

CAL15(140211)

**Historical Summary of AIDS in Haemophilia****1981 – 1985***Drafted in about 1988 (mainly as a summary of the references)*

- 1981 June/July First case reports of Pneumocystis pneumonia and Kaposi's sarcoma in homosexual men in Los Angeles and New York (MMWR 30, 250 and 305).
- 1982 July Case reports of 3 haemophiliacs with Pneumocystis pneumonia. First one presented in October 1981. Editorial Note suggests that immune suppression similar to homosexuals with Pneumocystis could have been due to agent transmissible by blood products. No two patients were known to have received concentrate from the same factor VIII batches (MMWR 31.365).
- During 1982 it became apparent that fatal Pneumocystis and Kaposi's sarcoma were spreading epidemically in homosexual populations. Homosexuals were also noted to be at risk of a syndrome of Persistent Generalised Lymphadenopathy (PGL) (MMWR, 31, 249) which possibly reflected an underlying immune disorder or possible a pre-AIDS syndrome. Non-Hodgkins lymphoma was also noted in homosexual men and was considered to be due to an infectious agent (MMWR 31, 277).
- 1982 September AIDS diagnosed in Drug Addicts first date? (MMWR 31, 507-14).
- 1982 December An additional 4 cases of AIDS in haemophilia were described. No common batches of factor VIII concentrate were identified (MMWR 31, 644).
- First case of transfusion-associated AIDS in California in 20-month old infant after multiple transfusions (MMWR, 31, 652).
- 1983 January First reports of two cases of AIDS in female sexual partners of i.v. drug addicts with AIDS. (MMWR 31, 697)
- Two cases reported of PGL in haemophiliacs with immune abnormalities similar to patients with AIDS. At this time it was unclear whether such individuals were likely to get AIDS but this study provided further evidence

## CAL15(140211)

for AIDS in haemophilia being caused by an agent transmissible in factor VIII concentrates (Ragni et al, Lancet i, 213).

Reports of low  $T_4$  and  $T_4/T_8$  ratio in severe haemophilia – conclude may be transfusion associated possibly as a response to antigenic load. None of the patients studied had clinical features of AIDS (Jones et al, Lancet i, 120).

Editorial in NEJM questioning whether it would be prudent to switch to cryoprecipitate (Desforgues, NEJM, 308, 94).

1983 March

Case reports of 3 haemophiliacs with AIDS

Elliot et al Ann Int Med 98, 290

Poon et al Ann Int Med 98, 287

Davis et al Ann Int Med 98, 284

Further report of immune abnormalities (low  $T_4$ ,  $T_4/T_8$  decreased,  $T_8$  increased) observed in apparently well young patients with haemophilia (Luban et al, Lancet i, 503).

It was unclear whether these abnormalities were due to "latent AIDS" caused by transmissible agent or whether they were the result of factor VIII concentrate per se.

Editorial in Ann Int Med discusses dilemma of how to treat haemophiliacs; author had reduced surgery and switched few patients from factor VIII concentrate to cryoprecipitate. (White Ann Int Med 98, 403).

Editorial Lancet – Are T cell abnormalities the submerged part of iceberg of which AIDS is the tip? Cites NEJM Editorial in January and White et al Ann Int Med 93, 403 for proposal to switch from concentrate to cryoprecipitate (Lancet i, 745). Writer asks why if there is an iceberg have not W. German haemophiliacs got AIDS (heavy uses of US concentrate). No strong argument for change of treatment policy.

1983 April

Hypothesis that alloantigens in factor VIII concentrate induce immune changes which make individuals more susceptible to infection by a transmissible agent (Shankey, AIDS Research 1, 83).

## CAL15(140211)

- 1983 May Retrovirus cultured by French workers from patient with PGL. This is first report of virus to be known as LAV (lymphadenopathy associated virus) later as HTLVIII and HIV1. (Barre-Sinoussi et al Science, 220, 868). Other workers noted an antibody in patients with AIDS which cross-reacted with HTLV1 (HTLV-MA; membrane associated antigen) Essex et al Science 220, 868.
- Further report of immune abnormalities in haemophiliacs. Of interest is the observation of an increased  $T_8$  numbers. Immunity was noted to be normal in individuals treated only with cryoprecipitate (Landay et al JCI 71, 1500).
- 1983 June General recommendations on treatment policy sent by Reference Centre Directors' to all Haemophilia Centre Directors in UK.
- 1983 July Absence of AIDS in Australian haemophiliacs possibly because do not use commercial factor VIII; all factor VIII is manufactured from locally produced volunteer donor blood. (Rickard et al, Lancet ii, 50).
- 1983 August A further report of immune abnormalities in asymptomatic haemophiliacs (de Shazo et al Ann Int Med 99, 159) but it still was not clear whether these were due to latent infection with an AIDS virus or due to factor VIII concentrate.
- 1983 September Raised interferon levels reported in haemophiliacs as in homosexuals. This was suggestive that haemophiliacs might be latently infected with an AIDS virus (Eyster et al NEJM 309, 585).
- 1983 October Another publication from Canada demonstrated immune abnormalities in haemophiliacs similar to AIDS patients. Those with severe haemophilia had greater degree of abnormality than those with mild form of haemophilia (Tsoukas et al Can Med Ass J, 129, 713) US National Haemophilia Foundations Recommendations issued October 22nd 1983 (details to be appended). Four haemophiliacs described with PGL like syndrome (Gervais, AIDS Research, 1, 197).
- 1983 November First UK AIDS case in haemophilia reported (Daly and Scott Lance ii, 1190).
- 1983 December Total of 21 cases of AIDS in haemophilia in US (19 haemophilia A; 2

## CAL15(140211)

haemophilia B) and 7 from outside US (MMWR 32, 613).

- 1984 January Wife of haemophiliac reported with AIDS – first evidence of heterosexual transmission in haemophilia (Pitchenik Ann Int Med 100, 62).
- 1984 February Study demonstrating 5/39 haemophiliacs positive for HTLV-MA (HTLV1) and that B2 microglobulin and Thymosin alpha 1 increased in haemophiliacs (Kreiss Ann Int Med 100, 178).
- This study demonstrated antibodies to HTLV1 which we now know are against HIV but cross react with HTLV1 ie they are a false positives. This early evidence that some haemophiliacs may be infected by a latent virus.
- 1984 April LAV(HIV) isolated as live virus from two haemophilia B patients – one having AIDS the other asymptomatic (Vilmer et al, Lancet i, 753).
- 1984 May Gallo and colleagues culture HTLVIII from two AIDS patients (Popovic et al Science 224, 497).
- Ratnoff in published lecture reviews his experience of immune disturbances and AIDS cases. Although acknowledges benefits of factor VIII concentrates wonders whether it would not have been prudent to use cryoprecipitate. States that his hospital has banned use of factor VIII concentrate except for severe life threatening bleeding. (Unfortunately this policy change was too late to prevent HIV infection) (Ratnoff J. Lab Clin. Med 103, 653).
- 1984 June Gallo et al report 100% AIDS patients have antibodies to HTLVIII (HIV) (Safai et al Lancet, i, 1438).
- French workers publish antibody prevalence in homosexuals to LAV (HIV1) in 75% of PGL, 38% AIDS and 18% healthy homosexuals (Brun-Vezinet et al, Lancet i, 1253).
- Editorial in British Medical Journal 288, 1782, accepts that AIDS is transmitted by blood products. 1/1000 USA haemophiliacs has AIDS but 50% have immune abnormalities.

## CAL15(140211)

Survey of European haemophiliacs reveals that 11 of 13,000 have AIDS and 179 have evidence of immune abnormalities. (Bloom Lancet i. 1452).

Study in Edinburgh of haemophiliacs in an apparently AIDS free area treated with factor VIII manufactured from locally collected blood demonstrated immune abnormalities comparable to US haemophiliacs who may be latently infected with AIDS virus (Carr et al Lancet i, 1431).

AIDS – New disease in Haemophiliacs affecting older aged individuals, high concentrate users. Use of clotting factor concentrate has dramatically reduced haemophilia mortality in 1970's. In 1982 haemorrhage may even case a death amongst haemophiliacs (Johnston, American Journal of Epidemiology, 121, 797).

1984 July

Selective growth of a LAV in CD4 lymphocytes of healthy carrier noted (Klatxmann et al Science 225, 59-67).

Study of Danish haemophiliacs 14/22 (64%) anti HIV positive – most had received US commercial factor VIII (Melbye et al Lancet ii, 40).

AIDS reported in haemophiliacs treated only with cryoprecipitate (Can Med Ass J 131, 45).

1984 August

Third group report ARV (AIDS Related Virus) from San Francisco patients – later found to be identical to HIV1 (Levy et al Science, 225, 840).

In a study of US haemophiliacs 72% anti LAV (HIV1) positive. T cell numbers in peripheral blood present in equivalent numbers in anti LAV positive and negative patients. This is further evidence that factor VIII per se modulates the immune system. Large users of factor VIII were more likely to be anti LAV positive (Ramsay et al Lancet ii 397).

1984 September London study of anti HTLVIII reported the following positivity rates AIDS 97% Homosexuals 59% Haemophiliacs 34% I.V. Drug Users 1.5% (Cheingsong-Popov et al, Lancet, ii, 477).

First report that retrovirus is heat sensitive and that heating freeze dried factor VIII to 68°C destroys the virus (Levy et al Lancet ii, 722).

## CAL15(140211)

- 1984 October Additional report that Cutter Laboratories had demonstrated heat sensitivity of HIV (MMWR 33, 589, 1984).
- Medical and Scientific Advisory Council of National Haemophilia Foundation of US "Recommendations Concerning AIDS and the Treatment of Haemophilia" October 13th.
1. Cryoprecipitate for infants and children less than 4 years.
  2. Newly identified patients never previously treated with factor VIII.
  3. All other patients should receive heat treated concentrates although only scant evidence for the efficiency of viral inactivation and safety.
  4. Patients should continue to treat bleeds with clotting factor as prescribed by the physician.
- 1984 November A study of US haemophiliacs reported that 65% are anti HTLVIII positive. At this stage it was not clear whether all individuals who were antibody positive were infected with HTLVIII or whether in some the virus had been cleared from the body as happens with most viral infections and the presence of antibody merely denotes previous infection (Nature Kitchen et al, 312, 367).
- 1984 December SNBTS introduced heat treated factor VIII concentrate. Initial supplies of heat treated commercial concentrates became available.
- Scotland reported that only 16% of haemophiliacs were anti HTLVIII positive compared to 59% Danes who had been treated with US commercial concentrate. Of a group of 11 patients who received no blood products 1979-84 none was anti HTLVIII positive. Only 2 of 7 patients treated with locally produced Scottish factor VIII concentrates were anti-HTLVIII positive. Higher prevalence of seropositivity in those who were large users of factor VIII concentrate (Melbye et al Lancet, ii, 1444).
- Lancet editorial – makes similar recommendations to NHF (Lancet, ii, 1433).

## CAL15(140211)

Another study of US haemophiliacs demonstrated 30/54 anti-HTLVIII positive with 20/21 with PGL being positive. 50% of anti HTLVIII negative patients of immune deficiency by skin testing (Tsoukas, NEJM, 311, 1514).

Haemophilia Centre Directors' Organisation sent out AIDS Advisory Document to all UK Haemophilia Centre Directors. Document discusses the various options for treatment and gives general recommendation for use of heated concentrates.

1985 January Reservations expressed by Bird et al (Lancet i, 162) about effect of heated concentrates on immune system, and that such material might provoke development of anti factor VIII inhibitors and promote HTLVIII by stimulating immune system of patient with partially heat denatured protein.

Child of haemophiliac develops AIDS due to wife becoming infected sexually and giving birth subsequently to infant who develops AIDS (Ragni et al Lancet i 133).

US Blood Collection Agencies Statement on strengthening donor screening – recommend anti HTLVIII screening (MMWR 34.1).

1985 February Use of cryoprecipitate is reported to be associated with lower risk of ARV (HIV) positively. Users of > 300 U/kg/year – i.e. large users; concentrate 26/26 positive while only, 2/6 cryoprecipitate users were positive. Virus cultured from one patient therefore at least one patient had active infection (Koerper et al Lancet i, 275).

Reply to criticism by Bird of heat treating factor VIII. Considers that immune abnormality in many haemophiliacs may be due to infusion of foreign proteins and that on current evidence only a minority of patients will get AIDS (Lancet i, 225) Bloom (Lancet i, 336) also replies to Bird's letter stating that at least two batches of NHS concentrate had transmitted HIV and urging use of heat treated concentrate.

A retrospective study using frozen serum samples from haemophiliacs in California and Georgia indicate that the first LAV positive sample was in 1978 but that most patients seroconverted in 1982/3. By the end of 1984

## CAL15(140211)

85% of patients were positive. The interpretation of anti-HIV positive result unknown; is it an immune reaction or has virus been neutralised and the individual no longer infected or does live virus co-exist with specific transfused from the bottles of factor VIII concentrate (Evatt, NEJM, 312, 483).

1985 February Preliminary evidence that dry heating of factor VIII concentrate (Haemofil T) renders it not infectious for LAV. No seroconversion in 18 patients observed. (Rouzioux et al Lancet i 271).

Study of haemophiliacs in UK; 9 of 15 treated with commercial and NHS concentrate seroconverted 1982-4 whereas 13 moderate and mild haemophiliacs treated with NHS and cryoprecipitate were all negative in September 1984 (Machin et al Lancet i, 336). Study from New York of T<sub>4</sub> numbers in haemophiliacs using concentrates compared to transfusion dependent B-thalassaemics and sickle cell patients. No patient had AIDS. T<sub>4</sub> numbers less in haemophiliacs. Concluded this is due to immune suppression and AIDS agent. No anti HTLVIII data on patients (Jason, JAMA, 253, 1140).

90% of patients with severe haemophilia who had been frequently treated are anti-HTLVIII positive. 0% anti-HTLV positive of individuals treated with factor IX, volunteer plasma or cryoprecipitate (Goedert, NEJM, 65, 492).

1985 March First ELISA test for anti-HTLVIII licensed by FDA in US.

Glasgow haemophiliacs who had received commercial concentrate seroconverted 1981-83 (Madhok et al, Lancet I, 524).

1985 (Continued) Case report of haemophiliac heterosexual contact who may have become infected by anal intercourse (Melbye NEJM).

Letter of Ratnoff listing morbidity and mortality due to AIDS or AIDS like syndrome in his patients. Comments that it is curious that only 5 of 84 haemophiliacs have opted for cryoprecipitate therapy (Ratnoff Ann Int Med 103, 412).



## CAL15(140211)

- 1985 April Cryoprecipitate usage is associated with lower rate of anti HIV positivity, 2 of 11 were anti HIV positive (McGrady AIDS Conference Atlanta). In a study of UK haemophiliacs 28 of 52 were anti HTLVIII positive and the chance of positivity was related to amount of factor VIII concentrate usage. None of 11 NHS factor VIII concentrate users were positive although two recipients of NHS factor IX concentrate had seroconverted.
- Reduction in T<sub>4</sub> cell numbers was similar in anti HTLVIII negative and positive individuals (Moffat et al, Brit. J. Haemat. 61:157).
- A further study reported similar reduction in T<sub>4</sub> and T<sub>4</sub>/T<sub>8</sub> in severe haemophiliacs treated with concentrates as mild as haemophiliacs and von Willebrands disease patients treated with cryoprecipitate or plasma (Kessler Lancet).
- 1985 (Continued) Review of haemophilia and AIDS by Levine – outline major clinical benefits of factor VIII concentrate therapy. States that AIDS cases in haemophilia reading 1%. Considers that attack rate has reached a peak and that only a minority of infected patients will get AIDS (Levine, Ann Int Med 103, 723).
- 1985 May Further report that heat treatment (Behring) destroys HTLVIII transmissibility (Lancet, Mosseler, i, 1111).
- 1985 June Bloom et al on behalf of UK Haemophilia Centre Directors advocates use of heat treated concentrates instead of non heated NHS product or cryoprecipitate because of rising prevalence of HIV in community. Urge the early introduction of anti HTLVIII screening of all donations by blood transfusion services (Bloom et al, BMJ 290, 1901).
- 1985 September Survey of Newcastle haemophiliacs treated with commercial and NHS factor VIII. Of 99 haemophilia A patients, 76 were anti-HTLVIII positive; 1 of 3 who had received only NHS concentrate was positive. Two patients with basal factor VIII 5-10% given concentrate rather than cryo were positive. Patient with mild haemophilia A given concentrate for major bleed became anti HTLVIII positive. Of 36 heterosexual contacts 3 were anti HTLVIII positive.
- 1985 (Continued) Anti-HTLVIII positivity compared between concentrate and cryoprecipitate

## CAL15(140211)

users in Seattle. In 1983 concentrate users 65% and cryoprecipitate users 31% positive and 1984 77% and 40% respectively were positive. Calculated that the risk of seroconversion from 1981 to 1984 3.9 times higher using concentrate compared to cryoprecipitate (Gjerset et al 66: 718, Blood).

1985 October Anti-HTLVIII screening introduced simultaneously by all transfusion centres in UK. Evidence that heating freeze dried factor VIII at 60°C for 30 hours (Armour) does not transmit HTLVIII (Felding et al, Lancet ii, 832).

Letter to Lancet considers that heating at 60°C for 10 hours should be adequate to kill 20 logs of IV in lyophilised factor VIII concentrate. This apparent degree of virus kill should be more than adequate to prevent HIV transmission. (Petricciani et al, Lancet ii, 890).

1985 November Data presented to demonstrate that in plasma exposed to ethanol in the cold (as happens in plasma fractionation to prepare factor VIII concentrate) results in substantial virucidal effect (Piszkiwicz, Lancet ii, 1188).