

## **Incidence of AIDS and excess of mortality associated with HIV in haemophiliacs in the United Kingdom: report on behalf of the directors of haemophilia centres in the United Kingdom**

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### **Abstract**

**Objective**—To estimate the cumulative incidence of AIDS by time since seroconversion in haemophiliacs positive for HIV and to examine the evidence for excess mortality associated with HIV in those who had not yet been diagnosed as having AIDS.

**Design**—Analysis of data from ongoing national surveys.

**Setting**—Haemophilia centres in the United Kingdom.

**Patients**—A total of 1201 men with haemophilia who had lived in the United Kingdom during 1980-7 and were positive for HIV.

**Intervention**—None.

**End points**—Diagnosis of AIDS; death in those not diagnosed as having AIDS.

**Measurements and main results**—Estimation of cumulative incidence of AIDS and number of excess deaths in seropositive patients not diagnosed with AIDS. Median follow up after seroconversion was 5 years 2 months. Eighty five patients developed AIDS. Cumulative incidence of AIDS five years after seroconversion was 4% among patients aged <25 at first test positive for HIV, 6% among those aged 25-44, and 19% among those aged ≥45. There was little evidence that type or severity of haemophilia or type of factor VIII or IX that had caused HIV infection affected the rate of progression to AIDS. Mortality was increased among those who had not been diagnosed as having AIDS, especially among those with "AIDS related complex." Thirteen deaths were observed among 36 patients diagnosed as having AIDS related complex against 0.65 expected, and 34 deaths in 1080 other patients against 22.77 expected; both calculations were based on mortality rates observed in haemophiliacs in the United Kingdom in the late 1970s.

**Conclusions**—Rate of progression to AIDS depended strongly on age. There is a substantial burden of fatal disease among patients positive for HIV who have not been formally diagnosed as having AIDS.

### **Introduction**

The proportion of people positive for HIV who proceed to develop serious disease as a result is still

uncertain. In this paper information from a recent survey of seroprevalence in haemophiliacs in the United Kingdom was combined with information on the development of AIDS to estimate the cumulative incidence of AIDS by time since seroconversion and its relation with the age of the patient, the type and severity of haemophilia, and the type of factor VIII or IX that gave rise to infection with HIV. In addition, information about mortality was used to assess the evidence for excess mortality among those known to be seropositive for HIV but not diagnosed as having AIDS.

### **Patients and methods**

Information on the numbers of male patients registered with haemophilia A or B who had lived in the United Kingdom in the period 1980-7 and had been tested and found to be seropositive for HIV was obtained from a recent survey of seroprevalence.<sup>1</sup> Information on the dates of the first seropositive test and of the latest seronegative test, if known, were also obtained from this source. Information on patients with AIDS was obtained from an ongoing survey carried out by the United Kingdom haemophilia centre directors' AIDS committee since 1983 and supplemented by information from the Communicable Disease Surveillance Centre at Colindale. Information on the type of factor VIII or IX received by the patients during 1980-7 was obtained from the ongoing national survey carried out in Oxford on behalf of the haemophilia centre directors. Information received by August 1988 has been included in the present report although, to ensure that reporting is as complete as possible, a cut off date of 31 December 1987 has been used in the analyses presented here. Additional information has been sought from the certified causes of death of haemophiliacs positive for HIV who have died. In a few instances in which a diagnosis of AIDS had not been recorded at the haemophilia centres the certified cause suggests that death may have been due to AIDS. It has not been possible to validate this suggestion and so these have not been included as deaths from AIDS in the analysis. They are, however, described in our discussion of the results.

For haemophiliacs positive for HIV the exact date of seroconversion is unknown, and so it has been estimated from the date of the earliest seropositive test and the date of the latest seronegative test, if known. If

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no seronegative test was available, it was assumed that the patient was seronegative on 1 January 1979. In estimating the date of seroconversion it was assumed that no patient was seropositive before 1 January 1979; that the probability of seroconversion was uniform in each of the periods 1 January 1979 to 1 July 1981, 1 July 1981 to 1 July 1985, and 1 July 1985 to 31 December 1987; and that the probability of seroconversion per unit time was in the ratio 18:58:1 in these three periods. This form for the distribution of seroconversions, and also the dates for the cut off points, were suggested from an initial analysis of the data in which the cumulative distribution of infections was estimated using the methods of Peto and Turnbull.<sup>11</sup> The values of the ratios for the probabilities of seroconversion per unit time were then estimated from the data, assuming that the latent period (the time between seroconversion and the development of AIDS) had a Weibull distribution, along the lines suggested by Brookmeyer and Goedert.<sup>4</sup> For the remainder of the analysis it was assumed for each patient that seroconversion took place on the date expected from the estimated distribution of seroconversions conditional on its lying between the dates of last seronegative and first seropositive tests.

The cumulative incidence of AIDS was estimated with the product limit method, which takes the differing lengths of follow up time of individual patients into account.<sup>5</sup> Patients who were known to have died without being diagnosed as having AIDS were censored on their date of death. Likelihood ratio tests were carried out to see if there were differences in latent period with the type and severity of haemophilia, the age on the date of the earliest seropositive test, and the type of factor that gave rise to HIV infection. Computation was carried out with PROC Lifetest in the SAS computer package.<sup>6</sup>

To estimate the number of deaths expected in patients reported as seropositive but not diagnosed as having AIDS the man years at risk in each age group was calculated by considering the time elapsed between the date of the first seropositive test and the date of death, diagnosis of AIDS, or 31 December 1987, whichever was the earliest. Expected numbers of deaths were then calculated by multiplying the number of man years in each age group by the corresponding age specific standard death rate.

Some patients were reported as having only "AIDS related complex" and others who had developed AIDS by the end of the study were reported as having it before they developed AIDS. The precise definition of AIDS related complex has never been clear; many clinicians have now ceased to use the term, and many patients with similar clinical conditions may not have been reported. We have, however, retained the term as we wished to use all the available data both to assist in examining the evidence for increased mortality among

those who had not been diagnosed as having AIDS and to confirm that our findings with regard to the differences in latent period according to age were not critically dependent on the precise clinical definition of AIDS. We have therefore divided our calculations of the observed and expected numbers of deaths in those not reported as having AIDS into those few patients reported as having AIDS related complex and those not so reported. We have also repeated our analysis of the cumulative incidence of AIDS to include those reported with AIDS related complex.

## Results

### CUMULATIVE INCIDENCE OF AIDS FROM ESTIMATED DATE OF SEROCONVERSION

Of the 1201 patients known to be seropositive and for whom a date of first seropositive test was available, 85 were diagnosed as having AIDS. One further patient diagnosed as having AIDS was reported, but as he did not seem to have been tested for HIV in any haemophilia centre he has been excluded from this analysis. Eighty two of the diagnosed cases had haemophilia A and three had haemophilia B. All three of those with haemophilia B and 67 those with haemophilia A had a severe coagulation defect (factor VIII or IX level <2% of normal).

The median follow up time after the estimated date of seroconversion until diagnosis of AIDS, death, or 31 December 1987 was 5 years 2 months, and only 8% of patients were followed for 6 or more years. When all patients were considered together as a single group 3% had developed AIDS by 3 years after their first seropositive test and 7% by 5 years. There was no significant difference in the pattern of latent periods for patients with haemophilia A as compared with haemophilia B ( $\chi^2=0.92$ ;  $p=0.34$ ), nor for patients with a severe coagulation defect compared with other patients ( $\chi^2=0.01$ ;  $p=0.91$ ). When, however, the patients were divided into three groups according to their age at the time of the first seropositive test there was strong evidence that the latent period varied with age, older patients having shorter latent periods than younger ones ( $\chi^2=32.36$ ;  $p<0.001$ ). Detailed results are presented separately for the three age groups in table 1 and figure 1. Three years after the estimated date of

TABLE 1—Estimated percentages of patients developing AIDS by time since estimated date of seroconversion

Age at date of positive test	Initial No of subjects	Total No diagnosed with AIDS	Time since estimated date of seroconversion (years)	Estimated percentage developing AIDS (approximate 95% confidence interval)
<25	579	23	3 5	1 (0.4 to 2) 4 (3 to 6)
25-44	452	33	3 5	2 (1 to 4) 6 (4 to 9)
≥45	170	29	3 5	9 (5 to 13) 19 (13 to 26)

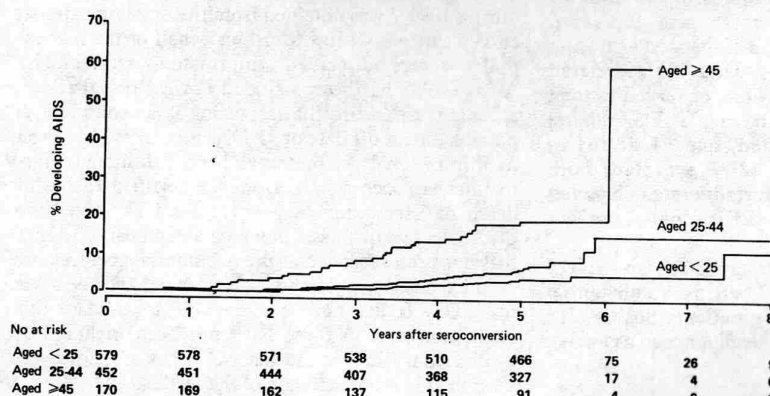


FIG 1—Estimated percentage of patients developing AIDS by time since estimated date of seroconversion and numbers of patients at risk

seroconversion 1% of patients aged under 25 years had developed AIDS whereas 2% aged 25-44 had developed it and 9% aged 45 and over; five years after seroconversion 4%, 6%, and 19% had developed AIDS. The numbers of men at risk at later periods in the three age groups are small and have standard errors too large to be of much value. When the analysis was repeated using six age groups rather than three there was a smooth trend towards decreasing latent period with increasing age at seroconversion throughout the age range from under 15 years to 55 years and above.

Twenty one patients, including two with AIDS, were recorded as having received only NHS factor VIII or IX during 1980-7, and 46 patients, including three with AIDS, were recorded as having received



only commercial materials in this period. There was no significant difference in the pattern of latent period for AIDS between these two groups of patients ( $\chi^2=0.37$ ;  $p=0.54$ ).

An additional 36 patients with haemophilia A and one patient with haemophilia B were reported as having AIDS related complex but not AIDS. When the analysis was repeated to include these patients the increasing incidence of disease with increasing age at date of first positive test remained and by five years after seroconversion 6%, 10%, and 25% of patients aged <25, 25-44 and  $\geq 45$  respectively had either been diagnosed as having AIDS or reported as having AIDS related complex (see table II and fig 2).

TABLE II—Estimated percentages of patients developing AIDS or "AIDS related complex" by time since estimated date of seroconversion

Age at date of positive test	Initial No of subjects	Total No diagnosed with AIDS	Time since estimated date of seroconversion (years)	Estimated percentage developing AIDS (approximate 95% confidence interval)
<25	579	34	3 5	2 (1 to 4) 6 (4 to 8)
25-44	452	50	3 5	5 (3 to 8) 10 (7 to 13)
$\geq 45$	170	38	3 5	13 (8 to 19) 25 (18 to 32)

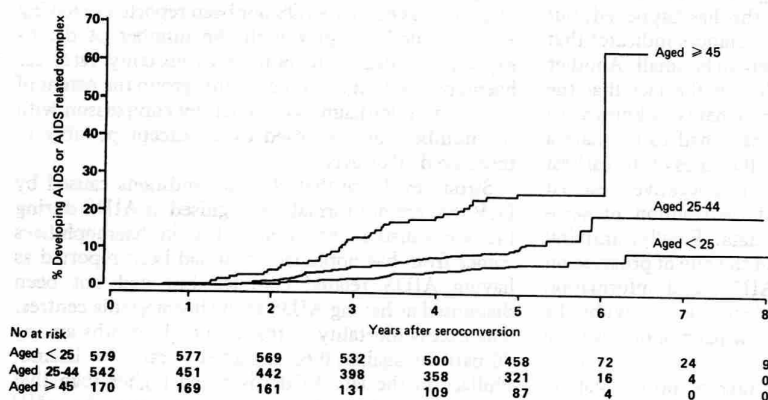


FIG 2—Estimated percentage of patients developing AIDS or reported as having "AIDS related complex" by time since estimated date of seroconversion and numbers of patients at risk

#### EVIDENCE OF EXCESS MORTALITY IN HIV POSITIVE PATIENTS BEFORE DIAGNOSIS OF AIDS

A total of 13 deaths, all in patients with severe haemophilia A, were reported up to the end of 1987 in patients who had been reported as having AIDS related complex but not AIDS. Only 0.65 deaths would have been expected if the age specific mortality in the group had been the same as that among patients with severe haemophilia A during 1976-80.<sup>7</sup> This excess was highly significant ( $p<0.001$ ). The causes of death in these patients were certified as aspergillosis pneumonia due to AIDS (one man aged 58), bronchopneumonia due to AIDS related complex (two men aged 24 and 61), bronchopneumonia due to herpes zoster (one man aged 33), septicaemia due to pyarthrosis (one man aged 34), cirrhosis due to non-A, non-B hepatitis (three men aged 43, 48, and 67), perforated peptic ulcer (one man aged 61), haemorrhage due to haemophilia (two men aged 44 and 72), poisoning with paracetamol and co-proxamol (one man aged 42), and suicide (one man aged 33).

A total of 34 further deaths were reported in patients known to be seropositive for HIV but who had not been diagnosed as having AIDS or AIDS related complex by the time they died. Thirty three of these patients had haemophilia A, 25 being severely affected, and one patient had haemophilia B. Only 22.8 deaths would have been expected if the age specific mortality

rates in the group had been the same as that among patients with severe haemophilia A during 1976-80.<sup>7</sup> This excess was significant ( $p=0.017$ ) and was evenly distributed in calendar time. When, however, the observed and expected deaths were examined separately by age a large part of the excess was found to be among those aged 70 years and over, in whom eight deaths were observed compared with only 1.09 expected (table III). The yearly death rate per 10000 observed among patients with severe haemophilia A aged 70 and above during 1976-80 was 408.<sup>7</sup> This is lower than the yearly death rates observed at these ages for all men in England and Wales during the same period—namely, 614 at ages 70-74, 960 at ages 75-80, and 1431 at ages 80-84. The possibility therefore exists that the rate observed among haemophiliacs for 1976-80 was unusually low for some reason; we therefore repeated the calculation of expected deaths using death rates specific to calendar year for England and Wales. The number of deaths observed among this group of haemophilia patients positive for HIV was still more than three times greater than expected, and the increase was highly significant with eight deaths in those aged over 70 compared with 2.15 expected (table III). These eight deaths were certified as due to: bronchopneumonia due to AIDS (one man aged 72), haemorrhage due to haemophilia (two men aged 71 and 76) or Christmas disease (one man aged 70), cerebrovascular accident (two men both aged 72), Parkinsonism (one man aged 82), and ischaemic heart disease (one man aged 76).

At ages below 70 the number of deaths observed was more than three times that expected according to the national rates, but it was only slightly greater than that expected by comparison with published mortality rates for severely affected patients with haemophilia A (26 observed, 21.68 expected; ratio of observed to expected deaths 1.2:1). For one death (at age 28) the cause was certified as unknown. Eleven deaths were certified as due to haemorrhage (in men aged 19, 20, 26, 27, 33, 38, 39, 39, 42, and 58) or a cerebrovascular accident (at age 69); three to heart disease (myocardial infarction at ages 45 and 51 and congestive cardiomyopathy at age 38); two to epilepsy (at ages 20 and 57); two to cirrhosis (at ages 47 and 51); and one each to bronchopneumonia (at age 69), poisoning (at age 31), suicide (at age 36), and drug abuse (at age 22). One death, however, was certified as due to bronchopneumonia due to AIDS (at age 42) and one to pancytopenia (at age 15). We were unable to obtain a death certificate for one death (at age 54), and the cause of death was reported by the haemophilia centre as due to liver disease with non-A, non-B hepatitis.

#### Discussion

##### CUMULATIVE INCIDENCE OF AIDS

Estimates of the proportion of patients infected with HIV who progress to serious disease are inevitably subject to a number of sources of uncertainty and potential bias. The first of these is due to the fact that not all potentially infected haemophiliacs have been tested for HIV. It is therefore possible that some patients whose HIV state would not otherwise have been known have been tested because they were experiencing symptoms. Including such patients will tend to inflate the estimated percentage of those with disease. Confirmation that this has happened to a small extent in this group is given by the fact that for seven cases of AIDS the reported date of diagnosis was either the same as, or in the same month as, the date of the first reported positive test. Further evidence is that, although only just over 80% of haemophiliacs who received blood products during 1980-7 are estimated to have been tested for HIV,<sup>1</sup> only one patient who was



TABLE III—Observed and expected deaths among patients with haemophilia A or B who were seropositive for HIV but had not been diagnosed with AIDS or "AIDS related complex"

Age group	No of deaths observed (O)	No of deaths expected (E) <sup>*</sup>	O/E <sub>1</sub>	No of deaths expected (E) <sub>2</sub> <sup>†</sup>	O/E <sub>2</sub>
<70	26	21.68	1.20	7.33	3.55
≥70	8	1.09	7.34	2.15	3.72
Total	34	22.77	1.49‡	9.48	3.58§

<sup>\*</sup>Expected deaths calculated from published age specific mortality rates for severely affected patients with haemophilia A for 1976-80.<sup>2</sup>

<sup>†</sup>Expected deaths calculated from annual age specific mortality rates for all men in England and Wales during 1981-5 (data supplied by Office of Population Censuses and Surveys).

<sup>‡</sup>p=0.017 (One sided test).

<sup>§</sup>p=<0.001 (One sided test).

diagnosed as having AIDS seemed not to have been tested at any haemophilia centre. The present cohort is different in this respect from many of the "prevalent" cohorts of other high risk groups that have been assembled in the United States.<sup>8</sup> A second bias that will reduce the estimated percentage of those with disease is that not all patients diagnosed as having AIDS may have become known to our survey. That AIDS was mentioned on the death certificates of two men who had not been reported as having AIDS or AIDS related complex may be evidence that this has happened, but that this occurred in only two instances indicates that any bias from this source is likely to be small. Another major source of uncertainty lies in the fact that the precise date of seroconversion remains unknown, so that in the present study we have had to estimate a value for each patient based on the dates of the earliest seropositive test, the latest seronegative test (if available), and the estimated distribution of seroconversions based on all the data. Finally, antiviral treatments may have influenced the rate of progression of seropositive patients to AIDS, and information about their use was not available in this survey; by the end of 1987, however, only a few haemophiliacs were receiving azidothymidine.

The findings give a lower rate of progression to AIDS than has been reported for patients receiving transfusions<sup>9</sup> and for homosexuals,<sup>11</sup> but they are in agreement with those of a recent study of seven cases of AIDS in 98 haemophiliacs positive for HIV in Sweden in which the cumulative incidence of AIDS five years after seroconversion was estimated to be 5%<sup>10</sup> and a study of 10 cases of AIDS in 92 seropositive haemophiliacs in Pennsylvania in which the cumulative five year incidence was about 11%.<sup>12</sup> In our study haemophiliacs aged over 45 on the date of their earliest seropositive test have almost five times more risk of developing AIDS by five years after seroconversion than those aged under 25. This difference is so pronounced and the evidence for it so strong that it is highly unlikely to be due to any biases or uncertainties in the data. No obvious relation between age at infection and time to occurrence of AIDS was seen in the Swedish data, but in the Pennsylvania series about 5% (two patients) of those aged 2-21 and 18% (eight patients) of those aged 22-64 had developed AIDS. An age effect has also been seen in a larger cohort of 577 haemophiliacs in the United States, in which the Pennsylvania series is included, in whom the annual conditional probability of AIDS five years after seroconversion was estimated to be 2% for those aged under 21 and 5% for those aged at least 21 (J J Goedert *et al*, fourth international conference on AIDS, Stockholm, 1988). A survey of 116 haemophilia treatment centres in the United States has also reported that patients with AIDS who attended the centres were older than patients without AIDS.<sup>13</sup> Age related differences in the latent period of AIDS have also been

reported among patients receiving transfusions,<sup>9</sup> with patients aged 60 and over having an estimated median latent period of 5.44 years against a median of 7.97 years in those aged 5-59; those aged 0-4 at infection had very short latent periods (estimated median 1.90 years). Another study of AIDS associated with transfusion in the United States has reported a mean incubation period of 2.4 years with children<sup>14</sup>; for adults it is about 4.5 years.<sup>15</sup> This effect is not present in haemophiliacs in the United Kingdom: of the 19 children aged less than 5 years on the date of their first seropositive test, none had developed AIDS and only one had been reported as having AIDS related complex by the end of 1987.

#### EXCESS MORTALITY IN PATIENTS POSITIVE FOR HIV BEFORE DIAGNOSIS OF AIDS

It has been suggested from an examination of trends in mortality statistics among unmarried men in England and Wales that infection with HIV may predispose to the development of fatal clinical conditions that are not currently recognised as being associated with the virus.<sup>16</sup> Failure to recognise such conditions will clearly lead to an underestimate of the proportion of patients developing serious disease. Comparison of the number of deaths observed among seropositive haemophiliacs who had neither been diagnosed as having AIDS nor been reported as having AIDS related complex with the number of deaths expected according to published mortality rates for haemophiliacs suggests that in this group the extent of any such underdiagnosis is small by comparison with the numbers of diagnosed cases, except possibly in those aged 70 or over.

Strong evidence that clinical conditions caused by HIV that are not formally recognised as AIDS during life are causing excess mortality in haemophiliacs comes from haemophiliacs who had been reported as having AIDS related complex but had not been diagnosed as having AIDS at the haemophilia centres. The excess mortality in this group (13 deaths among 36 patients against 0.65 expected at rates for haemophiliacs in the late 1970s) is much higher than that reported in the other patients positive for HIV (34 deaths among 1080 patients against 22.77 expected), and the certified causes of death suggest that at least four and possibly five of the excess deaths were due to acquired immunodeficiency. There is, moreover, some suggestion that a few more deaths were also due to the infection; bronchopneumonia due to AIDS (two patients) and pancytopenia (one patient) were the certified causes of death in patients for whom no reference to AIDS or AIDS related complex had been reported by the haemophilia centres or by the Communicable Disease Surveillance Centre. These findings confirm an earlier report from the Hemophilia Centre of Western Pennsylvania, where 22 of a group of 182 haemophiliacs died during 1978-86. Five of the deaths were due to AIDS, and three more occurred in patients positive for HIV antibody who did not fit the definition of AIDS of the Centers for Disease Control but whose death was suspected to be related to infection with HIV.<sup>17</sup> Thus, though it may be essential for comparative purposes to accumulate data on the incidence of clinically recorded AIDS, it is necessary also to recognise that there is a substantial burden of fatal disease among patients who have not been thought to fulfil all the criteria for the diagnosis of AIDS.

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