, Royal Hospital for Sick Children. *Epsont:* Haematology Laboratory, Epsom General Hospital. *Exeter:* Department of Haematology, Royal Devon and Exeter Hospital (Wonford). *Glasgow:* Haemophilia and Thrombosis Centre, Glasgow Royal Infirmary; Department of Haematology, Royal Hospital for Sick Children. *Harlow:* Department of Haematology, Princess Alexandra Hospital. *Harrogate:* Harrogate District Hospital. *Harrow:* Depart-

ment of Haematology, Northwick Park Hospital. *Hereford:* Department of Haematology, County Hospital. *Hillingdon:* Hillingdon Hospital. *Huddersfield:* Department of Haematology, Huddersfield Royal Infirmary. *Hull:* Department of Haematology, Kingston General Hospital. *Inverness:* Department of Haematology, Raigmore Hospital. *Ipswich:* The Ipswich Hospital. *Kettering:* General Hospital. *Kingston upon Thames:* Haematology Laboratory, Kingston Hospital. *Lancaster:* Department of Haematology, Royal Lancaster Infirmary. *Leeds:* Haemophilia Unit; Department of Paediatric Haematology, St jarncs' University Hospital. *Leicester:* Haemophilia Centre, Leicester Royal Intirmary. *Lincoln:* Lincoln County Hospital. *Liverpool:* Haematology Labm'atories,Royal Liverpool University Hospital; Department of Haematology, Royal Liverpool Children's Hospital, Alder Hey. *London:* Department of Haematology, Imperial College School of Medicine, Hammersmith Hospital; Department of Haematology, St Mary's Hospital; Department of Haematology, Great Ormond Street Hospital for Sick Children; Department of Haematology, Barts and The London Haemophilia Centre, Royal London Hospital; Haemophilia Centre, Royal Free Hospital; Department of Haematology, University College Hospital; Department of Haematology, King's College Hospital; Department of Haernatology Lewisham Hospital; Haemophilia Centre, St Thomas' Hospital; Department of Haematology, St Georgc's Hospital. *Luton:* Department of Pathology, Luton and Dunstable Hospital. *Manchester:* University Department of Haematology. Manchester Royal Infirmary; Department of Haematology, Royal Manchester Children's Hospital. *Mediua»:* Medway Maritime Hospital. *Milton Kcvues:* Department of Haematology, Milton Keynes Hospital. *Middlesborough:* Department of Clinical Pathology, Middlesborough General Hospital. *Newcastle upon Tyne:* Haemophilia Centre, Royal Victoria Infirmary. *Newport:* Department of Haematology, Royal Gwent Hospital. *Northantpton:* Department of Haematology, Northampton General Hospital NHS Trust. *Norwich:* Department of Haematology, Norfolk and Norwich Hospital. *Nottingham:* Department of Haematology, University Hospital, Queen's Medical Centre. *Oxford:* Oxford Haemophilia Centre, Churchill Hospital. *Peterborough:* Peterborough District Hospital. *Plymoutl«:* Derriford Hospital. *Ponsuiouth:* Central Laboratory, East Wing, St Mary's General Hospital. *Salisburv:* Department of Pathology, Salisbury District Hospital. *Sheffield:* Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital; The Roald Dahl Paediatric Haematology Centre, The Children's Hospital. *Slucusbur»:* Department of .Pathology, Shrewsbury Hospital (Copthorne North). *Southampton:* South Hampshire Haemophilia Centre, South Hampshire General Hospital. *Southend:* Department of Hacmatology, Southend Hospital. *St Lconards-On-Sea:* Conquest Hospital. *Stoke 01/ Trent:* Central Pathology Laboratory, North Staffordshire Hospital. *Sunderland:* The District General Hospital. *Swansea:* Swansea Haemophilia Centre, Singleton Hospital. *Taunton/Yeovil:* Department of Haematolcgical Medicine, Taunton and Somerset Hospital. *Thornton Heath:* Haematology Laboratory, Mayday Hospital. *Torquav:* Department of Haematology, Torbay Hospital. *Truro:* Department of Haematology, Treliske Hospital. *Tunbridge Wells:* Pembury Hospital. *Wuitclmvc«:* West Cumberland Hospital. *Winchester:* Pathology Laboratory, Royal Hampshire County Hospital. *Wolvemampton:* Department of Haemarology, New Cross Hospital. *Worcester:* Department of Haematology. Worcester Royal Infirmary NHS Trust. *Worthing:* Haematology Laboratory, Worthing Hospital. *York:* York District Hospital.

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Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HlV

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Since the 1970s, mortality In the hernophllla population has been dominated by human Immunodeficiency virus (HIV) and few reports have described mortality in unlnfected Individuals. This study presents mortality In 6018 people with hernophllla A or B In the United Kingdom during 1977 to 1998 who were not Infected with HIV, with follow-up until January 1, 2000. Given disease severity and factor inhibitor status, all-cause mortality did not differ significantly between hemophilla A and hemophilla B. In severe hernophllla, all-cause mortality did not change significantly during 1977 to 1999. During this period, It exceeded mortality in the general population by a factor of 2.69 (95% confidence interval [Cl): 2.37-3.05), and median life expectancy In severe hemophilla was 63 years. In moderatel mild hemophllla, all-cause mortality did not change significantly during 1985 to 1999, and median life expectancy was 75 years. Compared with mortality in the general pcputanon, mortality from bleedIng and Its consequences, and from liver diseases and Hodgkln disease, was Increased, but for ischemic heart disease it was lower, at only 62% (95% Cl: 51%-76%) of general population rates, and for 14 other specific causes It did not differ significantly from general population rates. There was no evidence of any death from variant Creutzfeldt-Jakob disease or from conditions that could be confused with it. (Blood. 2007;110:815-825)

Introduction

In the late 1960s the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) initiated a nationwide database for planning the care of people with congenital blood coagulation defects. From 1976 to 1998. it included details of all males diagnosed with hemophilia A or hemophilia B regardless of whether they required treatment. and it was updated each year adding newly diagnosed individuals.' The information held on the database has been used to carry out a study of mortality in the complete hcmophilia population of the United Kingdom over a period of 23 years. This paper presents information on people with hemophilia A or B who were not infected with human irnmunodcficiency virus (HIV). It describes how all-cause mortality varied with type and severity of hcmophilia, calendar period. and age, It also presents life expectancy, and mortality from specific causes of death, including deaths involving intracranial hemorrhuge or other bleeds. Mortality in those who were infected with HIV has been reported clscwhcre.? as has the influence of inhibitors on rnortuliry.'

Patients, materials, and methods

The present study includes all males with hemophilia A or B who were registered with the UKHCDO database during 1977 to 1998. Participating hernophilia centers arc listed in the Appendix at the end of this article. Their vital status on January I, Z000. was ascertained using information from Haemophilia Centres and the National Health Service Central registers. Death certificates were obtained 1'01' those who had died, and the underlying cause of death coded tu the ninth revision of the International Classification of Diseases.[4] This was done using the standard rules except that if the underlying cause was described as hernophilia due to some other, more specilie. cause then the more specific cause was taken. For example, if a death was described on the death ccrtiticute as caused by hepatitis due III hcrnophilia but with no mention of bleeding then it was classified as due lO hepatitis. Also. if a death was described as caused by hcmorrhagc due to hemophilia with no mention of any other condition it was classified as due 10 hemorrhage. However. deaths described as caused by bleeding and also by another condition. both due to hemophilia. were clussified as due 10 hcmophilia, Similarly. deaths described us caused by the late effects of hcmophilic bleeds were classified as duc 10 hcmophilia.

Infonnation on the cause of death was often available from the hemophiliu centers and was added to the information from the death certificate to identify individuals for whom intracranial hernorrhage, other bleeds. liver cancel'. 01' liver disease contributed in causing the death. All availuhle information on cause of death was also examined for neurologic conditions that might indicate variant Creutzfeldt-Jakob disease (vCJD) and, for those with hemophilia B, for u diugnosisof pulmonary embolism or disseminated intravascular coagulation (DIC). Approval for the study was obtained from the Central OXford Ethics Research Committee. The study was conducted in accordance with the Declaration of Helsinki.

Person-yearsat risk were calculated as the time from date of registration on the UKHCDO database to date lust seen. For most individuals this was the earliest of dale of death. date of emigration. or January I, Z000. However, for the few individuals who could not be traced on the National Health Service Registers, this was the date of lust recorded contact with a hernnphilia center. HIV testing became available late in 1984 and virtually all hemophiliu patients who had received potentially infected blood

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products were tested in 1985. For each I·IIV-infeeted individual, a date of seroconversion was estimated using the dates of all relevant HIV-positive and HIV-ngativc blood samples.' The median estimated date of HIV infection was December 1982, and for more than 80% of those who became infected the estimated date of seroconversion was during 1981 to 1983. For many hemophilia patients who died during 1980 to 1985. their HIV status was never determined and it has previously heen shown" rhat HIV had little impact on mortality prior to 1985. Therefore. those who were subsequently shown 10 be infected with HIV contributed to the person-years at risk until January I, 1985, or until their estimated date 01' seroconversion, if later, Deaths and person-yeurs at ages 85+ years were excluded from the analysis.

Person-years and deaths were subdivided by current age (5-year groups), calendar period (single years), whether the individual had ever developed inhibitors, and type and severity of hemophilia. Death rates were calculated as the ratio of the number of deaths 10 the number of person-years at risk. Factors influencing mortality were studied using Poisson regression. To compare the death rate from specific causes with national mortality rates, the number of deaths expected for each cause of death of interest was calculated by multiplying the person-years at risk by the corresponding age- and calendar yeur-spccific male national mortality rate, derived from the World Health Organization database (hllp:11 www.who.inl1whosislrnort/downloadlen/index.htllll). Significance tests and confidence intervals assumed that the number of observed deaths had a Poisson distribution and that the number of expected deaths was fixed. Significance tests were 2-sided. Calculations were carried out using version 5.0 of the computer package Stata (hllp:llwww.stala.cOm).

Results

Characteristics of the study population

There were 6018 males with hemophilia A or B registered on the UKJ-lCDO nationwide database during 1977 to 1998 who were either not infected with HIV or who died before January I. 1985 (Table I). Eighty-one percent (4874) had hemophilia A and 19.0% (1144) had hernophilia B. The vital status on January I, 2000, was established for all but 3.2% (194). Among the 1320 people with severe hernophilia. 18.9% (250) had died by the end of the follow-up period, as had 12.0% (177/1476) of people with moderate hernophilia and 13.5% (435/3222) of people with mild hemophilia.

Mortality from all causes

The annual age-specific death rate from all causes for people with severe hemophilia was nearly twice that for people with moderate or mild hcmophiliu (death rate ratio: 1.82; 95% confidence interval [CIl: 1.54-2.16: $P < .001$. after adjustment for calendar period, development of inhibitors and type of hemophilia). The all-cause death rates in people with moderate hcmophilia and people with mild hcrnophilia did not differ significantly from each other (adjusted death rate ratio: 1.15 for mild compared with moderate; 95% Cl: 0.95-1.39; $P = .15$). and in subsequent analyses moderate and mild hernophilia were considered together.

Among people with severe hernophilia, those with hcmophilia B had a somewhat lower all-cause death rate than those with hemophilia A (adjusted death rate ratio: 0.71), but the difference did not reach statistical significance (95% Cl: 0.49-1.04: $P = .07$), while among those with moderate/mild hernophilia the death rate from all causes was very similar in people with hemophilia A and hemophilia B (adjusted death rate ratio: 0.96: 95% Cl: 0.77-1.21; $P = .75$) (Table 2). The number of people with hernophilia B in the study was not large enough for separate analysis and, in subsequent analyses, hemophilia A and hemophilia B have been combined unless otherwise indicated.

Among people with severe hemophilia the all-cause death rates in calendar periods 1977 to 1984, 1985 to 1992, and 1993 to 1999 were very similar (death rate ratios adjusted for age. development of inhibitors, and type of hcmophilia: 1.00, 0.96 [95% Cl: 0.71-1.30], and 0.96 [95% Cl: D.71-1.31] in 1977 to 1984, 1985 to 1992, and 1993 to 1999, respectively: P for trend: .78). In contrast, among those with moderate/mild hemophilia the all-cause death rate in 198510 1992 and 1993 to 1999 was about 20% lower than in 1977 to 1984 (adjusted death rate ratios: 1.00. 0.81 [95% Cl: 0.65-1.0 Il and 0.79 [95% Cl: 0.64-0.98]). and the trend with calendar period reached statistical significance (P for trend: .(5).

In view of the calendar period-specific results. analyses of age-specific mortality and life expectancy considered time periods 1977 to 1999 for people with severe hemophilia and 1985 to 1999 for people with moderate/mild hernophiliu. In both severe and moderate/mild hemophilia, the death rate from all causes exhibited the same age pattern as that of the general population in that it was relatively high in children younger than 5 years, fell to a minimum at ages 5 to 14 years. and then rose progressively with increasing age (Table 3). At every age, the all-cause death rate in people with severe hemophilia was higher than that in people with moderate/mild hemophiliu, and the all-cause death rate in those with moderate/mild hemophiliu was higher than that of the general male population of the United Kingdom in 1999 (Table 3).

Table 1, Numbers of males In the United Kingdom with hemophllla A or B and registered In the UK Haemophilia Centre Doctors' Organisation nationwide database 1977 to 1998

	Infected wlthHIV	Not Infected with HIV'			
		Sevoret	Moderatot	MIldt*	Total
Typo of homophllla					
A	1204 (97.7)	2706 (84.0)	1110 (75.2)	1056 (80.2)	4874 (81.0)
B	28 (2.3)	516 (16.0)	366 (24.8)	262 (19.8)	1144 (19.0)
VIlal status on January 1,2000					
Alive and resident in United Kingdom	434 (35.2)	1013 (76.7)	1246 (84.4)	2636 (81.8)	4895 (81.3)
Dead	788 (63.9)	250 (18.9)	177 (12.0)	435 (13.5)	862 (14.3)
Emigrated	6 (0.5)	14 (1.1)	10'(0.7)	43 (1.3)	67 (1.1)
Lost to follow-up	4 (0.3)	43 (3.2)	43 (2.9)	108 (3.4)	194 (3.2)
Totall\	1232 (100.0)	1320 (100.0)	1476 (100.0)	3222 (100.0)..	6018 (100.0)

Data are presented as number 01patients (%).

'Includes all individuals who died prior to January 1. 1985, es HIV testing was not generally available before then and it has been shown that HIV had little Impact on mortality prior to 1985.'

tSevere: clotting factor concentration less than 1 international unll per dectliter, moderate: 1-5: mild: >5.

;Includes 121 Individuals with unknown severity.

IIExcludlng individuals treated in the United Kingdom who usually live overseas.

Table 2. Factors affecting mortality from all causes In males In the United Kingdom with hemophllla A or B who were not Infected with HIV, 1977 to 1999

	Severe hemophllla			Moderate/mild hemophllla		
	No. of deaths'	Death rate rallot		No. 01 deaths'	Death rate rallot	95%CI
Type .01hemophllla .						
A§	213	1.00		470	1.00	
B	33	0.71	0.49·1.04	90	0.96	0.77-1.21
P for difference		.07			.75	
Calendar period						
1977-1984+	108	1.00		146	1.00	
1985·1992	69	0.96	0.71-1.30	191	0.81	0.65-1.01
1993-1999	69	0.96	0.71-1.31	223	0.79	0.64-0.98
Plor trend		.78			.05	
Total deaths'	246			560		
Person-years'	27099			71651		

HIV-posilive patients were excluded from 1985 or dale of seroconverslon, if later.

— indicates not applicable.

'Deaths and person-years at ages 85+ years excluded.

tAdjusted for age. whether the patient had ever developed inhibitors. and either calendar period (analyses of type 01 hemophilla) or type of hemophilla (analyses of calendar period).

+Confldence interval.

§Baseline category.

Comparison with mortality rates In the general poputatlon

During 1977 to 1999, the all-cause death rate in severe hemophilia was higher than the corresponding age- and calendar year-specific all-cause death rate in the general male population by a factor of 2.69 (95% Cl: 2.37-3.05; $P < .001$). while for patients with moderate/mild hemophilia it was increased by a factor of 1.19 (95% Cl: 1.09-1.29; $P < .00$ I)(Table 4).

When specific causes of death were examined, mortality rates in the hemophilia population were significantly increased compared with those for the general male population for coagulation defects and for intracranial hcmorrhage (Table 4A "Causes that were significantly increased in the hemophilia population"). In children younger than 5 years. there was a total of 10 deaths from intracranial hernorrhage compared with only 0.013 expected (ratio of observed to expected deaths: 775.19 195% Cl: 371.74-1425.61]). Considering all ages, mortality was also increased compared with the general population for other hernorrhage, for injuries other than suicide and poisoning. for hepatitis and liver disease. and for liver cancer. Of the 42 deaths certified as due to injuries other than suicide or poisoning, either the death certificate or the cause of death information from the hernophilia center indicated that bleeding played a role in 20 (13 severe A, 3 moderate/mild A, 3 severe B, I moderate/mild B). Based on death certificate information. mortality was also increased from "ill-defined cerebrovascular disease" and for "diseases of the digestive system other than liver disease or gastrointestinal hemorrhage," and for most of the deaths in these 2 categories information from the hemophilia ccntcrs indicated that the death was partly or wholly due to bleeding. Mortality was increased for l-Jodgkin disease. based on a total of 4 deaths. For most of the specific causes of death that were Increased compared with the general male population the proportionate increase was substantially greater in people with severe than in people with moderate/mild hernophiliu (Table 4A "Causes that were significantly increased in the hemophilia population").

For ischemic heart disease. the mortality rate in the hemophilia population was only 62% of that in the general male population (95% Cl: 51%-76%) und the proportionate reduction was similar in patients with severe and moderate/mild hcmophilia, although the number of deaths from ischemic heart disease in patients with severe hcrnophilia was small, so that the deficit was not statistically

Table 3. Age-specific mortality rates from all causes In males In the United Kingdom with hemophllla A or B who were not Infected with HIV

	Severe hemophllla, 1977-1999'			Moderate/mild hemophllla, 1985-1999'			All males In the United Kingdom, 1999
	Ne. 01 deatha	Death rate per 1000 Y	95% Cl	No. 01 deaths	Death rate per 1000 Y	95% Cl	Desth rate per 1000 Y
Age, y							
0-4	13	5.1	3.0-8.8	6	2.0	0.9-4.6	1.5
5-14	4	0.7	0.2-1.7	4	0.5	0.2-1.3	0.1
15-24	15	2.6	1.6-4.4	9	1.1	0.8-2.0	0.7
25-34	28	5.8	4.0-8.4	16	1.7	1.1-2.8	1.0
35-44	26	8.0	5.6-11.7	16	2.0	1.2-3.3	1.6
45-54	41	17.8	13.1-24.1	35	5.8	4.2-8.1	4.1
55-64	51	. 39.2	29.8-51.5	71	15.4	12.2-19.5	11.2
65-74	41	66.7	49.1-90.5	135	43.0	36.3-50.9	32.3
75-84	25	133.0	89.9-196.8	122	91.7	76.8-109.5	81.1
Total deaths	246			414			

HIV-posltive patients were excluded from 1985 or date of seroconversion, if later.

-indicates not applicable.

'Results are shown for these calendar periods as all-cause mortalily did not change significantly during 1977-1999 in severe hemophilla or during 1985·1999 in moderate/mild hemophllla (Table 2).

Table 4. Cause-specific mortality during 19n to 1999 in males in the United Kingdom with hemophilia A or B who were not infected with HIV compared with national mortality

	Severe hemophilia			Moderate/mild hemophilia			Total	
Certified underlying cause of death OCD9 code)	Observed deaths	Expected deaths	OIE·	Observed deaths	Expected deaths	OIE·	OIE·	95% CI
A Causes that were significantly increased in the hemophilia population								
Coagulation defects etc (280-289)	14	0.25	55.56§	9	1.33	6.77§	14.55§	9.22-21.83
Intracranial hemOrrhage (ICH, 430-432)t	62	1.58	39.29§	64	6.89	9.29§	14.88§	12.40-17.72
Other or unspecified hemorrhage (OH. 459.0. 578)	27	0.08	341.77§	15	0.54	27.73§	67.74§	48.84-91.57
Injury excl suicide and poisoning (E800-999 excl.E850-869, E9SO-959,E980-989)	17	6.00	2.84§	25	16.34	1.53	1.88§	1.36-2.54
Hepatitis and liver disease (070, 570-573)	12	1.02	11.72§	35	4.70	7.44§	8.21§	6.03-10.91
Liver cancer (155)	10	0.30	32.89§	17	1.70	10.03§	13.51§	8.90-19.65
Ill-defined cerebrovascular disease (lOCO. 436-438)	20	3.48	5.76§	28	23.69	1.18	1.77§	1.30-2.34 •
Digestive system excl. liver and hemorrhage (520-579 excl. 570-573, 578)	4	1.60	2.49	16	8.90	1.80'	1.90'	1.16-2.94
Hodgkin disease (201)‡	1	0.20	4.98	3	0.61	4.94·	4.95·	1.35-12.67
AUcauses in category A	167	14.51	11.51§	212	64.69	3.28§	4.78§	4.32-529
B Ischemic heart disease (IHO, 410-414)	16	25.84	0.62	88	140.69	0.63§	0.62§	0.5HI.76
C Other causes								
Infections excl. hepatitis (001-139,279 excl. 070)	3	0.83	3.62	1	327	0.31	0.98	0.27.2.50
Non-Hodgkin lymphoma (200,202)	0	0.74	0.00	3	3.65	0.82	0.68	0.14-2.00
Other neoplasms (140-239 excl 155, 200-202)	15	2323	0.65	122	128.34	0.95	0.90	0.76-1.07
Endocrine disorders (240-278)	3	1.15	2.60	3	6.04	0.50	0.83	0.31·1.62
Mental disorders (290-319)	0	0.76	0.00	2	4.38	0.46	0.39	0.05-1.41
Nervous system disorders (320-389)	1	1.89	0.53	6	8.38	0.72	0.68	0.27-1.40
Ischemic stroke (IS. 433-435)	1	0.96	.1.04	3	5.38	0.56	0.63	0.17-1.62
Circulatory exclICH, OH. IDCO. IHO & IS (390-459 excl 410-414. 430-438, 459.0)	8	5.74	1.39	36	32.53	1.11	1.15	0.84-1.54
Pneumonia (480-486)	7	32t	2.18	21	18.87	1.11	1.27	0.84-1.83
Other respiratory (460-519 excl. 480-486)	7	5.27	1.33	23	31.80	0.72	0.81	0.55-1.16
Genitourinary diseases (580-629)	3	0.75	4.00	7	4.30	1.63	1.98	0.95-3.64
Musculoskeletal & *connective tissue* (710-739)	2	0.24	8.20	1	1.42	0.71	1.81	0.37-5.28
Other diseases (630-709, 740-799)	2	2.32	0.86	8	4.58	1.75	1.45	_O70-2.67 .
Suicide and poisoning (E850-869, E9SO-959,E9Bo-989)	7	3.88	1.81	15	12.51	1.20	1.34	0.84-2.03
AUcauses in category C	59	SO.97	1.16	251	265.43	0.95	0.98	0.87-1.10.
O Unknown cause	4			9		-	-	
AUcauses	246	91.33	2.69§	560	470.81	1.19§	1.43§	1.34-1.54

HIV-positive patients were excluded from 1985 or date ot *seroconversion.* it later.

- indicates not applicable.

'O/E (observed deaths/expected deaths) is the multiplicative factor by which the age- and calendar year-specitic mortality rate in the hemophilia population differs from the corresponding rate in the general population. 11 is sometimes known as the standardized mortality ratio.

tin children younger than 5 years. mortality from intracranial hemorrhage was as foUows: severe hemophilia 0: 8. E: 0.005. aIE: 1590.43§; moderate/mild hemophilia 0: 2. E: 0.008. aIE: 263.16§; Total aIE: 775.19§ (95% CI: 371.74-1425.61).

‡Two of the 4 deaths from Hodgkin disease were in individuals who had tested negative for HIV (in 1984 and 1986); for one there was no record of any treatment with a blood product, and tor one the diagnosis of hemophilia was made only aller the diagnosis ot Hodgkin disease.

significant when this group was considered by itself (Table 4B "Ischemic heart disease"),

For 14 other specific causes of death. including non-Hodgkin lymphoma, ischemic stroke, and suicide and poisoning, mortality rates in the hemophilia population did not differ significantly from those in the general male population for either severe hemophilia. or for moderate/mild hernophilia or for both groups combined (Table 4C "Other causes").

When thc analysis shown in Table 4 was repealed separately for those with hemophilia A and B the results were similar, In particular for ischemic heart disease the ratio of observed to expected deaths in hernophilia A was 0.64 (95% Cl: 0,52-0.79. based on 89 deaths) while in hernophilia B it was 0,54 (95% Cl: 0.30-0.88. based on 15 deaths),

Deaths involVing Intracranial or other hemorrhage

In both severe and moderate/mild hernophilia, the variation in the death rate with age for deaths from bleeding of any type and for deaths from intracranial hernorrhage resembled that for all causes. with high rates at ages younger 5 years, falling to a minimum at ages 5 to 14 years. and increasing progressively from age 15 years (Table 5). The death rates in people with hernophilia B were similar to those for people with hcmophilia A for bleeding of any type and for intracranial hcmorrhage, after adjusting for age, calendar period, and inhibitor status (death rate ratios B versus A: severe-bleeding of any type. 0.89 [95% Cl: 0.55-1.45] $P = .64$; iruracranial hcrnorrhage. 0.90 195% Cl: 0.48-1.69J $P = ,74$; moderate/mild-bleeding of any type, 0.94 [95% Cl: 0.61-1.45] $P = .78$: intracranial hemorrhage, 0,79 [95% Cl: 0.42-1.49J $P = .45$).

In severe hemophilia. when all patients (ie, both those who had developed inhibitors and those who had not) were considered together. the annual age-standardized mortality rate for deaths involving any type of bleed decreased progressively from 8.9 per 1000 during 1977 to 1984. to 8.3 during 1985 to 1992, and to 5,6 during 1993 to 1999 (P for trend: .05; Table 6). However, when the analysis was repeated removing those individuals who had developed inhibitors from the time that they were first reported, the annual mortality rate among people with severe hemophilia but who had not developed inhibitors did not decrease during the period studied. with values of 5,5. 4.9. and 5.6 per 1000 during 1977 to 1984, 1985 to 1992, and 1993 to 1999. respectively (P for trend: .90). For deaths involving intracranial hcrnorrhage. there was little evidence that the mortality rate changed during the period studied either in all patients with severe hernophilia (annual age-standardized mortality rates: 4,8. 4.8. and 3.4 per 1000 during 1977 to 1984. 1985 to 1992, and 1993 to 1999, respectively: P for trend: *040)* or when just those who did not develop inhibitors were considered (rates: 3,1, 3.5, and 3,5 per 1000, respectively), Similarly. among patients with moderate/mild hcmophilia, there was little evidence that the mortality rate for all deaths involving bleeding or for deaths involving intracranial hemorrhage decreased over the period studied after the exclusion of patients who developed inhibitors (Table. 6).

At ages younger than 5 years. intracranial hemorrhage was involved in II of a total of 13 deaths from all causes in severe hernophilia at ages younger than 5 years. and only 2 were in patients with inhibitors. while in moderate/mild hemophilia 3 of the 6 deaths at ages younger than 5 years involved intracranial hcmorrhage, and none was in a patient with inhibitors (Tables 5-6), The intracranial hernorrhage death rate in age group younger than 5 years did not change significantly with calendar period (P for trend in severe = ,99; P for trend inmoderate/mild = .68: Table 6).

Table 5. Age-specIfIc mortalIly rates for deaths InvolvIng bleeding or IntracranIal hemorrhage In males In the UnIted Kingdom with hemophIlIa A or B who were not Infected with HIV, 1977 to 1999

	Sovore homophIlIa				Moderate/mild hemophIlIa			
	No. 01deaths				No, 01deaths			
Age, y	Total	No. with Inhibitors	Death rate per 1000 y	95"10 CI'	Total	No. with Inhibitors	Death rate per 1000 y	95% CI
Deaths Involving bleeding 01any type								
0-4	11	2	4.3	2.4-7.8	3	0	0,6	0.2-2.4
5-14	2	1	0,3	0.1·1,3	2	1	0,2	0,0'0.7
15·24	9	4	1.6	0.6·3,1	4	0	0,3	0,1'0,6
25·34	15	5	3.1	1,9-5.1	5	2	0.4	0,2'0.9
35-44	22	9	6.3	4,2-9,6	11	1	1.1	.0,8-1,9
45-54	26	6	11,3	7,7-16,5	18	0	2,2	1.4,3,6
55·64	26	11	20,0	13,6·29,3	35	3	5.7	4.1-7.9
65·74	23	7	37.4	24.9·56,3	53	1	13,1	10,0'17,2
75·84	11	3	56.5	32.4·105,7	29	2	18.4	12.6'26.5
Total	145	46			160	10		
Deatha Involving Intracranial hemorrhago								
0-4	11	2	4,3	2.4·7,8	3	0	0,6	0.2'2.4
5·14	1	1	0,2	0,0·1,2	1	1	0,1	0,0'0,6
15·24	4	1	0,7	0.3-1.9	3	0	0.2	0.1'0.7
25-34	9	2	1.9	1,0·3,6	1	0	0,1	0,0'0,6
35-44	12	4	3.4	2.0-6.1	7	0	0.7	0,3·1.4
45-54	13	2	5,6	3,3-9,7	10	0	1,2	0,7'2.3
55·64	16	6	12,3	7,5·20,1	21	1	3.4	2.2-5.2
65·74	13	3	21,1	12,3-36.4	28	1	6,9	4,8·10,0
75-64	5	2	26,8	11,1-63.9	10	1	6.4	3.4-11,8
Total	64	23			64	4		

Includes all deaths willl bleeding/Intracranial hernorrhage mentioned on Ihe death certillcate or notified by the hemophilla center. HIV-positive patients were excluded from 1965 or dale of seroconversion, if later.

-Indicates not applicable,

'Confidence Interval.

Table 6. Trend with calendar period in mortality rate for deaths involving bleeding or intracranial hemorrhage in males in the United Kingdom with hemophilia A or B who were not infected with HIV, 1977 to 1999

	severe				Moderatelmild			
	All patients		Excluding inhibitors'		All patients		Excluding inhibitors'	
Calendar period	No. of deaths	Rate per 1000 vt (95% CI)	No. of deaths	Rate per 1000 yt (95%CI)	No. of deaths	Rate per 1000 yt (95% Cl)	No. of deaths	Rate per 1000 yt (95% Cl)
Deaths involvIn9 bleeding of any type. all ages								
19n-1984	72	8.9 (6.6-11.2)	44	5.5 (3.8-7.2)	46	2.5 (1.8-3.3)	43	2.0 (1.4-2.6)
1985-1992	41	8.3 (5.7-11.0)	24	4.9 (2.9-6.8)	55	2.0 (1.4-2.5)	52	1.6 (1.2-2.1)
1993-1999	32	5.6 (3.6-7.6)	29	5.6 (3.5-7.7)	59	. 1.8 (1.3-2.3)	55	1.6 (1.1-2.0)
Total deaths/person-years	145/27099	–	97/23833		*160fi1651*		150/70 *657*	
Pforlrend		.05	–	.90		.08		.16
Deaths involving intracranial hemorrhage. all ages								
19n-1984	39	4.8 (3.1-6.5)	25	3.1 (1.8-4.3)	26	*IA (0.8-1.9)*	24	1.1 (0.7-1.5)
1985-1992	24	4.8 (2.8-6.8)	17	3.5 (1.8-5.1)	34	1.2 (0.6-1.6)	33	1.1 (0.7-1.4)
1993-1999	21	*304(1.9-4.9)*	19	3.5 (1.9-5.1)	24	0.7 (0.4-1.0)	23	0.7 (0.4-0.9)
Total deaths/person-years	84/27099	–	61/23833		84/71 *651*		*80fi0657*	
Pfortrend		*040*	–	.58		.02		.07
Deaths involving intracranial hemorrhage. younger than 5 y‡								
19n-1984	5§	5.5 (2.3-13.1)	4	4.5 (1.7-12.1)	0	0.0	0	0.0
1985-1992	2¦	2.1 (0.5·8.3)	1	1.1 (0.2-7.8)	2"	*IA (004-5.8)*	2	*IA (0.4·5.8)*
1993-1999	4¶	5.9 (2.2·15.8)	4	6.7 (2.5-17.9)	1ft	0.6 (0.1-4:6)	1	0.7 (0.1-4.7)
Total deathsrperscn-years	11/2554	–	9/2376		3/3896		3/3838	
PfOrlrend		.99	–	.65		.68		.67

Indudes all deaths with bleedinglintracraniaJ nernorrnaqe mentioned on the death certificate or notified by the hemophilia center. HIV-positive patients were exduded from 1985 Ordate of seroconversion, if later.
— indicates not applicable.
"Exduding both deaths and person-years subsequent to the development of inhibitors.
tDeath rates direclly standardized for age to the age distribution of all patients.
‡All the deaths involving bleeding in patients younger than 5 years involved intracranial hemorrhage.
§HemophiliaA at ages: younger than 1 month. 10 months. 2.9 years. 3.9 years (with inhibitor). and 4.7 years.
iiHemophilia A at ages: younger than 1 month and 1.7 years (with inhibitor).
'IHemophilia A at ages: younger than 1 month (2 children) and 1.0 year. Hemophilia B at younger than 1 month.
""*Hemophilia* A at ages 1.4 and 2 *years.*
ttHemophilia A at younger than 1 month.

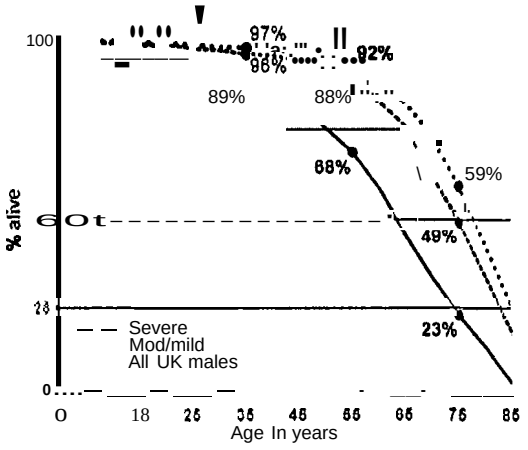

Figure 1. Survival In men In the United Kingdom with hemophllla who were not Infected with HIV and In the general male population of the United Kingdom in 1999. Calculations based on the data summarized in Table 3.

Of the 9 children younger than 5 years who died with intracrunial hemorrhage during 1977 to 1992.2 were younger than one month. one was 10 months. and the remainder were lA. 1.7. 2.0. 2.9. 3.9. and 4.7 years. while for the 5 such children dying during 1993 to 1999. 4 were younger than one month and one was aged I year. Four (I severe A at 10 months in 1980. 2 severe A in 1981 and 1988. and I moderate A in 1992. all at ages 1-4 years) were recorded as sporadic cases. I (severe A at I week in 1985) was recorded as coming from a known hemophilia family. and for the remainder no information was available.

Deaths Involving vCJD, pulmonary embolism, or DIC

Variant CfD was not mentioned specifically in the cause of death information for any individual. Nor was there any mention of any spongiform encephalopathy, or of any other condition that might be confused with these diseases. Of the 96 deaths that occurred in hemophilia B (44 of which involved bleeding), pulmonary embolism was reported in 2 patients (onc in 1981 in a patient with pancreatic cancer. and onc in 1987 as a postoperative complication). and DIC was reported in 2 patients (who died in 1980 and 1985).

Life expectancy

In severe bemophilia, the proportions of individuals surviving 10 ages 35. 55. and 75 years were 89%. 68%, and 23%. respectively (Figure I). and median life expectancy was 63 years (Table 7 "AII causes of death"), In moderate/mild hemophilia. the proportions surviving to ages 35, 45, and 55 were 96%. 88%, and 49%, respectively. and median life expectancy was 75 years. For ull United Kingdom males in 1999. median life expectancy was 78 years. Thus. in severe hemophilia median life expectancy was 15 years less than that of the general male population and in moderate/mild hemophilia it was 3 years less. To investigate how much of the reduction in life expectancy compared with the general population could be attributed to liver disease. the life expectancy calculations were repeated omitting all the deaths for which either the information on the death certificate or the information from the hcmophilia ccnter mentioned liver disease or liver cancer. In severe hcmophiliu, omission of the deaths associated with liver disease increased median life expectancy to 66 years, while for moderate! mild hemophilia median life expectancy increased to 77 years.

Discussion

StUdy design

This is the largest follow-up study ever performed of people with hcmophilia and it covers the longest period of follow-up. The study includes the complete population of United Kingdom residents diagnosed with hernophilia A or B during a period of more than 20 years. thus eliminating the possibility of bias that is present in studies based on cross-sectional surveys of hcmophilia populations, where there arc inevitably" number of nonrespondents, and in which children who die in the first few years of life lend to be underrepresented. leading to estimates of life expectancy from birth that arc higher than the true value. Additionally. the study has made use of the nationwide nagging system available in the United Kingdom via the National Health Service Central Registers to eliminate duplicate records for individuals who attended many hcmophilia ccnters or who changed their name. The central system of nagging has also enabled ascertainment of the appreciable number of deaths that occur in people with hemophilia but without the knowledge of any hernophilia ccntcr,

The study makes substantial use of the cause of death as given on the death certificate. Certified causes of death arc derived from information recorded at the time of the death and arc derived in a similar way for all deaths. regardless of whether the person involved had hemophilia. They thus provide an appropriate basis for assessing the magnitude of the overall death rate in the hernophilia population as a whole. and also for comparisons of cause-specific death rates between people with hcmophilia and the general population. For some analyses, the certified cause of death information was supplemented by information on cause of death

Table 7. Life expectancy from birth In males In the United Kingdom with hemophllla who were not Infected with HIV, and In the general male population of the United Kingdom

	Age until slated percentage of population survived, y			
Population	90%	75%	50%'	25%
All causes of deatht				
Males with severe hemophilia	33	50	63	74
Males with moderate/mild hemophilia	52	65	75	63
All males in the United Kingdom, 1999	58	69	78	65
Excluding all deaths with liver disease or liver cancer mentioned on death certificate or notified by hemophllla center‡				
Males with severe hemophilia	34	52	66	77
Males with moderate/mild hemophilla	56	67	77	64

"Median life expectancy.
tCalculations based on data summarized in Table 3.
;Excluding 38 deaths in severe hemophilla and 64 deaths in moderate/mild hernophilla.

obtained directly from the hemophilia center involved. Both types of information arc subject to limitations. For example. not all conditions present at the time of death may be included. Also, in a person with hemophilia and liver disease it may be difficult to distinguish between bleeding secondary to liver disease and unrelated to hemophiliu, and bleeding in which hemophilia plays a role. There is, therefore. inevitably some uncertainly in the specification of the underlying cause of death,

For the majority of the period covered by this report. mortality in the hcrnophilia population as a whole was dominated by deaths related to HIV. Consequently few reports in recent years have focused on mortality patterns in people with hernophilia who arc not infected with HIV and who. at present, form the majority of the hemophilia population in most countries. The current report has made use of the extensive information on HIV test results available for the United Kingdom hemophilia population, and from 1985 onward. which is when HlV-reluted mortality began to increase in this population," each HlV-infccted individual has been removed from the population under study on his estimated date of HIV seroconversion, thus enabling the number of person-years at risk in HlV-negativc individuals to be computed and creating appropriate denominators for the calculation of age-specific death rates in the Hlv-ncgutive hcrnophilia population. Similarly. the few individuals whose vital status could not be ascertained at the end of the follow-up were removed from the study population on the date they were last known to be alive.

Mortality from all causes and life expectancy

The all-cause mortality rate for the complete population of people with severe hemophilia changed little during the entire periud 1977 to 1999 (Table 2). and median life expectancy for those with severe hcmophilia was 15 years lower than for the general male population in 1999, at 63 compared with 78 years (Table 7). Most of the reduction in life expectancy in severe hemophilia was due to the consequences of bleeding. with liver disease making only a small contribution.

For moderate/mild hcmophilia, all-cause mortality was lower during 1985 to I999 than it had been during 1977 to 1984 (Table 2). This may either be a real decrease in mortality. or it may simply reflect an increase in the coverage by the database of individuals with moderate or mild clotting defects who do not need regular treatment. During 1985 to 1999, the all-cause mortality rate in moderate/mild hernophiliu remained stable (Table 2) and median life expectancy was 75 years. 3 years less than that of the general male population in 1999 (Table 7) and most of the difference was accounted for by liver disease.

Our estimated median life expectancy from birth of 63 years in severe hernophilia is greater than the value of 57 years at birth reported for the 1960s and 1970s in Sweden,[6] and similar to the value of 63 years at birth reported during 1973 to 1985 in the Netherlands," and 61 years from age I year during 1971 to 1980 reported in the United States." It is, however, considerably less than the 73 years at age I year reported for severe hernophiliu in the absence of HIV infection during 1980 to 1995 in Canada? or the 69 and 70 years from age I year reported during 1985 to 1992 and 1992 to 200 I. respectively. in the Netherlands.[10,11] In the recent Dutch study.[11] the age-specific death rate for HIV-negarlvc individuals with severe hemophilia exceeded that for the general population by a factor of 2.8 (95% Cl: 1.9-4.2), very similar to the factor of 2.69 (95% Cl: 2.37-3.(5) seen in the present study (Table 4). It is. however. unclear why the Dutch study found a near normal life expectancy despite an increased death rate compared with the general population, but one possible explanation might be that the Dutch study underestimated the death rate in young people with severe hcmophilia. It is notable that in the Dutch study the youngest participant was 4 months old and that no deaths were reported in children aged younger than 10 years,[11] compared with 14 deaths at ages younger than 5 years from intracranial hernorrhage in the United Kingdom study (Table 6). It is clear that some deaths were missing in a previous analysis of mortality in people with severe hcrnophilia in the United Kingdom. which wrongly concluded that there was a "near normal expectation of life."[12] The present study suggests that it is still premature to assume that people with severe hemophilia who do not have HIV infection have a normal life expectancy, as some recent authors have done.P:"

Mortality from Intracranial or other hemorrhage

A previous analysis of mortality in this population, focusing on the effect of inhibitors. found that the substantial increase in mortality associated with the development of inhibitors in people with severe hernophilia in the late 1970s had disappeared by the end of the I990s.[3] There has, however. been no corresponding decrease in mortality from intracranial hcmorrhagc or from other bleeds in the remainder of the hemophilia population. Mortality rates from intracranial hcrnorrhage and from bleeding of any type were similar in hcmophilia A and hcmophiliu B, both for patients with a severe disorder and for those with a moderate/mild disorder. Thus the present study provides no support for the hypothesis that hernophilia B is less severe clinically than hemophilia A.[16]

A study of the causes of death in people with hemophilia in Sweden during 1957 to 1980 reported that intracranial hcmorrhage accounted for 38% (15/39) of all deaths in people with severe hcmophilia.'? and the proportion of deaths involving intracranial hernorrhage was only slightly lower than this in the present study, at 34% (84/250). Intrucruniul hernorrhage was also found to be the leading cause of death in studies covering this time period of people with hemophilia at all ages in the Netherlands." the United States,[18,19] and France.P The French study-? reported 3 deaths from intracranial hcmorrhage in nconates during the 1990s.

Primary prophylaxis was not widely used in the United Kingdom until the early 1990s when evidence became available leading to confidence that heat-treated products were free of the risk of viral infections.[2,20-22] and it has never been given on a regular basis to babies younger than about a year, those with significant joint damage. and those with moderate or mild hemophilia. However, from around 1990. children with severe hernophiliu but no appreciable joint damage have been started on prophylaxis from the age of about 18 months and, once started, continue to receive it. In view of this. it noteworthy that of the 9 children younger than 5 years old who died with intracranial hemorrhage during 1977 to 1992,6 were older than one year, while of the 5 such children dying during 1993 to 1999. the oldest was aged one year. Although the numbers involved arc small. this indicates that prophylaxis may be reducing death from intracranial hcmorrhagc in the United Kingdom hcmophiliu population.

Mortality from cardiovascular disease

There was a clear reduction in thc number of deaths from ischemic heart disease compared with the number expected from general population rates. as has previously been observed in studies of mortality in people with hernophilia in the Netherlands[7] (I death observed. 5 expected) and Greece-' (I death observed. 4 expected). A study of hospital discharge rates in hemophilia in the United

States also found a dccrease.P' In the present study. the age-specific death rate from ischemic heart disease was 62% of that in the general population. This is a smaller proportionate reduction than was observed in the Dutch and Greek studies. However. as thc present study is based on a total of 104 deaths from heart disease compared with only I in each of the Dutch and Greek studies, thc present estimate is likely to be the more stable one.

The proportionate reductions in mortality from heart disease were virtually identical in severe and in moderate/mild hemophiliu, at 38% and 37%. respectively (Table 4) and were similar to the value observed in a recent study of mortality from ischemic heart disease among carriers of hernophilia[25] (36%, based on 39 deaths). This argues against a gradually increasing protective effect as concentrations of factor VIII and IX decrease and in tavor of a threshold effect. A detailed study of Dutch patients has shown that the reduction in ischemic heart disease in the hernophilia population cannot be attributed to differences in cardiovascular risk factors such as blood pressure or cholesterol level." Thus it is likely that the reduced mortality from ischemic heart disease seen in people with hernophilia or carriers of the disease is a consequence of some aspect of hcmophilia, although the causal pathway by which this occurs is not yet fully understood.

In the present study, the number of deaths certified as due to ischemic stroke was also lower than the number expected, at 0.63, which would be consistent with hernophilia having a protective effect against ischemic stroke as well as ischemic heart disease (Table 4). However. this estimate is based on only 4 deaths so that the ratio was not significantly different from unity. Also, as in other studies based on death certificates, the death certificate did not specify whether the stroke was ischemic or hernorrhugic for many of the deaths attributed to stroke. Therefore, as yet. no conclusions can be drawn as to the level of ischemic stroke in the hemophiliu population compared with the general population.

Mortality from other causes

Mortality from liver diseases, including liver cancer. was substantially increased compared with mortality in the general population, as would be expected given the high rates of infection with hepatitis C in the hcrnophilia population during the period studied. For causes other than liver diseases. hcmorrhagc, causes indirectly due to bleeding such as accidents. and cardiovascular disease. mortality rates in the hernophilia population were similar to those of the population as whole (Table 4). The small increase in mortality from Hodgkin disease seems likely to be a chance occurrence, and there was no evidence of an increase in non-Hodgkin lymphoma, despite the high levels of hepatitis C infection in this population, although the numbers involved arc small and the data arc insufficient to rule out a weak relationship.Pr" There was no evidence of increased mortality from cancer in general or from infections other than hepatitis as have sometimes been suggested.[7,2Y,.n] and the suicide level in people with hemophilia was similar to that in the general population. Variant ClD was first described in 1996. some 10 years after the first reports of bovine spongiform encephalopathy in cattle in the United Klngdom." While our findings provide some reassurance that people in the United Kingdom with hcmophilia who have received large pool concentrates derived from British plasma have not been affected by this condition, we recognize that this study covers only the first few years of the potential latent period. and a separate surveillance study for this condition has been established by UKHCDO.

Concluding remarks

This study has made use of the UKHCDO nationwide database, together with the ability to ascertain vital status on a nationwide basis via the National Health Service central registers and, for those who have died, the certified cause of death. It has, for the first time, characterized life expectancy and cause-specific mortality in a large hcrnophilia population that was not infected with HIV. The results show that. despite the advances that took place in the rreaunent Or hemophilia during the last 2 decades of the 20th century, mortality from intracranial hemorrhage changed little in the absence of factor inhibitors. They also showed that life expectancy in severe hernophiliu was still 15 years lower than that of men in the general population at the end of the 20th century, while in moderate/mild disease was 3 years lower.

The prospects for the future are good. The study confirms that there is a substantial reduction in mortality from ischemic heart disease in people with hernophilia compared with the general population and, more importantly, the results arc consistent with a substantial reduction in mortality from intracranial hcmorrhage among those receiving prophylaxis. If it is possible to continue studies such as this into the future. then the findings of the present study will form a useful baseline with which future mortality patterns in hernophilia populations can be compared, thus obtaining a quantitative measure of the effect of innovations in hemophilia care on mortality.

Acknowledgments

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Authorship

Contribution: RJ.S., S.W.K.. P.L.F.G.,and S.C.D. coordinated data collection; S.C.D. designed the statistical analysis: S.C.D. and S.W.K. carried out the statistical analysis; all authors participated in the preparation of the report.

A complete list of the participating institutions of the UK Haemophilia Centre Doctors' Organisation can be found in the Appendix.

Conflict-of-interest disclosure: The authors declare no competing Iinancial interests.

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Appendix

United Kingdom Haemophilia Centres contributing data to this study: Aberdeen: Grampian Area Haemophilia Centre, Aberdeen Royal Infirmary.

Ashford: Haematology Laboratory, Ashford Hospital. Bangor: Haemophilia Centre, Ysbyty Gwynedd. Barnstaple: Department of Haematology. North Devon District Hospital. Basingstoke: The North Hampshire Haemophilia Centre. North Hampshire Hospital. Bath: Department of Haematology, Royal United Hospital (North). Bedford: Department of Haematology, Bedford Hospital Trust. Belfast: Northern Ireland Haemophilia Comprehensive Care Centre, Belfast City Hospital: Royal Belfast Hospital for Sick Children. Birmingham: Haemophilia Unit. Queen Elizabeth Hospital: Department of Haematology, The Binningham Children's Hospital National Health Service Trust. Bluckburn: Department of Haematology, Blackburn Royal lntirmary, Bourncmouth/Poole: Department of Haematology, Poole General Hospital. Bradford: Bradford Haemophilia Centre; Department of Paediatrics, Bradford Royal Infirmary. Brighton; Department of Haematology, Royal Sussex County Hospital. Bristol: Avon Haematology Unit. Bristol Oncology Centre; Department of Oncology/ Bone Marrow Transplantation. Royal Hospital for Sick Children. Bury SI. Edmunds: Thc West Suffolk Hospital. Cambcrlcy: Department of Pathology. Frimley Park Hospital. Cambridge: Departrnent of Clinical Haematology, Addcnbrookc's Hospital. Canterbury: Hucmophilia Centre. Kent and Canterbury Hospital. Cardiff: Department of Hacmutology, University Hospital of Wales. Carlisle: Department of Pathology, Curnherland Infirmary. Carshalton: Department of Hacmarology, St Helier Hospital. Chelmsford: Department of Haematology. Broomficld Hnspital. Chcrtscy: Department of Pathology, St Peter's Hospital. Chichester: Haematology Laboratory, St Richard's Hospital. Colchester: Department of Haematology, District General Hospital. Coventry: Department of Haematology. Walsgravc Hospital National Health Service Trust. Derby: Derbyshire Royal Inlirmary, Dorchester: Department of Haematology, West Dorset Hospital. Dundee: Haemophilia Unit, Ninewclls Hospital. Eastbourne: Department of Huernatology, District General Hospital. Edinburgh: Haemophilia Centre, Royal Infirmary; Department of Haematology, Royal Hospital for Sick Children. Epsom; Haematology Laboratory, Epsom General Hospital. Exeter: Department of Haematology, Royal Devon & Exeter Hospital (Wonford). Glasgow: Haemophilia and Thrombosis Centre. Glasgow Royal Infirmary; Department of Haematology, Royal Hospital for Sick Children. Harlow: Dcpanment of Haematology, Princess Alexandra Hospital. Harrogate: Harrogate District Hospital. Harrow: Department of Haematology. Northwick Park Hospital, Hereford: Department of Haematology, County Hospital. Hillingdon: Hillingdon Hospital. Huddersfield: Dcparuncnt of Haematology, Huddersfield Royal Infirmary, Hull: Department of Hacmatology, Kingston General Hospital. Inverness: Department of Haematology, Raigmore Hospital. Ipswich: The Ipswich Hospital. Keucring: General Hospital. Kingston upon Thames; Haematology Laboratory, Kingston Hospital. Lancaster: Department of Hucmatology, Royal Lancaster Infirmary. Leeds: Hacmophilia Unit; Department of Paediatric Haematology, St James' University Hospital. Leicester: Haemophilia Centre, Leicester Royal Infirmary, Lincoln: Lincoln County Hospital. Liverpool: Haematology Laboratories, Royal Liverpool University Hospital; Department of Haemntology, Royal Liverpool Children's Hospital. Alder Hey. London: Department of Haematology. Imperial College School of Medicine, Hammersmith Hospital; Department of Haematology, St Mary's Hospital; Department of Haematology, Great Orrnond Street Hospital for Sick Children: Department of Haematology, Barts and The London Haemophilia Centre, Royal London Hospital; Haemophilia Centre, Royal Free Hospital; Department of Haematology, University College Hospital; Department of Haematology, King's College Hospital; Dcpartrnent of Hacmutology, Lewisham Hospital: Haemophilia Centre, SI Thomas' Hospital; Department of Hacnuuology. St GCOJ'ge's Hospital. Luton: Department of Pathology, Luion and Dunstahle Hospital. Manchester: University Department of Haematology, Manchester Royal Infirmary: Department of Haematology, Royal ManchesterChildren's Hospital. Mcdway: Medway Maritime Hospital. Milton Keynes: Department 01' Haematology, Milton Kcyncs Hospital. Middlesborough: Department of Clinical Pathology. Middlesborough General Hospital. Newcastle upon Tyne: Haemophilia Centre, Royal Victoria Infirmary. Newport: Department of Haematology, Royal Gwent Hospital. Northampton: Department of Haematology, Northampton General Hospital National Health Service Trust. Norwich: Department of Haematology, Norfolk and Norwich Hospital. Nouingham: Department 01' Haematology, University Hospital, Queen's Medical Centre. Oxford: Oxford Haemophilia Centre. Churchill Hospital. Peterborough: Peterborough District Hospital. Plymouth: Dcrriford Hospital. Portsmouth: Central Laboratory, East Wing, St Mary's General Hospital. Salisbury: Department of Pathology. Salisbury District Hospital. Sheffield: Sheffield Haemophilia and Thrombosis Centre. Royal Hallamshirc Hospital; The Rould Dahl Paediatric Haernutology Centre, The Children's Hospital. Shrewsbury; Department of Pathology, Shrewsbury Hospital (Copthorne North). Southampton: South Hampshire Haemophilia Centre, South Hampshire General Hospital. Southend: Department of Haematology, Southend Hospital. St Lconards-On-Sea: Conquest Hospital. Stoke on Trent: Central Pathology Laboratory, North Staffordshire Hospital. Sundcrland: The District Gencral Hospital. Swansea: Swansea Haemophilia Centre, Singleton Hospital. Tauruon/Yeovil: Department of Haernatological Medicine, Taunton and Somerset Hospital. Thorn-Ion Heath: Haematology Laboratory, Mayday Hospital. Torquay: Department of Haematology, Torbay Hospital. Truro: Department of Haematology, Treliske Hospital. Tunbridge Wells: Pcmbury Hospital. Whitehaven: West Cumberlund Hospital. Winchester: Pathology Laboratory, Royal Harnpshire County Hospital. Wolverhampton: Department of Haematology, New Cross Hospital. Worcester: Department of Haematology, Worcester Royal lnfirmary National Health Service Trust. Worthing: Haematology Laboratory, Worthing Hospital. York: York District Hospital.

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More conviction on HIV and AIDS

A thorough study of the death-rate among British haemophilia patients with or without HIV Infection will, for most people, be sufficient proof that the Infection leads to AIDS.

NOT much has recently been heard from those who hold that HIV has nothing or little to do with the causation of AIDS. The letter from Sarah C. Darby *et al.* on page 79 of this issue will be a further reason for discretion of their part. A group of epidemiologists has studied the total membership of the British National Haemophilia Register between 1977 and 1991, using it to tell the respective fates of those who were or were not infected with HIV during the period from 1979-86, when blood products in Britain and most other places were contaminated by HIY. The total of 1,227 people infected at that time amounts to roughly a fifth of the 6,287 people on the register. The most dramatic outcome of the study is that the death rate (from all causes) among those infected with HIV has been roughly ten times greater than among the uninfected, and that the death-rate among the infected is not influenced by the clinical severity of their haemophilia. The group estimates that 85 per cent of the deaths among the infected patients were caused by HIV.

This further evidence of the association of HIV with untimely death is important for several reasons. For one thing, it is the largest study of its kind yet carried out. Where statistical data are used to support claims of association, sheer numbers are important; close on 1,000 of those on the register have died since 1978, enough to make the interpretation statistically significant. It is also relevant that the numbers lost to the register through emigration from Britain and other unspecified causes is small at 3.5 per cent. Suggestions that the conclusions of the study are vitiated by the loss of data for a biased group of individuals, perhaps because those in good health tend to quit the register, are in this case entirely untenable.

The status of this important contribution to the understanding of AIDS must nevertheless be clearly appreciated. It is well known that no amount of statistical argument can by itself prove that a disease is actually caused by the agent with which it is statistically associated. That is why some people still believe that cigarette smoking is not a cause of lung cancer and cardiovascular disease, for example. Even now, there will be ingenious people constructing hypotheses by which the association described can be explained by mechanisms other than those that appear to stare one in the face.

The view that AIDS is caused not by HIV as such but by the injection of drugs of various kinds, "recreational drugs" particularly, and also drugs used as medicines, will nevertheless be more difficult to sustain in the light of the evidence from Darby *et al.* The ten-fold increase of the death rate among those carrying HIV will seem to most people to be sufficient, although it entails the assumption that the treatment of patients for their haemophilia would have depended only on the severity of the disease, not on whether they were infected with HIV.

Yet it is safe to predict that there will be complaints from the obstinate community of the unconvinced that Darby *et al.* have failed to provide full details of the drug regimen followed by the 6,000 people on the register, and that until they do, their conclusion has no force.

The mistake in that opinion, if voiced, would be twofold. First, the data now published are of interest and importance in their own right, as further evidence (if such were needed) that HIV is almost invariably linked with AIDS. As such, they are addressed to the research and medical community at large, not to the company of the unconvinced. Second, the sad truth about debates on controversial issues in science is that there may come a point at which dissenters forfeit the right to make claims on other people's time and trouble by the poverty of their arguments and the exasperation they have caused. The world (to judge from *Nature's* postbag) is full of people who believe that Einstein's relativity is a pack of lies, but who cannot make the claim on other people's attention they would wish.

The tragedy, in the case of HIV and AIDS, is that disbelief in the role of HIV in AIDS has spread from beyond a small company in the research community to a large part of the AIDS community itself. The reasons are unremarkable and pathetic in the strict sense of that word: it is at least uncomfortable for an infected person to know that HIV infection will lead eventually to AIDS. Not for nothing is the knowledge often called a "death sentence". The remedy is not, of course, to pander to wish-fulfilment, but to redouble effort in the laboratory and the clinic. Those who have made the running in the long controversy over HIV in AIDS, Or Peter Duesberg of Berkeley, California, in particular, have a heavy responsibility that can only be discharged by a public acknowledgement or error, honest or otherwise. And the sooner the better. 0

threonine phosphorylation can affect integrin adhesiveness", the substrates involved have not been identified[18].

A model has been proposed in which integrins are endocytosed at the rear of the cell and are recycled forward 19.21. Many integrins, including αvβ3, have been shown to be endocytosed", and it has been shown that recycling receprors are preferentially inserted at the leading edge of migrating cells". It has been difficult to test this model because inhibitors of constitutive endocytotie recycling are nonselective". Because αvβ3 integrins on neutrophils require a specific signalling mechanism to be released from the substrate and endocytosed, we could selectively block this process.

To study endocytosis of αvβ3 integrins, we used a monoclonal antibody that binds to av without blocking binding to vitronectin". (Preincubation with this antibody does not affect the distribution of β3 integrins in the lower adherent membrane of control or [Ca2+]i-buffered cells.) Neutrophils were incubated in suspension with the antibody, plated on vitroneetin and then stimulated to migrate. After 5 min the cells were fixed, permeabilized and labelled with a fluorescent secondary antibody. Figure *3a, c* shows top and side views of a migrating neutrophil. The av integrin is found in numerous vesicles throughout the cell. These vesicles may correspond to the specific granules that were shown previously to contain a vitronectin receptor". Because the primary antibody was initially bound to the surface of intact cells, these integrins must have been endocytosed into the cell.

When $[Ca^{2+}]_i$ was buffered, the integrins were found clustered toward the rear of the cell on the lower surface (Fig. *3b, d).* The low level of intracellular staining in the [Ca2+]i-buffered cells shows that essentially all of the recycling integrins had become trapped on the lower surface during the 5 min that the cells were attached to vitronectin. In separate experiments (not shown), β3 integrins were localized in control or $[Ca^{2+}]_i$-buffered cells by fixing the cells, permeabilizing them and then labelling with antibodies to β3 cytoplasmic domains and fluorescent secondary antibodies. The distribution of the total β3 pool was similar in both cases to the distribution of labelled av shown in Fig. 3. This indicates that essentially all of the αvβ3 integrins are cycling between the surface and endosomes and that they become trapped on the adherent membrane when [Ca2+1 i is buffered.

As shown schematically in Fig. 4, preferential insertion of αvβ3 integrins at the leading edge along with [Ca2+1i-regulated detachment and clearance from the adherent cell surface provides a mechanism for creating a gradient of adhesive strength from the front to the rear of a migrating cell. The inability of neutrophils to migrate on adhesive substrates when this process is blocked provides a clear demonstration that in these cells recycling of integrins to the front of the cell is required for continued migration on vitronectin. 0

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Mortality before and after HIV infection in the complete UK population of haemophiliacs

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DURING 1977-91, 6,278 males diagnosed with haemophilia were living in the UK, During 1979-86, 1,227 were infected with the human immunodeficiency virus (HIV-I) as a result of transfusion therapy (median estimated seroconversion date, October 1982). Among 2,448 with severe haemophilia, the annual death rate was stable at 8 per 1,000 during 1977-84; during 1985-92 death rates remained at 8 per 1,000 among HIV-seronegative patients but rose steeply In seropositive patients, reaching 81 per 1,000 in 1991-92. Among 3,830 with mild or moderate haemophilia, the pattern was similar, with an initial death rate of 4 per 1,000 in 1977-84, risIng to 85 per 1,000 in 1991-92 in seropositive patients. During 1985-92, there were 403 deaths in HIV seropositive patients, whereas 60 would have been predicted from rates in seronegatives, suggesting that 85% of the deaths in seropositive patients were due to HIV infection. Most of the excess deaths were certified as due to AIDS or to conditions recognized as being associated with AIDS.

Since 1976 the UK National Haemophilia Register' has included all UK residents diagnosed with haemophilia A (classical haemophilia, factor VIII deficiency) or haemophilia B (Christmas disease, factor IX deficiency). During 1977-91,2,448 males with severe haemophilia, and 3,830 males with moderate or mild haemophilia were included in the Register and, on) January 1993, 82% were alive, 15% had died and 3% were lost to follow-up (Table J),

During 1979-86, blood products used to treat haemophilia carried a risk of HIV-) infection, and 4,043 patients (2,037 severe, 2,006 moderate or mild) are recorded as having received

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TABLE 1 Males Included in the UK National Haemophilia Register, 1977-91, by severity of haemophilia, HIV-test status and vital status

Vital status on 1 January 1993	Severe haemophIliacs" Tested seropositive for HIV		Moderate or mild haemophIliacst Tested seropositive for HIV		All patients
	No	Yes	No	Yes	
Alive and living in the UK	1,195 (84%)	673 (66%)	3,132 (86%)	135 (65%)	5,135 (82%)
Dead	198 (14%)	341 (33%)	326 (9%)	72 (35%)	937 (15%)
Emigrated	2 (0.1%)	6 (0.6%)	16 (0.4%)	0 (-)	24 (0.4%)
Lost to follow-up	33 (2%)	0 (-)	149 (4%)	0 (-)	182 (3%)
Total	1,428 (100%)	1,020 (100%)	3,623 (100%)	207 (100%)	6,278 (100%)

Several smaller haemophilia cohorts from the UK reported previously are included in the present study[16-19,23,24]. Vital status was ascertained from Individual Haemophilia Centres and the National Health Service Central Registers. For each person a 'date last seen' was established. For those lost to follow-up this was the date of last contact with a Haemophilia Centre. whereas for other patients it was the earliest of: date of death, date of emigration. or 1 January 1993. HIV test results were collected in a series of annual surveys starting in 1985 (ref. 3). For 441 patients who were tested and found to be seropositive. the results of a previous seronegative test were available. Patients diagnosed or treated in the UK but living abroad are excluded. as are the few female patients. In addition. two severely affected patients (Including one who had been tested seropositive for HIV) and two moderately affected patients, whose years of registration were after they had died, were excluded.

• Factor VIII or IX level of less than two international units per dl.

t Includes 104 patients with unknown severity, two of whom were tested seropositive for HIV.

potentially infected treatments. A reliable test for HIV antibodies! became available to Haemophilia Centres early in 1985. Among those who were alive on 1 January 1985,78% of potentially infected severe patients and 52% of moderate/mild patients had been tested by December 1985, rising to 90 and 74% respectively by January *1993*. One thousand and twenty severe patients and 207 moderate/mild patients were found to be infected with HIV (described as tested seropositive) (Table I). For many patients, stored serum samples enabled the seroconversion date to be estimated reasonably precisely' 5. The median estimated date of seroconversion was October 1982 for severe patients (range, June 1979-0ctober 1986) and December 1982 for moderate/mild patients (range, October 1979-March 1986).

The annual death rate in patients with severe haemophilia remained steady at 8 per 1,000 during 1977-84, but then rose progressively to 38 in 1991-92 (Fig. la). This increase was confined to patients who tested seropositive for HIV and among whom the death rate increased steeply from 1985, reaching 81 in 1991-92; but in patients not tested as seropositive, the death rate during 1985-92 was 8 per 1,000, much as during 1977-84 (Fig. le). Among moderate/mild patients, the death rate during 1985-92 was 5 per 1,000, much as its value of 4 per 1,000 during 1977-84 (Fig. *lb)*. However, when HIV-seropositive patients were considered separately, the death rate again rose steeply during 1985-92 (Fig. Id). Death rates during 1985-92 for patients tested for HIV and found not to be infected (tested seronegative) were close to rates for patients of unknown HIV status within each severity group (Table 2). Thus little, if any, HIV-associated mortality has gone undetected.

The severely affected haemophiliacs had a higher initial mortality rate and also received much more transfusion therapy than patients with moderate/mild haemophilia, yet the excess death rate associated with HIV seropositivity was similar in patients with severe and with mild/moderate haemophilia (Table 2). In both groups excess mortality associated with HIV seropositivity increased progressively with time, the rates being 19, 34, 53 and 76 per 1,000 in the periods 1985-86, 1987-88, 1989-90 and 1991-92, respectively, for both groups combined (95% confidence intervals (Cls): 13-26,26-42,43-63,63-89). Treatment, by prophylaxis against *Pneumocystis carinii* pneumonia" or with zidovudine[7,22], has been widespread for HIV-infected haemophiliacs since about 1989. However, the steady increase in the excess death rate from 1985 to 1992 suggests that in this population the increasing impact of HIV-associated mortality has not been halted by these treatments. This study includes deaths only to 1992, and so does not permit examination of data following widespread use in the UK of high purity factor concentrates.

Use of the certified cause of death allows comparison of mortality rates from specific causes with those for the nation as a whole. Among patients with severe haemophilia who were not tested seropositive for HTV, there were significant increases in mortality during 1985-92 from coagulation defects, intracranial haemorrhage, injury, poisoning and suicide, and from hepatitis, liver disease and primary liver cancer, which are associated with chronic hepatic infections (Table 3). For all these causes corn-

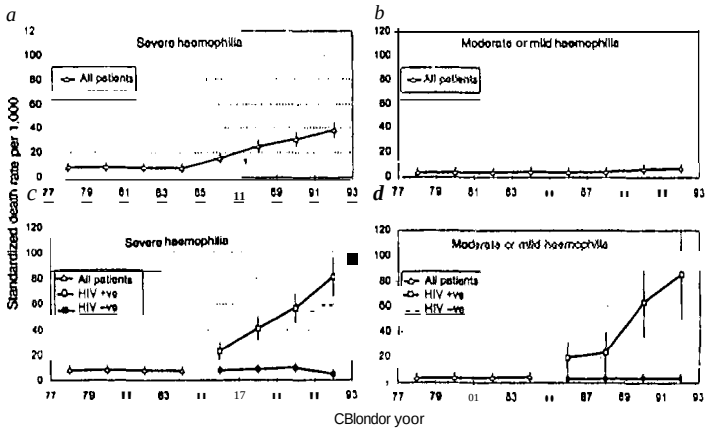

FIG.1 Annual death rates per 1000. directly standardized for age. and 95% confidence Intervals. by calendar year and severity of haemophilia. Panels a and b give values for all patients in each severity group. Panels c and d give separate values for HIV seropositive patients and patients not known to be HIV seropositive from 1985. Rates were obtained by calculating death rates (ratio of observed deaths to person-years at risk) in age-groups <15, 15-24. 25-34, 35-44. 45-54. 55-64, 65-84 by calendar period (1977-78. 1979-80•... ,1991-92). Person-years at risk were calculated by considering the length of time from registration to the date last seen (see Table 1) for each patient. Observed deaths and person-years over age 84 were excluded. After early 1985, patients becoming '" are likely to have been tested. Therefore. here and in Tables 2 and 3, patients tested seropositive for HIV with estimated seroconverston dates before 1 January 1985 are counted as seropositive from 1 January 1985, while the 93 patients with estimated seroconversion dates on or after 1 January 1985 contribute to the group of those not tested seropositive until their date of sercconverslon. estimated as in ref. 4. For age-standardization. a weighted average of the age-specific death rates was calculated, with weights proportional to the total number of person-years at risk in the HIV seropositive patients in the whole period 1985-92 for both severity groups combined. Confidence Intervals were calculated using the normal approximation.

TABLE 2 Observed deaths, annual death rates per 1,000, and annual excess death rates per 1,000 In HIV-seroposltlve haemophiliacs, by severity of haemophilia and calendar period

	Patients with severe haemophilia								
	All severely affected patients		HIV status						Excess death rate In seropositive patients"
			Unknown		Seronegative		Seropositive		
	O§	Death rate	0	Death rate	0	Death rate	0	Death rate	
1977-78	25	7.9	25		0		0		
1979-80	30	8.1	30		0		0		
1981-82	31	7.9	31		0		0		
1983-84	30	7.5	23		0		7t		
1977-84	116	7.9 (6.4-9.4)+							
1985-86	66	15.6	15	6.2	8	15.0	43	23.9	16.2
1987-88	98	25.0	11	8.2	13	9.3	74	41.3	33.6
1989-90	118	30.7	9	10.0	13	9.9	96	56.8	49.2
1991-92	136	37.9	8	6.1	7	3.6	121	80.8	73.2
1985-92	418	27.1 (24.4-29.8)	43	7.3 (4.7-9.8)	41	8.1 (5.4-10.9)	334	49.1 (43.7-54.4)	41.4 (35.8-47.0)

	Patients with moderate or mild haemophilia								
	All moderately or mildly affected patients		HIV status						Excess death rate in seropositive patients"
			Unknown		Seronegative		Seropositive		
	0	Death rate	0	Death rate	0	Death rate	0	Death rate	
1977-78	21	3.4	21		0		0		
1979-80	28	3.5	28		0		0		
1981-82	33	3.6	33		0		0		
1983-84	50	4.2	46		1†		3t		
1977-84	132	3.7 (3.0-4.5)							
1985-86	49	3.8	31	2.8	5	2.4	13	19.4	16.3
1987-88	46	4.1	22	3.4	14	2.0	10	23.8	20.6
1989-90	69	6.5	28	2.4	19	4.6	22	63.0	59.9
1991-92	78	6.9	28	2.8	26	4.1	24	84.7	81.6
1985-92	242	5.4 (4.5-6.3)	109	2.9 (2.2-3.6)	64	3.5 (2.3-4.6)	69	45.2 (33.7-56.7)	42.1 (30.6-53.6)

Death rates calculated and age-standardized and confidence intervals calculated as for Fig. 1. Observed deaths and person-years over age 84 were excluded. Separate death rates for: (1) patients tested seronegative for HIV, and (2) patients of unknown HIV status, calculated by subdividing observed deaths and person-years during 1985-92 among those not tested seropositive for HIV into those who tested seronegative, with no potentially Infected treatments recorded during the same or a subsequent calendar year, and others.

• Excess death rates obtained by subtracting from each calendar perlod-, age- *and* severity-specific death rate for HIV·seroposil/ve patients, the corresponding age- and severity-specific rate for seronegative patients and patients of unknown serostatus combined, 1985-92. Age standardization and confidence intervals for excess death rates calculated as in Fig. 1.

t HIV testing was not generally available before 1985. Although some patients dying before this were tested, testing was not carried out retrospectively for the majority of patients who died. Therefore death rates by HIV status cannot be calculated before 1985. The certified causes of death of the 10 known seropositive patients dying in 1983-84 were: haemophilia (2), suicide (2), cerebrovascular accident, cirrhosis, coronary thrombosis, diabetes mellltus, myocardial infarction, renal failure. None suggests Immunodeficiency. Before 1985 only one death, In a patient not reported as tested for HIV by any Haemophilia centre, was certified as due to AIDS.

‡ 95% confidence Intervals in parentheses.

§ 0, observed deaths.

bined (category B) the ratio of observed to national expected deaths *(O/E)* was 13.3(95% CI 10.0-17.2). Most of these associations have been reported elsewhere for haemophiliacs[9]. Ischaemic heart disease mortality was lower than expected, as in other haemophilia populations[10]. For other causes, mortality was similar to that in the general population *(O/E* = 1.1, 95% CI 0.7-1.7, category D). Patterns of cause-specific mortality for all patients with severe haemophilia during 1977-84 were similar (data not shown).

During 1985-92, 403 deaths occurred in seropositive patients and for 235 of these the certified cause was AIDS (ICD-9 code 279.1; Table 3). For the remaining 168 deaths in HIV-seropositives, there were significant excesses for many causes indicative of AIDS, including infections, non-Hodgkin's lymphoma and pneumonia, and also significant excesses for causes associated with haemophilia. Information received from the Haemophilia Centres indicates that many of these patients had in fact developed AIDS, indicating that in AIDS patients there is a tendency to attribute cause of death to diseases associated with haemophilia or AIDS rather than to AIDS itself. However, not all the excess mortality in patients tested seropositive for I-IIV appears to be due to recognized AIDS indicator diseases, and some may be due to other conditions such as liver disease.

The UK National Haemophilia Register data provide a unique opportunity to examine the impact of HIV-I infection in a complete population where almost all potentially infected individuals have been tested. These are the first data to document that, in a large and complete population, mortality among those who by chance were infected with HIV increased more than tenfold while remaining unchanged over time in those who escaped infection (Fig. 1c, *d* and Table 2). Assuming that the

TABLE 3 Cause-specific mortality during 1985-92 by HIV status compared with national mortality

Certified cause of death (ICD-9 codes)	Tested seropositive for HIV					
	No·			Vest		
	0‡	*E*§	*O/E*	0	*E*	*O/E*
(A) AIDS, HIV, etc. (279.1)	0	0.10	0.0	235	0.12	1,958.3···
(B) Causes significantly increased In severe haemophilia without HIV						
Hepatitis and liver disease (070, 570-573)	6	0.37	16.2···	11	0.30	37.0···
Liver cancer (155.0-155.1)	2	0.11	18.7·	1	0.07	15.1
Coagulation defects, etc. (280-289)	33	0.11	307.2···	72	0.06	1,155.7···
Intracranial haemorrhage (ICH, 430–432)	5	0.49	10.2···	1	0.37	2.7
Injury, poisoning and suicide (E800-999)	10	3.14	3.2··	8	3.68	2.2
All causes in category (B)	56	4.21	13.3"·	93	4.47	20.8"·
(C) Ischaemic heart disease (IHD, 410-414)	5	10.37	0.5	5	5.74	0.9
(D) Other causes						
Infections excl. hepatitis (001-139, excl. 070)	0	0.23	0.0	1111	0.14	75.6·"
Hodgkin's disease (201)	0	0.06	0.0	2¶	0.07	29.1"
Non-HodgkIn's lymphoma *(200, 202)*	0	0.29	*0.0*	12	*0.21*	57.1···
Other neoplasms excl. liver (140-239 excl. 155.0-.1 and 200-2)	9	9.38	1.0	7#	5.28	1.3
Endocrine disorders excl. AIDS, HIV, etc. (240-279 excl. 279.1)	1	0.50	2.0	1	0.30	3.3
Mental disorders (290-319)	0	0.35	0.0	2	0.25	8.1
Nervous system incl. dementia (320-389)	1	0.78	1.3	6	0.54	11.2···
Circulatory excl. IHD and ICH (390–459 excl. 410–4 and 430-2)	7	3.86	1.8	6	1.85	3.2·
Pneumonia (480–486)	0	0.63	0.0	12	0.31	38.6"·
Other respiratory (rest of 460-519)	2	2.14	0.9	2	0.99	2.0
Digestive system excl. liver (520-579 excl. 570-573)	0	0.63	0.0	3	0.34	8.7·
Musculoskeletal and connective tissue (710-739)	1	0.11	9.0	2	0.06	33.8·
Other diseases (580-709,740-799)	1	1.03	1.0	2☆	0.36	5.5
All causes in category (D)	22	20.00	1.1	68	10.70	6.4···
(E) Death certificate not located	1			2		
All causes	84	34.68	2.4···	403	21.03	19.2·"

Death details obtained from the Office of Population Censuses and Surveys (OPCS) or the General Register Offices (GRO) in Edinburgh or Belfast. Underlying cause coded to the ninth revision of the International Classification of Diseases (ICD·9)2o by OPCS. The final certified cause may differ from that available to the public if the certifier Indicates that further information may become available, and later supplies this confidentially. This system, little used In the 1970s, Is commonly used for HIV-related disease[21]. The numbers of deaths with final certified cause in each category were obtained from OPCS and the GROs and the number of deaths certified to code 279.1 Increased by 47, from 188 to 235 for patients tested seropositive for HIV and remained at zero for patients not tested seropositive. Observed and expected deaths over age 84 *are* excluded.

••• $P < 0.001$, •• $P < 0.01$, • $P < 0.05$ (two-sided Poisson test).

• Patients with severe haemophilia not tested seropositive for HIV.

t Patients with severe or moderate/mild haemophilia tested seropositive for HIV. 83% of person-veers are *for* patients with severe haemophilia.

‡ 0, observed deaths.

§ *E,* expected deaths from national rates, calculated by multiplying the number of person-years in each calendar year and *5-year* age group by the corresponding death rate *for* males In England and Wales.

‖ Septicaemia, viral encephalitis, herpes zoster, retrovlrus Infection (2), toxoplasmosis (4), *Pneumocystls* (2). All suggest immunodeficiency, except possibly septicaemia.

¶ Review of the clinical notes for one of these patients showed that he had a cerebral non-Hodgkln's lymphoma as well as Hodgkin's disease.

One case each of carcinoma of bronchus, duodenum, colon, rectum, pancreas, osterosarcoma and neurofibromatosis.

☆ For both deaths the certificate Indicated that the cause was unknown.

death rate during 1985-92 among infected patients would, in the absence of HIY, have been close to that for uninfected patients, 60 deaths would have been predicted, whereas 403 deaths in fact occurred, an excess of 343. Thus 85% of the deaths in HIY seropositive patients are likely to have been caused by HIY. This large excess, together with the temporal pattern of the increase in those who became infected, the similarity of the excess death rate associated with HIY infection regardless of the severity of haemophilia, and the large increase in mortality from conditions not usually associated with haemophilia, demonstrate particularly clearly the enormity and the specificity of the effect of HIY-I infection on mortality in this population. 0

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The impact of HIV on mortality rates in the complete UK haemophilia population

UK Haemophilia Centre Doctors' Organisation

Objective: To estimate the effect of HIV-1 infection on subsequent mortality in a complete population.

Design: Prospective cohort study.

Subjects: A total of 7250 haemophilic males were registered in the UK Haemophilia Centre Doctors' Organisation database, 1977 - '1998. Most were infected with hepatitis C virus. In the early 1980s, 1246 were infected with HIV-I from contaminated clotting factor concentrate. The main outcome measure was the date of death.

Results: During 1977-1984 annual mortality in severely haemophilic males was 0.9%. For those with HIV, annual mortality increased progressively from 1985 reaching over 10% during 1993-1996 before falling to 5% in '1997-1999, whereas without HIV it remained approximately 0.9% throughout 1985-1999. For moderately/mildly haemophilic males the annual mortality was 0.4% during '1977-1984. Without HIV it remained approximately *OAO/"* throughout 1985-'1999, but with HIV it was similar to that in severe haemophilia with HIV. Survival was strongly related to age at HIV infection. The large temporal changes in mortality with HIV were largely accounted for by HIV-related conditions. Without HIV annual liver disease mortality remained below 0.2% throughout 1985-1999, but with HIV it was 0.2% during 1985-1990, 0.8% during 1991-1996, and 0.8% during '1997-1999.

Conclusion: These data provide a direct estimate of the effect of HIV·1 infection on subsequent mortality in a population with a high prevalence of hepatitis C. From approximately 3 years after HIV infection, large, progressive increases in mortality were seen. From 1997, after the introduction of effective treatment, substantial reductions occurred, although mortality from Jiver disease remained high.

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Keywords: Cohort study, haemophilia, hepatitis C virus, highly active antiretroviral therapy, HIV, liver disease, mortality

Introduction

In most H[V-infected groups it is impossible to estimate directly the effect of infection on subsequent mortality because information is lacking on the mortality rates that would have occurred in its absence. People with haemophilia are a notable exception. In the early 19805. they were exposed to H[V-l infection through treatment with plasma-derived clotting factor concentrates. New infections ceased in the mid-1980s when donor screening and viral inactivation procedures during concentrate manufacture were introduced. By then, however, many patients had been infected. Mortality and disease incidence in the complete VK haemophilia population before and after infection with HIV have previously been reported [1–4]. This paper

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Powerpoint results summarizing these results are available on http://www.ctsu.ox.ac.uklprojects/ukhcdo/

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updates that evidence and reports on mortality rates since the introduction of effective treatment for HIV with highly active antiretroviral therapy (HAART) in Inid-1996. Before the rnid-1980s, haemophilia treatment also carried a near certain risk of hepatitis C virus (HCV) infection, and the majority of this population, including almost all those with severe haemophilia, were infected 15-81. Data on mortality from liver disease are therefore also presented.

Methods

The UI(Haemophilia Centre Doctors' Organisation (UKHCDO) has maintained a nationwide register of individuals diagnosed with haemophilia A (factor VIII deficiency) or 13 (factor IX deficiency) since 1976 191. The register is updated continuously using data on newly diagnosed individuals and deaths received from individual haemophilia centres. In addition, the vital status on 1 january 2000 of registered individuals was checked with the UK Office for National Statistics.

HIV-1 testing became available late in 1984, and virtually all haemophilia patients who had received potentially infected blood products were tested very shortly afterwards, Information on HIV test results and AIDS diagnoses has been collated [1-3,10,11]. Previously stored blood samples for some individuals enabled an estimation of the seroconversion date for all those infected. For over 80% the estimate was during 1981-1983, with the median December 1982. The definition of AIDS was always that currently in use in the UK 1121.

Individual information on HCV status is not available. Information on treatment with high HCV risk products is, however, held in the database, and studies in small groups have shown that close to 100% of those treated before 1985 were infected with HCV, with a single exposure to large-pool concentrate usually causing infection 1.5-7,13].

For each individual, the person-years at risk were calculated from the date of registration on the database until the date of death or emigration or, for those still alive and in the UI(, 1 January 2000. For the few whose vital status on 1 January 2000 could not be established, their contribution to the person-years was taken to end on the last date when they were known to be alive. Annual death rates, directly standardized for age IJ 41 using the distribution of person-years in the HIV-infected individuals in age groups less than 20, 20-29, 30-39, 40-49 and over 50 years, were calculated for all causes and for individual causes by calendar year, haemophilia severity and, from 1985, I-ITV status. Death certificates were obtained for individuals who had died, and the underlying cause was coded to the 9th revision of the International Classification of Diseases [15], except if the underlying cause was described as haemophilia as a result of some other, more specific cause (e.g, AIDS, hepatitis), then the more specific cause was taken whenever appropriate. All deaths certified as being caused by AIDS or an AIDS-defining condition, or occurring in individuals reported as having developed an AIDS-detining condition shortly before death, were classified as H IV related.

For the Hl V-infected group, survival from 1 January 1985 to 1 January 1987, 1 January 1989, ..., 1 January 1997, and 1 January 2000 was calculated separately for those aged 1-14, 15-34, 35-54 and over 55 years at infection using the equation:

$$5(1) = \exp\left\{-\sum_i n_i O_i^+ / Y_i^+\right\} \qquad (1)$$

where $S(l)$ is the probability of surviving to time t; n_i, O_i^+, and Y_i^+ are the numbers of calendar years, observed deaths and person-years, respectively, in the ith calendar period, and summation is over calendar periods to time t. The survival that HIV-infected individuals would have experienced without infection was also calculated by replacing O_i^+ in equation (I) by

$$E_i^+ = \sum_j Y_{ij}^+ O_j^- / Y_j^-,$$

where O_j^- and Y_j^- arc the numbers of observed deaths and person-years in I-lIV-uninfccrcd individuals with severe haemophilia in the jth 5-year attained-age group during 1985-1999, Y_{ij}^+ is the number of person-years in the jth attained-age group in HIV-infected individuals in calendar period i, and summation is over all attained-age groups. Relative survival [16] was calculated by considering the excess number of deaths in HIV-infcctcd compared with uninfected individuals, i.e. by replacing O_i^+ in equation (1) by $iO; - E_i^+$). Calculations were completed using the computer package Stata 1.171.

Results

Of the 7250 haemophilic men and boys living in the UI< during 1977-1998 and registered on the UKHCDO database, 2262 had severe (clotting factor concentration < 1 IU/dl), and 4988 had moderate/mild haemophilia. Among those with severe haemophilia, 952 were infected with HlV (53% of those alive on I january 1985), whereas 294 individuals with moderate/

mild haemophilia were infected (7% of those alive on 1 January 1985). The lower proportion among those with moderate/mild haemophilia reflects the lower treatment frequency in this group. Arnong HIV-infcctcd individuals, 65.8% of those with severe and 59.9% of those with moderate/mild haemophilia had died by 1 January 2000, whereas for H[V-uninfected individuals the proportions who had died were much lower, at 18.3% for those with severe and 13.0% for those with moderate/mild haemophilia (Table 1).

During 1977-1984, mortality in individuals with severe haemophilia remained constant at 0.9% (Table 2). Among HlVvuninfected individuals, mortality remained at this level during 1985-1999. ln contrast, among HIV-infecred individuals, mortality increased progressively to 2.5, 4.3, 5.8, 8.1, and 12.7% in the years 1985-1986, 1987-1988, 19S9-1990, 1991-1992, and 1993-1994, respectively (Fig. I). In 1995-1996 annual mortality was 11.3%, before falling to 5.3% in 1997-1999, after the introduction ofHAAR.T. For individuals with moderate/mild haemophilia, annual mortaliry during 1977-1984 was 0.4%. This is half the corresponding value in individuals with severe haemophilia, and the difference is principally caused by the lower mortality from causes involving bleeding. For individuals with moderate/mild haemophilia without HIV, annual mortality remained at 0.4% throughout 1985-1999. For individuals with moderate/mild haemophilia with H[V, annual mortality increased progressively, to 2.5, 2.6, 5.9, 8.1,11.5, and 13.1% in years 1985-1986, 1987-198S, 1989-1990,1991-1992, 1993-1994, and 1995–1996, before falling to 2.9% in 1997-1999.

The UKHCDO database indicated that all but 10 of the HIV-infected individuals had received high HCV risk products, as had 895 of the H[V-uninfected individuals with severe haemophilia (92% of those born before 1985), and 2497 of the HIV-uninfected individuals with moderate/mild haemophilia (64% of those born before 1985). Enquiries at haemophilia centres showed that UKHCDO treatment records were not comprehensive, and that all 10 of the remaining HIV-infected individuals and many others with severe haemophilia were also likely to have received high HCV risk products, When the analyses in Table 2 were repeated excluding those with no recorded exposure to high HeV risk products, the results were essentially unchanged: annual mortality in those with severe haemophilia was 0.9% (0.5-1.2), 0.9% (0.6-1.3), 1.0% (0.6-1.4), and 0.9% (0.6-1.3) during 1977-1978, 1979-1980. 1981-1982 and 1983-1984, whereas for those with severe haemophilia without HIV annual mortality during 1985-1986, 1987-1988, 1989-1990, 1991-1992, 1993-1994,1995-1996 and 1997-1999 was 0.9% (0.5-1.2), 0.9% (0.5-1.4), 0.9% *(004-104),* 0.6% (0.2-0.9), 0.9% (0.5-1.4), 1.2% (0.7-1.7), and 0.7% (0.4-1.1), respectively. For moderate/mild haemophilia the corresponding values during 1977-1978, 1979-1980, 1981–1982, 1983-1984, 1985-1986, 1987-1988, 1989-1990, 1991-1992, 1993-1994, 1995-1996 and 1997-1999 were 0.5% (0.3-0.7), 0.5% (0.3-0.6), 0.4% (0.2-0.5), 0.5% (0.4-0.7), 0.4% (0.2-0.5), 0.4% (0.2-0.5), 0.5% (0.3-0.7), 004% (0.3-0.6), 0.5% (0.3-0.6), 0.4% (0.3-0.6), and 0.4% (0.3-0.5), rcspecrively.

A strong gradient in mortality was observed with age at HIV infection: for those infected at ages 1-14 years, 57% of those alive on 1 january 1985 survived to I January 2000, whereas for those infected at ages 15-34, 35-54 and over 55 years, 38, 12, and 2%, respectively, survived to 1 january 2000 (Fig. 2). Some age gradient would be expected without H[V: mortality among the HlVvuninfected individuals suggests that, without H[V, survival in the HlV-infected group to 1 january 2000 in the four age-at-infection groups would have been 98, 92, 69, and 39%, respectively. When mortality in the HIV-infecred individuals was corrected for deaths

Table 1. Numbers of males in the UK with haemophilia A or B and registered in the UK Haemophilia Centre Doctors' Organization national database 1977-1998, together with vital status on 1 January 2000.

	Severe haemophilia[a]		Moderate or mild haernophilla"		
	Infected with HIV·I		Infected with *HIV-1*		
	Yes[c]	No	Yes[c]	No	Total
Alive and resident in UK	318 (33.4)cl	1013 (77.»	116 (39.5)	3882 (82.7)	5329 (73.5)
Dead	626 (65.8)	240(10.3)	176 (59.9)	608 (13.0)	1650 (22.8)
Emigraled	5 (0.5)	14 (1.1)	1 (oj)	53 (1.1)	73 (1.0)
Lost to follow-up	3 (0.3)	43 (3.3)	1 (0.3)	151 (3.2)	198 (2.7)
Total"	952 1100.D)	1310 (100.0)	294 ClOO.O)	4694 (100.01	7250 (100.0)

"Concentration of clotting factnr in the blood less than 1 IU/eII. "Includes 123 individuals with unknown severity, two of whom were infected with HIV·I. "Includes 12 individuals (nine severe, three moderate/mild) who died before I January 1985 whose *HIV* status was established using stored blood samples and two individuals (one severe, one moderate/mild) who died in 1984 for whom no HIV test was carried out but who, from their symptoms, are likely to have been infected with HIV. "Column percentages in brackets. "Excluding individuals treated in the UI(who usually live overseas.

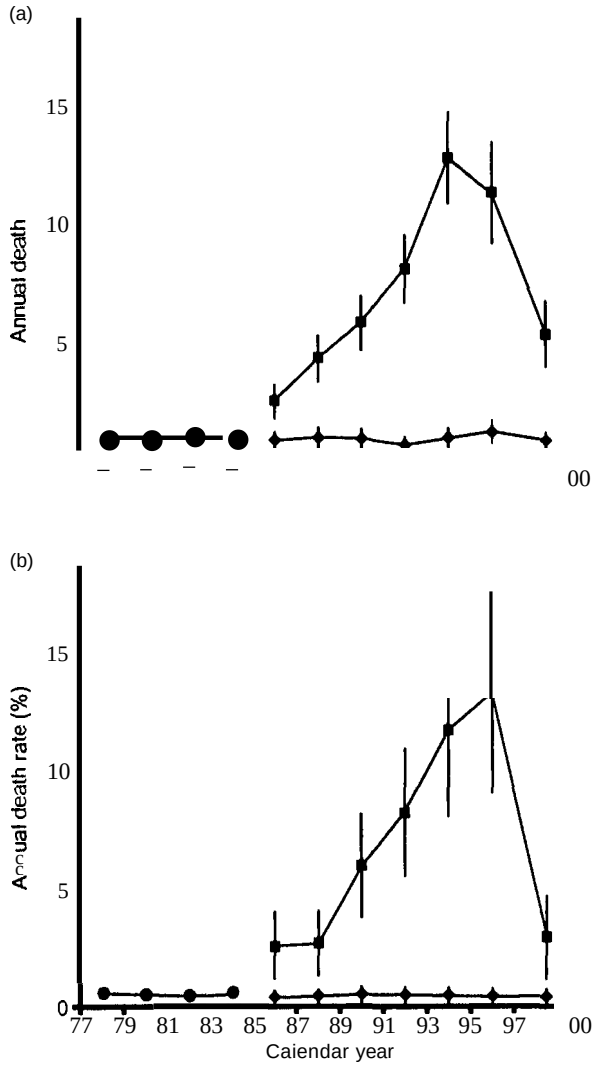

Fig. 1. Annual death rate (%), standardized for age, in haemophilic males in the UK by severity of haemophilia, calendar year and, from 1985, HIV status. (a) Severe haemophilia; (b) moderate or mild haemophilia. Vertical lines are 95% confidence intervals - - 1977-1984: all; • 1985-1999: HIV positive; • 1985-1999: HIV negative.

that would have been expected without HIV, a srrong age gradient remained: relative survival to 1 January 2000 in those aged 1-14, 15-34,35-54 and Over 55 years at HIV infection was 59, 41, 18 and 4%, respectively.

Of the 788 deaths in HlVvinfected individuals during 1985-1999,610 were HIV related, and annual mortality from HIV-related causes rose from 3.0% during 1985-1990 to 8.4% during 1991-1996 and then fell to 2.9% during 1997-1999. For all causes of death the temporal pattern was similar with annual mortality at 4.0, 10.3 and 4.7% in 1985-1990, 1991-1996 and 1997-1999 (Table 3). Considering the 178 deaths not classified as HIV related, annual mortality rose from 1.0% in 1985-1990 to 1.9% in 1991-1996, then fell slightly, to 1.8%, in 1997-1999. These values are considerably higher than those for HlV-uninfccred individuals. in whom annual mortality from all causes (standardized for age and haemophilia severity) was 0.8% (0.6, 1.0), 0.8% (0.6, 1.0), and 0.7% (0.5, 1.0) during 1985-1990, 1991-1996, and 1997-1999, respectively.

Among HIV-infected individuals, 59 of the 178 deaths not classified as HIV related were from liver disease, including seven liver cancers, and annual mortality from liver disease was 0.2% in 1985-1990, rising to 0.8% in 1991-1996 and remaining at 0.8% in 1997-1999. Among the deaths classified as HIV related, a further 27 were certified as being caused by liver disease: when these were included annual liver disease mortality was 0.2% (CLl, 0.3), 1.2% (0.9, 1.5), and 1.2% (0.6,1.7) in 1985-1990, 1991–1996, and 1997-1999, respectively. In contrast, among HIV-uninfected individuals annual liver disease mortality was Cl.09% (0.05, 0.13) during 1985-1999, and 0.05% (D.Ol, 0.08), 0.11% (0.04, 0.18), and 0.14% (C1.04, 0.23) during 1985-1990,1991-1996, and 1997-1999, respectively. The exclusion of patients with no recorded high HeV risk exposure had little effect in the HIV-uninfected group: annual liver disease mortality in this restricted group during 1985-1999 was 0.10% (C1.06-0.14), whereas values during the years 1985-1990, 1991-1996, and 1976-1999 were 0.05% (0.01–0.09), 0.12% (0.05-n.19) and 0.13% (OJJ4-0.23), respectively.

For deaths classified neither as HIV related nor from liver disease. annual mortality in HIV-infected individuals varied little during 1985-1999, taking values 0.9, 1.1 and 1.0% during 1985-1990.1991-1996 and 1997-1999. respectively (Table 3). whereas for HIV-uninfected individuals the corresponding values were appreciably lower, at 0.7% (0.6. 0.8) during *1985*-1999. and 0.7% (0.5, 0.9), 0.7% (0.5, 0.9), and 0.6% (0.3, 0.8) during 1985-1990, 1991-1996, and 1997-1999, respectively. For the 119 deaths in Hl V-infected individuals, all available information regarding cause was inspected. No common pattern was apparent. although several suggested immunodeficiency (see previous analyses of these data [1.2]). There was no evidence that death was caused by a toxic effect of HAART in the information regarding the 14 deaths occurring during 1997-1999.

Discussion

The infection of 1246 UK haemophilic males with HIV-1 during the early 1980s offers unusual insight

Table 2. Annual death rates (%) in males with haemophilia in the UK, 1977 -1999.

	Infected with HIV-l		
Calendar year	Yes	No	All individuals
Severe haemophilia			
1977-1978			0.9 (0.5–1.3)[a]
1979-1980			0.9 (0.6-1.3)
1981-1982			1.0 (0.6-1.3)
1983-1984			0.9 (0.6-1.3)
1985-1986	2.5 (1.8-3.3)	O.B (0.5-1.2)	1.8 (1.3-2.2)
1987–1988	4.3 (3.3-5.:n	1.010.5-1.4)	2.8 (2.2-3.4)
1989-1990	5.B 14.7-6.9)	0.9 (0.4-1.3)	3.3 (2.7-3.9)
1991-1992	8.1 (6.6-9.5)	0.6 (0.3-1.0)	4.10.4-4.9)
1993-1994	12.7 (10.B-14.6)	0.9(0.5-1.4)	6.0 (5.1-6.9)
199.1-1996	11..3 (9.2–13.4)	1.2 (0.7-1.7)	5.114.2-6.0)
1997-1999	5.3 (3.9-6.7)	0.8 (0.5-1.1 i	2.2 (1.7-2.7)
Moderate or mild haemophilia			
1977-1978			0.5 (0.3-0.7)
1979-1980			0.4 (0.3-0.6)
1981-1982			0.4 (0.3-0.5)
1983-1984			0.5 (OA-O.7)
1985–1986	2.5 (1.1-4.0)	0.4 (0.2-0.5)	*0.5 W.3-0.7)*
1987-1988	2.6 (1.2-4.0)	0.4 (0.3-0.6)	0.6 (0.4–0.8)
1989-1990	5.9 (3.7-8.0)	0.5 (0.3-0.7)	0.8 (0.6-1.1)
1991-1992	8.1 (5.4-10.8)	0.5 (0.3-0.6)	1.0 (0.8-1.3)
1993-1994	11.5 (7.9-15.1)	0.4 (0.3-0.5)	1.0 (0.7-1.2)
1995-1996	13.1 (8.9-17.3)	0.4 (0.3-0.5)	0.9 (0.7-1.1)
1997-1999	2.9 (1.2-4.6)	0.4 (0.3-0.5)	*0.5 (004-0.6)*

[a]Age-standardized annual death rates per 100 person-years at risk and 95% confidence intervals.

into the impact of this virus on mortality. The reasons for this are: the chance of infection depended only on how much clotting factor concentrate an individual needed 1181, and which particular batches he received; the infections took place during a short time period and within a clearly defined total population that had a wide age-range; a reliable test for HTV antibodies had become available shortly after the infections occurred; the testing of those potentially infected was essentially complete; the previously stored blood samples enabled the seroconversion date to be estimated, and it has been possible to calculate mortality separately for HIV-infected individuals and others.

There are, inevitably, a number of limitations to this study. One is that the vital status onl January 2000 of 73 individuals who emigrated and 198 individuals lost to follow-up is unknown. If their subsequent mortality has been similar to the mortality among those with complete follow-up, the study results would be unchanged. However, if their mortality differs, some bias may have occurred. For H TV-infected individuals, only 10 are involved. With such a small number, the study results would scarcely be affected even if they had substantially increased or decreased mortality compared with all HIV-infected individuals. Arnong the l-IIV-uninfected individuals the numbers emigrating are also small in relation to the total and therefore, once again, the differences between their mortality and that of those who did not emigrate would make little difference. The number of Hl'V-uninfected individuals lost to follow-up is larger. If they had lower mortality than those with complete follow-up. then the study results would not change. Some bias might occur if they had substantially higher mortality, but this is unlikely because individuals in poor health are unlikely to lose contact with their haemophilia centre.

In the entire UK haemophilia population, annual mortality was constant during 1977-1984, at approximately 0.9% in severe haemophilia, and 0.4% in moderate/mild haemophilia. From 1985, mortality in those not infected with HTV remained essentially unchanged but, among the infected individuals, mortality rose progressively by large amounts. Among those infected, the timing of the increase was identical in the two severity groups, and in each calendar period mortality rates were similar in size in the two groups, despite the different proportions infected and their different mortality rates in the absence of infection (Fig. 1). Survival was poorer in HTV-infected individuals than in uninfected individuals at all ages (Fig. 2). However, a much larger proportion of individuals remained alive by the end of the follow-up period for those who were younger when infected, even after correcting for the mortality expected in the absence of l-ITV. Such an age gradient would be anticipated from the greater number of thymic cells in younger individuals, giving a greater possibility for the ongoing replenishment of the CD4 T-cell population [19J.

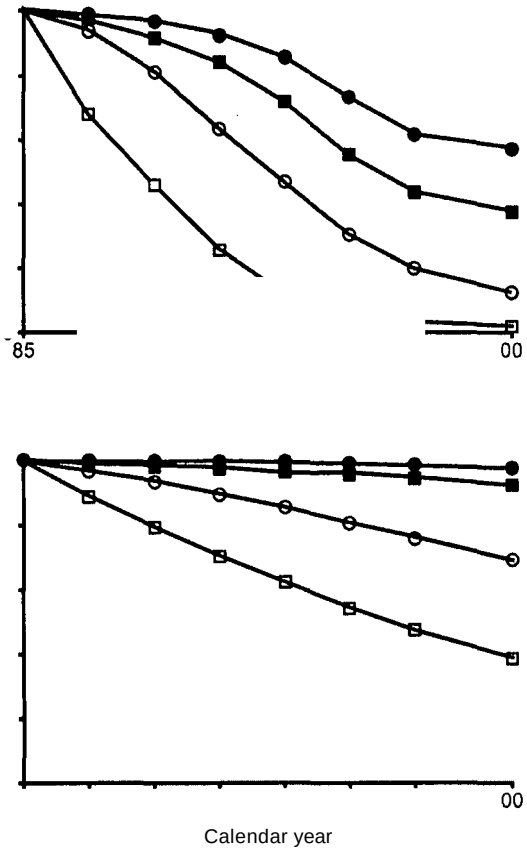

Fig. 2. (a) Survival in HIV-infected haemophilic males in the UK by calendar year for individuals infected at ages 1-14, 15-34, 35-54 and over 55 years; (b) expected survival based on mortality rates in those who were not infected. The numbers of individuals alive on .) January 1985 who were infected with HIV at ages 1-14 (el, 15-34 (.), 35-54 (0), and over 55 years (0) were 312, 606, 255 and 59, respectively.

This haemophilia population has a high prevalence of HCV infection, and another limitation of this study is that individuals cannot formally be classified by HCV status. Sensitive tests to detect antibodies to HCV antigens became available only in the I990s, and serum samples for this large population were not stored systematically. There is thus no possibility of ascertaining the HCV status for many who died before this. A surrogate marker of HCV infection is, however, available, which suggests that nearlyIOO'X, of the HIV-infected individuals and almost all others with severe haemophilia and born before 1985 were infected with HCV 15,6J. Among those with moderate/mild haemophilia and without l-lIV, some individuals have never needed treatment with blood products and probably remain free of I-ICV. Nevertheless, when those without documented high HCV risk exposure are excluded, the study results scarcely change.

The impact of eo-infection with HCV on mortality in HIV infection is hard to estimate precisely. Before 1997 it was probably proportionately small, because during this period liver disease was the certified cause of death for only 9% of the deaths in HIV-infected individuals. Studies comparing HIV-infected individuals in different exposure categories, some of whom would have had much lower HCV prevalence, have also found no appreciable effect of exposure category on survival before the HAART era [201.

During 1997-1999, mortality fell sharply in HIV-infected individuals, both in severe and in moderate/mild haemophilia (Fig. I). A similar fall, occurring shortly after the introduction of HAART, has been reported in other groups [21–23], and clearly demonstrates the impact of HAART. However, at the end of the present follow-up period, mortality in HIV-infected individuals still remained substantially higher than in HIV-uninfectcd individuals. Both the large increase in mortality up to 1996 and the subsequent fall were chiefly caused by changes in mortality from HIV-related causes (Table 3). However, when mortality from other causes was examined separately, a substantial increase over time remained, with the value during 1991-1996 almost double that for 1985-1990 and no appreciable decline in 1997-1999. The increase was entirely caused by an increase in liver disease, which during 1997-1999 was the certified cause of death for over 25% of deaths in HIV-infected individuals. This tallies with findings in other studies of HIV/HCV eo-infection in which liver disease has also emerged as a leading cause of death in recent years [13,24,251. The treatment of HCV infection with a combination of IFN-a and ribavirin became widespread in the UK during 2000 [261. Therefore its impact on liver disease in this population is, as yet, unknown.

For deaths that were classified neither as HIV related nor from liver disease, mortality remained virtually constant during 1985-1999, albeit at a higher level than that of HIV-uninfected individuals. It seems likely that at least some of these deaths were attributable to HIV, although there was no indication that the individuals concerned had developed an AIDS-defining condition. J-1AAR.T has been associated with several categories of major toxic effects 127], but there was no evidence of any deaths occurring as a result of HAART in this population.

UK Haemophilia Centre Doctors' Organisation

Analysis and Writing Committee

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Table 3. Annual death rates (%) during 1985-1999 in males with haemophilia in the UK who were infected with HIV.1, by calendar period and cause of death.

	Calendar period			Total
Cause of death	1985-1990	1991-1996	1997-1999	1985–1999
All causes				
No. of deaths	257	462	69	788
Death rate[a]	4.0 (3.5, 4.5)	10,3 (9.4, 11,2)	4.7 (3,6, 5.9)	6.3 (5,9, 6.8)
Hlv-related"				
No. of deaths	190	378	42	610[c]
Oeath rate	3.0 (2.6, 3.4)	8.4 (7.6, 9.2)	2.9 (2.0,3.9)	4,9 (4.5, 5.3)
All other causes				
No. of deaths	67	84	27	178
Death rate	1.0 (0.8,1 ,3)	1,9 (1.5, 2.3)	1.8 (1.1,2.4)	1.4(1.2,1.6)
Liver disease				
No. of deaths	10	36	13	59[d]
Death rate	0.2 (0,1, OJ)	0.8 m.5,1.0)	*0,8 (004, 1.3)*	0.5 (0.4, 0.6)
Others				
No. of deaths	57	48	14	119
Death rate	0.9 (0.7,1.1)	1.1 (0,8, *IA)*	1.0 (0.5, 1.4)	1,0 (0,8,1.1)

[a]Age-standardized annual death rate per 100 person-years at risk (95% confidence interval), "Deaths certified as caused by AIDS or an AIDS-defining condition, or occurring in individuals who had heen reported as having developed an AIDS-defining condition shortly before death, [c]Includes 27 deaths in which liver disease was reported as the underlying cause: four in 1985–1990;18 in 1991-1996; five in 1997-1999. One of these, who died in 1996, had liver cancer. When these 27 deaths are included, the annual death rate (%) from liver disease in HIV-infected patients was 0,7 (0.5, 0,8) during 198.5-1999 and 0.2 (0,1,0,3), 1,2 (0.9,1 .5), and 1,2 (0.6,1,7) during 1985-1990, 1991-'1996, and 1997-1999, respectively. [d]Includes seven liver cancers: one in 1985-1990, four in 1991-1996, and two in 1997-1999.

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Data collection was carried out by Rosemary Spooner, Sau Wan Kan, Paul Giangrande and Sarah Darby. The statistical analysis was designed by Sarah Darby and carried out by Sarah Darby and Sau Wan Kan, All members of the Analysis and Writing Committee participated in the preparation of the report.

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ment of Haematology, Northwick Park Hospital. *Here-[ord:* Department of Haematology, County Hospital. *Hillingdon:* HiUingdon Hospital. *Huddersticld:* Department of Haematology, Huddersfield Royal Infirmary. *Hull:* Department of Haematology, Kingston General Hospital. *Inverness:* Department of Haematology, Raigmore Hospital. *Ipswich:* The Ipswich Hospital. *Kettering:* General Hospital. *Kingston upon Thames:* Haematology Laboratory, Kingston Hospital. *Lancaster:* Department of Haematology, Royal Lancaster Infirmary. *Leeds:* Haemophilia Unit; Department of Paediatric Haematology, St jarnes' University Hospital. *Leicester:* Haemophilia Centre, Leicester Royal Infirmary. *Lincoln:* Lincoln County Hospital. *Liverpool:* Haematology Laboratories, Royal Liverpool University Hospital; Department of Haematology, Royal Liverpool Children's Hospital, Alder Hey. *London:* Department of Haematology, Imperial College School of Medicine, Hammersmith Hospital; Department of Haematology, St Mary's Hospital; Department of Haematology, Great Ormond Street Hospital for Sick Children; Department of Haematology, Barts and The London Haemophilia Centre, Royal London Hospital; Haemophilia Centre, Royal Free Hospital; Department of Haematology, University College Hospital; Department of Haematology, King's College Hospital; Department of Haematology, Lewisham Hospital; Haemophilia Centre, St Thomas' Hospital; Department of Haematology, St Gcorgc's Hospital. *Luton:* Department of Pathology, Luton and Dunstable Hospital. *Manchester:* University Department of Haernarology, Manchester Royal !nfirmary: Department of Haematology, Royal Manchester Children's Hospital. *Medway:* Medway Maritime Hospital. *Milton Keynes:* Department of Haematology, Milton Keynes Hospital. *Middlesborough:* Department of Clinical Pathology, Middlesborough General Hospital. *Newcastle upon Tvuc:* Haemophilia Centre, Royal Victoria Infirmary. *Newport:* Department of Haematology, Royal Gwent Hospital. *Northampton:* Department of Haematology, Northampton General Hospital NHS Trust. *Norwich:* Department of Haematology, Norfolk and Norwich Hospital. *Nottinghasn:* Department of Haematology, University Hospital, Queen's Medical Centre. *Oxford:* Oxford Haemophilia Centre, Churchill Hospital. *Peterborough:* Peterborough District Hospital. *Plymouth:* Derriford Hospital. *Portsmouth:* Central Laboratory, East Wing, St Mary's General Hospital. *Salisbury:* Department of Pathology, Salisbury District Hospital. *Sheffield:* Sheffield Haemophilia and Thrombosis Centre, Royal Hallarnshire Hospital; The Roald Dahl Paediatric Haematology Centre, The Children's Hospital. *Shrewsbury:* Department of Pathology, Shrewsbury Hospital (Copthorne North). *Southampton:* South Hampshire Haemophilia Centre, South Hampshire General Hospital. *Southend:* Department of Haematology, Southend Hospital. *St Leonards-On-Sea:* Conquest Hospital. *Stoke on Trent:* Central Pathology Laboratory, North Staffordshire Hospital. *Sunderland:* The District General Hospital. *Swansea:* Swansea Haemophilia Centre, Singleton Hospital. *Taunton /Yeovil:* Department of Haernatological Medicine, Taunton and Somerset Hospital. *Thomton Heath:* Haematology Laboratory, Mayday Hospital. *Torquav:* Department of Haematology, Torbay Hospital. *Truro:* Department of Haematology, Treliske Hospital. *Tunbridge Wells:* Pernbury Hospital. *Whitehavell:* West Cumberland Hospital. *Windicstcr:* Pathology Laboratory, Royal Hampshire County Hospital. *Wolverhampton:* Department of Haematology, New Cross Hospital. *Worcester:* Department of Haematology. Worcester Royal Infirmary NHS Trust. *Worthing:* Haematology Laboratory, Worthing Hospital. *York:* York District Hospital.

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