Hemostasis & Thrombosis

Progression to acquired immunodeficiency syndrome in 94 human immunodeficiency virus-positive hemophiliacs with long-term follow-up

Jose Ignacio Lorenzo, Federico Moscardó, José López-Aldeguer,* José Antonio Aznar

Unidad de Coagulopatías Congénitas, *Unidad de Enfermedades Infecciosas, Hospital La Fe, Valencia, Spain

Correspondence: José Ignacio Lorenzo, M.D., Ph. D., Unidad de Coagulopatías Congénitas, Hospital La Fe, Avda. Campanar, 21 46009 Valencia, Spain. Phone/Fax: international +34-963868752 - E-mail: jlorenzoh@aehh.org

Background and Objectives. Human immunodeficiency virus (HIV) infection was transmitted to many hemophilics treated with non-inactivated factor concentrates before 1986. The aim of this study was to know the long-term incidence of AIDS and risk factors for its development in HIV-infected hemophiliacs.

Design and Methods. This study was a retrospective analysis of 94 HIV-infected hemophilics. The cumulative incidence of AIDS during a follow-up of 16 years from seroconversion was determined by Kaplan-Meier analysis, and potential risk factors were also studied by multivariate analysis.

Results. The 16-year estimated incidence of AIDS was 38% (95%CI 27%-52%). The AIDS incidence was significantly higher in patients with hemophilia B ($p <0.0001$), older age at seroconversion ($p=0.0004$), lower CD4 counts at seroconversion ($p=0.004$), and lower concentrate consumption during follow-up ($p=0.02$), than it was in those patients without these characteristics. However, only hemophilia type and age at seroconversion remained significant in the multivariate analysis, with a relative risk of 0.06 (95%CI 0.02-0.20) for hemophilia A and 1.04 (95%CI 1.01-1.06) for every year of increase in age at seroconversion. The severity of hemophilia, history of inhibitors and concentrate consumption before seroconversion were not significantly associated with AIDS development.

Interpretation and Conclusions. A considerable proportion of HIV-infected hemophiliacs remained AIDS-free 16 years after seroconversion. The risk of AIDS was particularly high in patients with hemophilia B and for patients who were older at seroconversion.
©2001, Ferrata Storti Foundation

Key words: hemophilia, HIV infection, AIDS, risk factors

The widespread use of contaminated clotting factor concentrates (CFC) in the late 1970s and early 1980s led to a high incidence of human immunodeficiency virus (HIV) infection among patients with hemophilia. Several studies have reported information on the influence of patient characteristics or HIV infection markers on mortality and progression to acquired immunodeficiency syndrome (AIDS) in hemophiliacs.[1-10] Apart from the HIV load in plasma, which is at present recognized as the most important indicator of disease progression, a number of variables have been associated with an increased risk of AIDS development in these patients. These include older age at the time of seroconversion, presence of p24 antigen, high β_2-microglobulin levels and a fast rate of decrease of $CD4^+$ cell counts.[1-10] The effect of other factors on the prognosis of HIV infection in hemophiliacs is, however, unclear. It has been suggested that cytomegalovirus infection is a risk factor for developing AIDS[8,11] but this point has not been confirmed by other authors.[12] Finally, hemophilia-related variables, such as the type and severity of the hemophilia, CFC consumption and the existence of an inhibitor history have also been studied as potential risk factors for progression to AIDS.[5,7-9,13] We studied 94 hemophiliacs undergoing a long-term follow-up in order to determine the progression to AIDS and the influence on the rate of AIDS development of the following variables: age at seroconversion, type and severity of hemophilia, inhibitor history, CFC consumption and initial $CD4^+$ cell count.

Design and Methods

Patients

We studied 94 HIV-positive hemophiliacs (88 with hemophilia A and 6 with hemophilia B) who had been treated at our center before 1985. All the patients had received treatment with CFC without viral inactivation. Since the end of 1985 only virally inactivated CFC have been used. For 19 patients the date of seroconversion was estimated as the mid-point between the last negative and the first positive samples. For patients with-

out a negative sample, we used the date of first CFC exposure instead, but only when this date was not earlier than 1980 (6 patients). For the remaining 69 patients, June 1982 was assumed to be the seroconversion date, because the prevalence of HIV seropositivity among exposed patients at our center had already reached 50% by 1983, whereas by 1986 it had only increased by an additional 12%.[14] Of the 94 patients of this study, 59% were known to be HIV-positive by the end of 1983, 76% by the end of 1984, and 89% by the end of 1985. Ten patients whose first HIV-positive sample was obtained in 1986 or later were considered to be already infected by the end of 1985, when virally safe CFCs were introduced. The estimated year of seroconversion was 1982 in 68 patients (72%), 1983 in 9 patients (10%), 1984 in 5 (5%) and 1985 in the remaining 12 patients (13%). AIDS was defined according to the criteria established by the Centers for Disease Control (CDC) in 1993.[15]

Routine follow-up examinations were done three times a year. The patients who were exposed to CFCs between 1975 and 1985 at our center were also tested for HIV and subsequently included in the study if HIV-positive. There were only two patients who were not tested. One of these patients (with hemophilia A) died in 1983 and the other (a 57-year old patient with severe hemophilia B) was lost to follow-up in 1986. Neither of them had had clinical manifestations of HIV-related diseases, according to retrospective reviews of their clinical records.

Patients were treated with anti-retroviral drugs in accordance with accepted criteria at each time. Highly active anti-retroviral therapy (HAART), including protease inhibitors, was introduced in 1996, and about a third of all patients had been treated with HAART by the end of the study for a median period of 19 months (range 5 to 34 months).

Since 1995, the presence of HIV antibodies has been tested for by an enzyme-linked immunosorbent assay and confirmed by Western-blot. Frozen stored samples taken from 70 patients in 1983 and 1984 were tested for HIV antibodies in 1985.

Variables

Hemophilia was considered severe when the deficient coagulation factor was less than 1 IU/dL, moderate when it was between 1 and 5 IU/dL and mild when it was over 5 IU/dL. Patients were considered to have factor VIII inhibitors when the titer of antibodies was higher than 10 Bethesda units/mL or if the antibody persisted for longer than one year. For every patient, we determined the total CFC (TCFC) consumption before seroconversion and the annual CFC (ACFC) consumption per kilogram of body weight from 1985 to 1995. CD4+ cell counts were performed by indirect immunofluorescence in 1983 and 1984. Since 1985 CD4+ cell counts have been determined by flow cytometry. Only CD4 counts performed in 1983 and 1984 were considered as valid initial (baseline) CD4 counts.

Statistical methods

To determine the risk of developing AIDS, the Kaplan-Meier method was used, establishing the estimated date of seroconversion as the starting point. Follow-up covered a period from the estimated date of seroconversion to December 1998. Observations were censored on the date the patients were last known not to have AIDS. Sixteen patients were censored before 1998; 13 (censored between 1983 and 1995) died of causes other than AIDS and the remaining 3 (censored in 1984, 1996 and 1997) were lost to follow-up. The comparison of survival curves was made by the Mantel-Cox test, with testing for trends when appropriate (three or more ordered categories). In order to take into account the simultaneous influence of several covariates on the rate of AIDS development, a multivariate Cox regression analysis was performed and relative risks were calculated. The proportionality assumption of the multivariate model was tested by examining the parallelism between the log minus log function plots for different values of each covariate and by simultaneously including with each covariate a time-dependent term (defined as the interaction between the natural logarithm of the time and the covariate). The model fulfilled the proportionality assumption reasonably, as log minus log function plots were roughly parallel, and the time-dependent terms were clearly not significant. Only 81 patients had complete data on all covariates considered in multivariate analysis. However, once a model was obtained, it was calculated again considering only the significant, selected covariates, in order to allow the maximum number of patients to be included in the final model. Models incorporating only hemophilia type and age included the whole cohort, as these two covariates were available for all patients.

For multivariate analysis age was entered as a continuous variable, and the other covariates were coded as follows: hemophilia type, A=1, B=0; hemophilia severity, mild=1, severe or moderate=2; CD4 counts, <500/µL=1, 500-1000=2, >1000=3; TCFC, <200,000 IU=1, >200,000 IU = 2; ACFC, <500=1, 500-1500=2, >1500=3; inhibitor, yes=0, no=1. CD4 counts, TCFC and ACFC were also tested as continuous variables. The potential associations between pairs of variables was examined by the Student's t-test, ANOVA, linear regression or the chi-squared and Fisher's exact tests, as appropriate. p values <0.05 were considered to be statistically significant.

Results

Patients' characteristics

The main characteristics of the 94 patients are shown in Table 1. Mean age at the time of seroconversion was 17.3 years (median 14.3, range 1.1-65.5). Almost half of the patients (48%) were under the age of 15 at the time of seroconversion and 70% had severe hemophilia. The first available CD4+ cell count was subsequent to 1984 for 9 patients, and in these cases the value of initial

**Table 1. Characteristics of the patients and number developing AIDS**

Characteristic	No. of patients (% of total)	AIDS (% of those with the characteristic)	p value*
Age at seroconversion (years)			
≤15	45 (48%)	9 (20%)	
16-30	35 (37%)	16 (46%)	<0.0005
>30	14 (15%)	6 (43%)	
Hemophilia type			
A	88 (94%)	26 (30%)	<0.0001
B	6 (6%)	5 (83%)	
Hemophilia severity			
Mild or moderate	28 (30%)	10 (36%)	0.7
Severe	66 (70%)	21 (32%)	
TCFC consumption before seroconversion (IU)			
<200,000	31 (33%)	10 (32%)	0.8
≥200,000	58 (62%)	21 (36%)	
ACFC consumption (IU/kg/y)			
≤500	22 (23%)	11 (50%)	
500-1,500	51 (54%)	18 (35%)	<0.02
>1,500	17 (18%)	2 (12%)	
CD4+ cell count (cells/µL)			
≤500	22 (23%)	11 (50%)	
500-1000	37 (39%)	12 (32%)	<0.004
>1000	26 (28%)	6 (23%)	
History of inhibitors			
Yes	7 (7%)	2 (29%)	0.5
No	87 (93%)	29 (33%)	

*Based on comparison of Kaplan-Meier curves for AIDS development.

CD4 count was considered to be missing. Mean follow-up for AIDS development was 161.6 months (range 10-196.1 months).

Progression to AIDS and mortality

Of the 94 patients, 31 (33%) developed AIDS (Table 1). Forty-two patients died, 13 of them without developing AIDS (four of these 13 died from chronic hepatitis C virus (HCV)-liver related complications). Of the 29 patients who died after developing AIDS, death was due to AIDS-related causes in 24, and hepatic failure in one, while in the remaining 4 patients the cause of death was unknown. The Kaplan-Meier estimate for the rate of progression to AIDS after 16 years of follow-up was 38% (95%CI 27-52%)(Figure 1). No patient developed AIDS during the last twenty months of the study period. Patients with hemophilia A had an estimated rate of progression to AIDS at 16 years of 34% (95%CI 23-48%) while those with hemophilia B had an estimated rate of 83% (95%CI 48-99%; p <0.0001) (Figure 2A). There were no significant differences in initial CD4 counts or CFC consumption between hemophilia A and hemophilia B patients (Student's t-test). According to the severity of hemophilia, the estimated rate of AIDS development was 36% in severe hemophilia (95%CI 24-51%), and 43% in mild or moderate disease (95%CI 23-
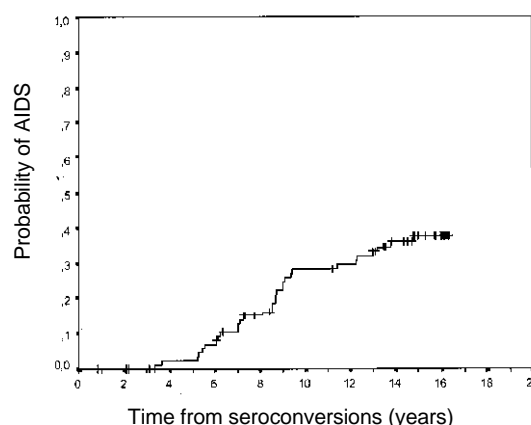
Figure 1. Overall probability of AIDS development for the 94 HIV-positive hemophiliacs.

70%), without significant differences. The estimated rate of AIDS development was 21% (95%CI 12-36%) in patients younger than 15 years, 56% (95%CI 37-76%) in patients between 16 and 30 years and 63% (95%CI 33-91%) in those over 30 years (p=0.0004) (Figure 2B). Significant differences were also found according to the initial CD4+ cell counts. The rate of progression to AIDS was higher (p <0.004) in patients with a CD4+ cell count less than 500/µL (66%, 95%CI 43-88%) than in those with a count between 500 and 1000/µL (36%, 95%CI 21-56%) and in those with an initial count greater than 1000/µL (24%, 95%CI 11-47%) (Figure 2C).There were no significant differences in 16-year rate of AIDS development according to the existence of prior inhibitor history or TCFC consumption before seroconversion (33% vs 38% and 41% vs 34%, respectively). Eleven of the 22 patients with ACFC consumption of 500 IU/kg/year or less after seroconversion developed AIDS, in comparison to 18 of 51 with ACFC consumption between 500 and 1,000 IU/kg/year, and 2 of 17 with more than 1,000 IU/kg/year. The rates of progression to AIDS for these three groups were 55% (95%CI 32-81%), 39% (95%CI 25-57%) and 13% (95%CI 3-43%), respectively, with significant differences (p <0.02) (Figure 2D). Mean ACFC use was similar in patients aged < 15, 15-30 and >30 (differences not significant according to ANOVA) and the correlation between ACFC use and age was not statistically significant.

In the multivariate analysis, only age at seroconversion and the type of hemophilia were independently associated with progression to AIDS. The relative risk of AIDS development was 0.06 for patients with hemophilia A (95%CI 0.02-0.20), which means that patients with hemophilia B have a 16 times higher risk than hemophilia A patients, and 1.04 (95%CI 1.01-1.06) for every year of increase in age at seroconversion. The CD4 cell count (p=0.07) and other variables such as hemophilia severity (p=0.17), ACFC consumption after sero-
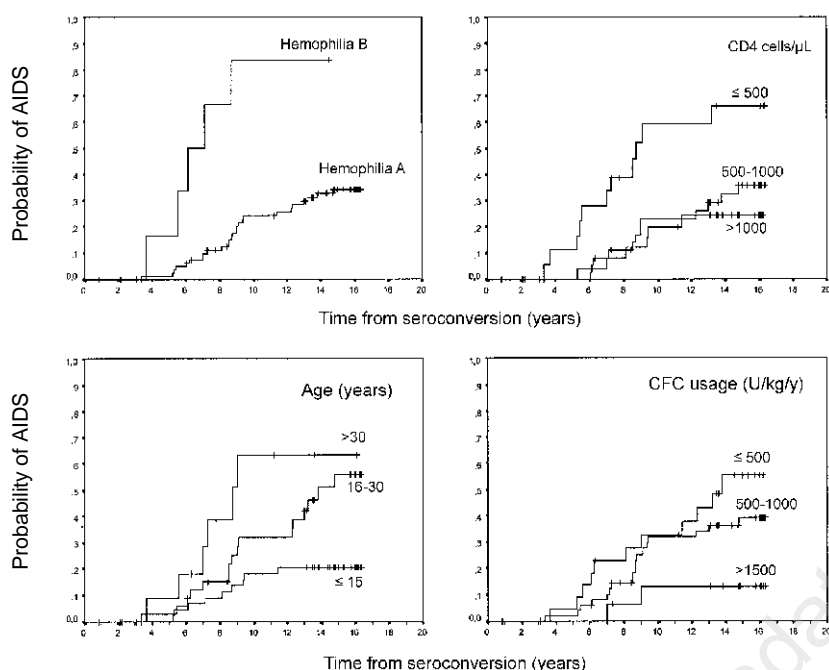
Figure 2. Probability of AIDS development according to haemophilia type (A), age at seroconversion (B), baseline CD4⁺ cell count (C), and annual CFC usage after seroconversion (D).

conversion (p=0.18), TCFC usage prior to seroconversion (p=0.74), and history of inhibitors (p=0.96) were not significant once hemophilia type and age had entered the model. However, the CD4⁺ cell count was statistically significant in the multivariate analysis when either age or hemophilia type, but not both, was also considered. ACFC consumption was significantly associated with AIDS development when hemophilia type, but not age, was simultaneously included in the model. Inclusion of ACFC, TCFC and CD4 counts as continuous variables did not change the results meaningfully.

Discussion

In this cohort of 94 patients from a single unit, the estimated rate of AIDS development was 38%. In other published studies of hemophilia patients with a long term follow-up, varying between 10 and 16 years, the rates of progression to AIDS varied between 36% and 58%.[3,6-10] Although the follow-up in this study is one of the longest, the rate of AIDS development is one of the lowest. This could be explained in part by the younger age at seroconversion in our patients compared with patients in the other studies.

The percentage of patients who died in other cohorts varied from 23% to 56%.[3,6-10] In our cohort, 42 patients (45%) died during the follow-up, which tallies with the figures given in other studies. A considerable number of patients (13/42) died before they developed AIDS, and in all these cases death was due to causes other than HIV-related conditions. In 4 of the 13 patients who died without developing AIDS death was due to conditions related to HCV liver disease. It is known that HCV liver disease is more aggressive when the patient is co-infected with HIV.[16-18] Our results, like those of other studies,[3,9,10] show that HIV-infected hemophiliacs have increased mortality due to non-related HIV conditions.

The role of the patient's age in the progression to AIDS in HIV-infected hemophiliacs was shown by Eyster *et al.*[17] and subsequently by other authors.[1-10,19] In agreement with their conclusions we observed a higher estimated rate of AIDS development in patients who were older at seroconversion. By multivariate analysis, age was confirmed to be an important independent risk factor for the development of AIDS in our cohort. However, the strongest predictor of progression to AIDS was the type of hemophilia. Patients with hemophilia B had a 16-fold higher risk of AIDS progression than those with hemophilia A. Although the type of hemophilia has not been considered as a prognostic factor in most studies, similar results have been previously reported by some authors.[5,8] In a large group of 767 HIV-positive hemophiliacs, Schinaia *et al.* found a higher progression to AIDS among factor IX recipients than among factor VIII recipients. In their multivariate analysis the type of replacement therapy (factor IX or factor VIII) was the second most important factor predicting the progression to AIDS. Roosendaal *et al.*[8] suggested that patients with hemophilia B and hemophilia A with inhibitors have a higher risk of developing AIDS than patients with hemophilia A without inhibitors, which could be related to a higher consumption of prothrombin complex concentrates (PCC) and activated prothrombin complex concentrates (aPCC). Although we did not find a higher rate of progression to AIDS in patients with hemophilia A and inhibitors, i.e. patients who were often treated with aPCC, we believe that the use of PCC would be the most plausible explanation for the worse prognosis in our hemophilia B patients. PCC use could be associated with

a faster progression of HIV infection because PCC were more highly contaminated than factor VIII concentrates, or because they were contaminated with particularly aggressive virus phenotypes. Some viral phenotypes have been associated with a rapid loss of CD4 cells and could be a factor influencing disease progression.[20] Other explanations for our findings, such as host factors, might also be possible. Hemophilia B patients could have had a higher degree of prior immune impairment, secondary to replacement therapy, than hemophilia A patients, which would explain faster disease progression following infection. However, some reports have not shown any differences in the rates of AIDS development between patients with hemophilia A and B,[6] and indeed there has even been a descrption of a lower risk of progression to AIDS in hemophilia B.[7]

A relation between the rate of decline of the CD4+ cell count with the risk of developing AIDS has been reported[2,4,10,20,21] Lee *et al.*[2] found that although the decline of CD4+ cell count was similar in different age groups, older patients had a lower CD4+ count at HIV seroconversion. Moreover, a significant decrease in CD4+ counts has also been described during the first 10 years of life in HIV-negative hemophiliacs.[22] Since the decline of CD4+ cells in HIV-infected patients is part of the natural history of HIV infection, and therefore a consequence rather than a cause of disease progression, we preferred not to consider the rate of decline of CD4+ counts as a covariate in this study. We found that patients with a lower initial CD4+ cell count had a higher rate of progression to AIDS. This association remained significant when either age or hemophilia type was entered into the multivariate model. However, when both age and hemophilia type were considered, the association was not significant. These findings suggest that the apparent association between initial CD4+ count and progression to AIDS in HIV hemophiliacs may be due, in part, to interrelations between the CD4+ counts, hemophilia type and age at seroconversion.

In agreement with other series[6,7,10,13] we did not find a significant relationship between the severity of hemophilia and progression to AIDS. Astermark *et al.*[9] showed a tendency to a slower progression in patients with moderate disease than in those with severe hemophilia, but the differences were not statistically significant. The possible influence of hemophilia severity on the progression to AIDS would have to be due to the amount of substitution therapy administered. *In vitro* studies suggest that low and intermediate purity CFC can interact with immune function and cause inhibition of lymphocyte proliferation and interleukin-2 production by T-lymphocytes, as well as a downregulation of human monocyte function.[23-25] By contrast, other reports have failed to demonstrate that the amount of low or intermediate purity CFC has any deleterious influence on CD4+ count in HIV positive hemophiliacs.[5,10,26-29] Moreover, a higher mean ACFC consumption has been reported in association with a lower risk of AIDS.[9,13] Montoro *et al.*,[13] in a cohort of 225 HIV-infected hemophiliacs,

which included most of our patients, found that patients with a lower ACFC consumption had a higher mortality, even after adjusting for the patient's age. In the subset of our patients included in the aforementioned study there was only a marginal trend in the effect of CFC consumption on mortality. The explanation for the apparently favorable effect of the CFC was unknown. In the present re-analysis of our cohort, the univariate analysis showed that patients with lower ACFC consumption had a higher rate of progression to AIDS than those who used more ACFC. Although mean ACFC consumption was similar in different age groups, and there was no significant correlation between ACFC and age, ACFC use did not enter the regression model after adjustment for the age of the patients. This might be due to the existence of a non-significant relationship between the two variables according to standard statistical methods (mean comparisons, correlation), but important enough to neutralize the influence of ACFC use on the risk of AIDS when analyzed by the multivariate proportional hazards regression method.

The rate of AIDS development among our patients seems to have decreased markedly in the last two years of the study period, apparently in connection with the introduction of HAART. However, in this study we have not examined the possible significance of the plateau observed in the curves of AIDS development and whether this plateau might be attributed to the introduction of HAART. This is mainly because the follow-up of the treated patients is still very short and a group of similar untreated patients is not available for comparison.

In conclusion, hemophilia B and older age at seroconversion are the most important risk factors in predicting the progression to AIDS in HIV hemophiliacs, and both variables have to be taken into account when assessing other potential risk factors or the relative effectiveness of anti-retroviral therapy regimes in hemophiliacs. The influence of hemophilia replacement therapy in HIV positive patients remains unclear, but we cannot rule out its possible role in the progression to AIDS.

Disclosures

Conflict of interest: none.

Redundant publications: less than 50% overlapping with papers published in Sangre 1992; 37:169-74, and Blood 1995; 86:2213-9.

Manuscript processing

Potential implications for clinical practice

Hemophilia B and older age at seroconversion are the most important risk factors in predicting the progression to AIDS in HIV hemophiliacs.

References

1. Chorba TL, Holman RC, Strine TW, Clarke MJ, Evatt BL. Changes in longevity and causes of death among persons with hemophilia A. Am J Hematol 1994; 45:112-21.
2. Lee CA, Phillips A, Elford J, et al. The natural history of human immunodeficiency virus infection in a hemophilic cohort. Br J Haematol 1989; 73:228-34.
3. Sabin C, Phillips A, Elford J, Griffiths P, Janossay G, Lee C. The progression of HIV disease in a hemophilic cohort followed for 12 years. Br J Haematol 1993; 83:330-3.
4. Goedert JJ, Kessler CM, Aledort LM, et al. A prospective study of human immunodeficiency virus type 1 infection and the development of AIDS in subjects with hemophilia. N Engl J Med 1989; 321:1141-8.
5. Schinaia N, Ghirardini AM, Mazzucconi MG, Tagariello G, Morfini M, Chiarotti F. Clinical factors associated with progression to AIDS in the Italian cohort of HIV-positive hemophiliacs. G.I.C.C. Gruppo Italiano Coagulopatie Congenite. Thromb Haemost 1994; 72:33-8.
6. Boufassa F, Carré N, Deveau C, et al. HEMOCO: a French prospective study of hemophiliacs infected by human immunodeficiency virus type 1 (HIV-1). Hematol Cell Ther 1996; 38:193-8.
7. Altisent Roca C, Ayestarán Altuna A, Tusell Puigbert JM, Oliveras Martin J, Montoro Ronsano JB, Vila Baucells M. Progression of HIV infection in a cohort of hemophiliacs over an 11-year period. Med Clin (Barc) 1995; 104:411-4.
8. Roosendaal G, van der Schouw Y, Mauser-Bunschoten E, Borleffs J, van den Berg H. Progression to AIDS in relation to clinical factors and clotting product consumption. A 14-year follow-up of a cohort of 52 Dutch HIV-1-infected hemophilic patients. Vox Sang 1998; 75: 261-6.
9. Astermark J, Johnsson H, Stigendal L, Lethagen S, Berntorp E. HIV-disease progression in Swedish haemophiliacs and the influence of replacement therapy. Haemophilia 1997; 3:277-82.
10. Touloumi G, Karafoulidou A, Gialeraki A, et al. Determinants of progression of HIV infection in a Greek hemophilia cohort followed for up to 16 years after seroconversion. J Acquir Immune Defic Syndr Hum Retrovirol 1998; 19:89-97.
11. Sabin CA, Phillips AN, Lee CA, Janossy G, Emery V, Griffiths PD. The effect of CMV infection on progression of human immunodeficiency virus disease in a cohort of haemophilic men followed for up to 13 years from seroconversion. Epidemiol Infect 1995; 114:361-72.
12. Rabkin CS, Hatzakis A, Griffiths PD, et al. Cytomegalovirus infection and risk of AIDS in human immunodeficiency virus-infected hemophilia patients. National Cancer Institute Multicenter Hemophilia Cohort Study Group. J Infect Dis 1993; 168:1260-3.
13. Montoro JB, Oliveras J, Lorenzo JI, et al. An association between clotting factor concentrates use and mortality in human immunodeficiency virus-infected hemophilic patients. Blood 1995; 86:2213-9.
14. Lorenzo JI, Molina R, Arilla MJ, Dasí MA, Monteagudo E, Aznar JA. Human immunodeficiency virus infection in hemophiliacs: prevalence and current clinical situation. Sangre 1991; 36:451-5.
15. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep 1992; 41:1-19.
16. Darby SC, Ewart DW, Giangrande PL, Dolin PJ, Spooner RJ, Rizza CR. Mortality before and after HIV infection in the complete UK population of haemophiliacs. UK Haemophilia Centre Directors' Organisation. Nature 1995; 337: 79-82.
17. Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr 1993; 6: 602-10.
18. Telfer P, Sabin C, Devereux H, Scott F, Dusheiko G, Lee C. The progression of HCV-associated liver disease in a cohort of haemophilic patients. Br J Haematol 1994; 87:555-61.
19. Darby SC, Rizza CR, Doll R, Spooner RJ, Stratton IM, Thakrar B. 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. BMJ 1989; 298:1064-8.
20. Greenough TC, Brettler DB, Kirchhoff F, et al. Long-term nonprogressive infection with human immunodeficiency virus type 1 in a hemophilia cohort. J Infect Dis 1999; 180: 1790-802.
21. Shen MC, Hu FC, Lin JS, Hsie SW, Hung CC, Chung CY. Human immunodeficiency virus infection in haemophiliacs in Taiwan: the importance of CD4 lymphocyte count in the progression to acquired immunodeficiency syndrome. Haemophilia 1998; 4:115-21.
22. Phillips AN, Sabin CA, Elford J, Bofill M, Janossy G, Lee CA. Use of CD4 lymphocyte count to predict long-term survival free of AIDS after HIV infection. BMJ 1994; 309: 309-13.
23. Phillips AN, Lee CA, Elford J, et al. More rapid progression to AIDS in older HIV-infected people: the role of CD4+ T-cell counts. J Acquir Immune Defic Syndr 1991; 4:970-5.
24. Thorpe R, Dilger P, Dawson NJ, Barrowcliffe TW. Inhibition of interleukin-2 secretion by factor VIII concentrates: a possible cause of immunodepression in haemophiliacs. Br J Haematol 1989; 71:387-91.
25. Hay CR, McEvoy P, Duggan-Keen M. Inhibition of lymphocyte IL2-receptor expression by factor VIII concentrate: a possible cause of immunosuppression in haemophiliacs. Br J Haematol 1990; 75:278-81.
26. Eibl MM, Ahmad R, Wolf HM, Linnau Y, Gotz E, Mannhalter JW. A component of factor VIII preparations which can be separated from factor VIII activity down modulates human monocyte functions. Blood 1987; 69:1153-60.
27. Gjerset GF, Pike MC, Mosley JW, et al. Effect of low- and intermediate-purity clotting factor therapy on progression of human immunodeficiency virus infection in congenital clotting disorders. Transfusion Safety Study Group. Blood 1994; 84:1666-71.
28. Deitcher SR, Tuller J, Dugdale M. Effect of intermediate- and high-purity factor VIII concentrates on immune function in HIV-seropositive haemophiliacs as assessed by quantitative CD4 counts. Haemophilia 1997; 3:265-9.
29. Sabin CA, Pasi J, Phillips AN, Lilley P, Elford J, Lee CA. The use of intermediate-purity clotting factor concentrates and HIV disease progression in men with haemophilia. Haemophilia 1996; 2:78-81.