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INFECTED BLOOD INQUIRY

EXHIBIT WITN2988005

FACTS ON AIDS, HCV & HAEMOPHILIA TREATMENT AS REPORTED IN THE PUBLIC LITERATURE

TAB #	DATE	PUBLICATION	EVENT
1	1967	Biggs, R., "Thirty Years of Haemophilia Treatment in Oxford," *British Journal of Haemotology*, Vol. 13, p. 452-63.	This article details the clinical course in the UK of people who suffer from haemophilia.
2	1972	Kasper, C.K. and Kipnis, S.A., "Hepatitis and Clotting-Factor Concentrates," *Journal of the American Medical Association*, Vol. 221, No. 5, p. 510.	The study reports observations of newly-diagnosed patients with haemophilia treated with concentrates; authors conclude "that older children and adults who have had little exposure to blood products are at a high risk of developing clinical hepatitis after introduction of clotting-factor concentrates."
3	November 1972	Alter, H.J., Holland, P.V. et al., "Posttransfusion Hepatitis after Exclusion of Commercial and Hepatitis B Antigen-Positive Donors," *Annals of Internal Medicine*, Vol. 77, No. 5, pp. 691-99.	First publication detailing the existence of non-A, non-B Hepatitis (NANBH) after treatment with commercial factor concentrates.
4	1975	Biggs, R., Rizza, C.R.C., Blackburn, E.K. et al., "Factor VIII Concentrates Made in the United Kingdom and the Treatment of Haemophilia Based on Studies Made during 1969-72. Report of the Medical Research Council's Blood Transfusion Research Committee Working Party on the Cryoprecipitate Method of Preparing AHF Concentrates," *British Journal of Haematology*, Vol. 27, pp. 391-405.	During the period considered, a total of 62 deaths were recorded. Of the 62 deaths, 29 or almost half were directly the result of haemophilia.
5	1 May 1975	**UK Document:** UK Department of Health and Social Security [DHSS] Letter to All Regional Medical Officers regarding "Blood Donation	"[I]t is not necessary to discontinue the collection of blood at prisons and similar institutions as long as all donations are subjected to one of the more sensitive [Hepatitis B surface antigen (HBsAg)] tests."

TAB #	DATE	PUBLICATION	EVENT
		and Hepatitis."	
6	1 March 1976†	US Department of Health, Education, and Welfare, *Unsolved Therapeutic Problems in Hemophilia: Proceedings of a Conference Sponsored by Bureau of Biologics, FDA; Division of Blood Diseases and Resources, NHLBI and National Hemophilia Foundation*, DHEW Publication No. (NIH) 77-1089, (Fratantoni, J.C. and Aronson, D.L. Eds.).	This publication contains reports by various scientists and haemophilia treaters regarding pooled factor concentrates, cryoprecipitate and hepatitis. Report by UK treaters on the mortality of UK haemophiliacs, causes of death listed were: 1) intra-cerebral bleeding, 2) intra-abdominal bleeding (retroperitoneal or perirenal bleeding, intramural hematomas of intestine), 3) gastrointestinal bleeding (haematemisis and malaena, peptic ulcer) and 4) miscellaneous causes which included non-haemorrhagic deaths.
7	July 1976	Hoofnagle, J.H., Gerety, R.J., Thiel, J. and Barker, L.F., "The Prevalence of Hepatitis B Surface Antigen in Commercially Prepared Plasma Products," *Journal of Laboratory and Clinical Medicine*, Vol. 88, No. 1, pp. 102-13.	"Use of more sensitive and more reliable tests for HBsAg will probably reduce contamination of plasma pools with HBsAg to undetectable levels…however the "high risk" plasma products (fibrinogen, antihemophiliac factor (AHF), Factor IX concentrate) must still be considered capable of transmitting hepatitis and used only with the strictest indications."
8	20 August 1978	**UK Document**: Craske, J., Public Health Laboratory, Withington Hospital, Manchester, UK, *Report of the Haemophilia Centre Directors' Hepatitis Working Party – 1978.*	Dr. John Craske summarizes his visit to the Hepatitis Laboratory at the United States Food and Drug Administration's (FDA) Bureau of Biologics (BoB), Bethesda, near Washington. He discusses his intent, "to undertake some collaborative work which will involve attempts to reproduce NANBH in chimpanzees by transfusion of suspect batches of factor VIII identified in surveys in the UK."
9	1981	Gerety, R.J. and Eyster, M.E., "Hepatitis Among Hemophiliacs" in *Non-A, Non-B Hepatitis*, (Gerety, R.J. Ed.) Academic Press, New York, pp.	This book chapter discusses exposure to hepatitis as a result of replacement therapy and attempts to prevent transmission of hepatitis. "Results of these studies indicate that a significant degree of histologically confirmed liver disease is common in hemophiliacs."

† Also referenced in the UK Tainted Blood Campaign Accusations Document or on its website timeline. This symbol (†) is used throughout the document and carries the same meaning.

TAB #	DATE	PUBLICATION	EVENT
		97-117.	
10	5 June 1981†	CDC, "Pneumocystis Pneumonia – Los Angeles," *Morbidity and Mortality Weekly Report [MMWR]*, Vol. 30, No. 21, pp. 250-52.	The CDC first reports new, previously unknown pneumocystis carinii pneumonia (PCP) cases discovered in young, sexually active male homosexuals. "[O]bservations suggest the possibility of a cellular immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystis and candidiasis."
11	31 July 1981	**UK Document:** UK DHSS Letter to HM Treasury, London regarding "Blood Products Laboratory [BPL] – Redevelopment." [Author and Recipient Unknown.]	"The present laboratory cannot meet the demands for products nor can it comply with modern pharmaceutical manufacturing standards." A 1979 inspection report of the Blood Products Laboratory (BPL) by the Medicines Inspectorate concluded, "if BPL were a commercial operation we would have no hesitation in recommending that manufacturing should cease until the facility was upgraded to a minimum acceptable level."
12	January 1982	Bove, J.R. et al., "Report of the *Ad Hoc* Committee on ALT Testing," *Transfusion*, Vol. 22, No. 1, pp. 4-5.	"Therefore, at this time we do not advise routine donor testing for [alanine aminotransferase] ALT as a means of reducing the incidence of non-A, non-B hepatitis."
13	14 July 1982†	National Hemophilia Foundation [NHF], "Hemophilia Patient Alert #1," *Hemophilia Newsnotes*.	"The Centers for Disease Control (CDC) issued a report that three hemophiliacs had developed rare and unusual infections associated with a condition in which there is a decrease in the body's ability to combat disease." "IMPORTANT REMEMBER, CDC IS NOT ADVISING A CHANGE IN TREATMENT REGIMEN AT THIS TIME. IF THERE ARE ANY QUESTIONS, CONTACT YOUR PHYSICIAN OR HEMOPHILIA TREATMENT CENTER."‡
14	16 July 1982†	CDC, "Pneumocystis Carinii Pneumonia among Persons with Hemophilia A," MMWR, Vol. 31, No. 27, pp. 365-67.	"CDC recently received reports of three cases of Pneumocystis Carinii Pneumonia (PCP) among patients with Hemophilia A and one without underlying disease. Two have died; one remains critically ill. All three were heterosexual males; none had a history of intravenous (IV) drug abuse… For each patient, records of administration of Factor VIII concentrate were

‡ Similar advice was reprinted in all NHF recommendations through the end of 1985.

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			reviewed to determine manufacturer and lot numbers. No two of the patients are known to have received concentrate from the same lots."
15	19 July 1982	NHF, "Pneumocystis Carinii Pneumonia," Chapter Advisory No. 2.	This newsletter summarizes a meeting called by the Office of Biologics (OoB) and CDC. "The purpose of the meeting was to discuss facts relating to a disease of unknown origin which results in an immuno-suppressive condition which has been reported in three cases of people with hemophilia...It is important to know at this time the risk of contracting this immuno-suppressive agent is minimal and CDC is not recommending any change in blood product use."
16	27 July 1982[†]	Foege, W.H., *Summary Report on Open Meeting of PHS [Public Health Service, FDA] Committee on Opportunistic Infections in Patients with Hemophilia.*	This document outlines a meeting held to consider the significance of opportunistic infections PCP in three patients with haemophilia. The underlying disease is renamed Acquired Immune Deficiency Syndrome (AIDS).
17	30 July 1982	NHF, "Acquired Immune Deficiency Syndrome (AIDS)," *Hemophilia Newsnotes*, Medical Bulletin No. 2, Chapter Advisory No. 3.	This newsletter summarizes a meeting held to determine the significance of immune dysfunction in three haemophiliacs. It concludes that surveillance of haemophilia patients should begin immediately to gather more evidence to determine whether the three haemophiliacs had AIDS and that efforts should be intensified to assure the safety of Factor VIII and other blood products. It also notes that the underlying disease has been renamed AIDS.
18	1 September 1982	Mannucci, P.M., Colombo, M. and Rizzetto, M., "Nonprogressive Course of non-A, non-B Chronic Hepatitis in Multitransfused Hemophiliacs," *Blood*, Vol. 60, No. 3, p. 655-58.	"Eleven hemophiliacs with chronic liver disease were studied prospectively for six years...study of the serum, intrahepatic markers for Hepatitis B, and delta viruses suggests that chronic liver disease is non-progressive in hemophiliacs who have no intrahepatic viral markers." "Even though these studies clearly show that there is a spectrum of histologic abnormalities in hemophiliacs, there are still a number of unanswered questions concerning their clinical significance."
19	3 September 1982	CDC, "Hepatitis B Virus Vaccine Safety: Report of an Inter-Agency	"Beginning in 1978, a disease or group of diseases were recognized, manifested by Kaposi's sarcoma and opportunistic infections, associated with a specific defect in cell-mediated immunity. This group of clinical

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		Group," *MMWR*, Vol. 31, pp. 465-67.	entities, along with its specific immune deficiency, is now called AIDS."
20	October 1982	Aledort, L.M., "Current Concepts in Diagnosis and Management of Hemophilia," *Hospital Practice*, pp. 77-92.	"Replacement therapy is available in two forms: wet and dry. Among the wet products (fresh frozen plasma and cryoprecipitate) and dry products (lyophilized cryoprecipitate and factor concentrates), dried Factor VIII and IX concentrates are generally preferred…"
21	9 December 1982†	NHF, "Acquired Immune Deficiency Syndrome (AIDS) Update," *Hemophilia Newsnotes*, Chapter Advisory No. 4.	This newsletter summarizes the CDC's AIDS update reporting four additional cases of Haemophilia A patients with AIDS. "It is NHF's point of view that patients and parents should be aware of the potential risks. If you have any questions regarding this matter, they should be directed to your treating physician and/or NHF."
22	1983	Kernoff, P., "AIDS and Haemophilia" *The Bulletin*, (The Haemophilia Society ed.).	"I think it's beyond doubt that many haemophiliacs in this country will have the same sort of test changes that were found in America. So far as possible differences between National Health Service (NHS) and commercial concentrates are concerned, we don't know yet, although I expect we soon shall. It wouldn't surprise me if there weren't any differences. If there are, we shall have to scratch our heads to understand why. But to jump to the conclusion that commercial concentrates are more dangerous than NHS concentrates would certainly be premature."
23	13 January 1983†	Memorandum from Edward O. Carr, President of the American Association of Blood Banks [AABB], to AABB Institutional and Associate Institutional Members regarding "Joint Statement on Acquired Immune Deficiency Syndrome (AIDS) Related to Transfusion."	"We realize that there is no absolute evidence that AIDS is transmitted by blood or blood products, and we understand the difficulty in making recommendations based on insufficient data. There is a need for additional information about this disease."
24	17 January 1983	NHF, "AIDS: NHF Medical and Scientific Advisory Council Develops Position; NHF and Industry Meet,"	Medical and Scientific Advisory Council (MASAC) met and issued twelve recommendations addressed to physicians treating patients with haemophilia, Factor VIII manufacturers and the blood-banking industry. "There is still insufficient data to develop specific recommendations with

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		Hemophilia Information Exchange: AIDS Update, Medical Bulletin No. 5, Chapter Advisory No. 6.	respect to preferred blood product use (i.e., Factor VIII concentrate or cryoprecipitate) in the treatment of severe hemophilia."
25	March 1983	White, G.C. and Lesesne, H.R., "Hemophilia, Hepatitis and the Acquired Immunodeficiency Syndrome [AIDS]," *Annals of Internal Medicine*, Vol. 98, No. 3, pp. 403-04.	This article discusses the various infectious agents that may be transmitted to a blood product recipient, including hepatitis and AIDS and describes the dilemma providers are facing in deciding whether to treat a haemophiliac patient with a product that may contain the AIDS virus or face uncontrollable bleeding.
26	4 March 1983	CDC, "Prevention of Acquired Immune Deficiency Syndrome (AIDS): Report of Inter-Agency Recommendations," *MMWR*, Vol. 32, No. 8, pp. 101-03.	"Although the cause of AIDS remains unknown, the PHS recommends....As a temporary measure, members of groups at increased risk for AIDS should refrain from donating plasma and/or blood. This recommendation includes all individuals belonging to such groups, even though many individuals are at little risk of AIDS. Centers collecting plasma and/or blood should inform potential donors of this recommendation. The FDA is preparing new recommendations for manufacturers of plasma derivatives and for establishments collecting plasma or blood. This is an interim measure to protect recipients of blood products and blood until specific laboratory tests are available."
27	4 March 1983[†]	US Department of Health and Human Services [DHHS] Press Release regarding the Public Health Service's [PHS] recommended measures to prevent the transmission of AIDS.	The US Public Health Service issues recommendations to reduce the risk of acquiring and transmitting AIDS.
28	9 March 1983	NHF, "Update: AIDS Related Developments," *Hemophilia Newsnotes*, Chapter Advisory No. 7.	This newsletter lists the PHS' recommendations directed at reducing the risk of AIDS transmission. Issues discussed include sexual contact, blood and plasma donation, screening procedures, transfusions, and working toward developing safer blood products.
29	28 March 1983	**UK Document**: UK National Institute for Biological Standards and Control [NIBSC] Letter to the UK DHSS	"The US [is] taking steps to avoid the use of blood from high risk groups in the preparation of certain blood products."

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		regarding "AIDS." [Author and Recipient Unknown.]	
30	4 May 1983	**UK Document**: Letter from The Haemophilia Society [UK] to its members containing Arthur Bloom's statement on reports of AIDS in American haemophiliacs.	"We are no strangers to infective diseases, such as hepatitis, which can be transmitted by factor concentrates. Recent evidence indicates that in this respect at any rate concentrates prepared from British blood are not necessarily safer than those prepared in the United States....The cause of AIDS is quite unknown and it has not been proven to result from transmission of a specific infective agent in blood products...the importation of licensed blood products has always been strictly monitored and controlled....Thus whilst it would be wrong to be complacent, it would equally be counter-productive to alter our treatment programmes radically."
31	10 May 1983	**UK Document**: Letter regarding "Imports of Blood Products." [Author and Source Unknown.]	"Licensed products must satisfy the requirements of the [Medicines] Act for safety quality and efficacy."
32	24 June 1983†	CDC, "Acquired Immunodeficiency Syndrome (AIDS) Update -- United States," *MMWR*, Vol. 32, No. 24, pp. 309-11.	As of 20 June 1983, the United States [and its territories] has a total of 1,641 cases of AIDS. "Groups at highest risk of acquiring AIDS continue to be homosexual and bisexual men (71% of cases), IV drug users (17%), persons born in Haiti and now living in the US (5%), and patients with hemophilia (1%)."
33	24 June 1983	**UK Document**: Letter from Arthur Bloom and Charles Rizza, Haemophilia Centre Directors Organisation, regarding "Acquired Immune Deficiency Syndrome." [Recipient Unknown.]	"So far one possible case [of AIDS] has been reported to our organisation. This patient (A/1) conforms to the definition published by the CDC in Atlanta, Georgia but cannot be considered a definite case. We are not aware of any other definable patients amongst the UK haemophilic population..." "It was agreed that there is as yet insufficient evidence to warrant restriction of use of imported concentrates in other patients in view of the immense benefits of therapy but the situation will be constantly reviewed. Following the meeting [of the Reference Centre Directors] on 13th May, the Licensing Authority was asked to consider the implications for us of the revised recommendations of the American Food and Drug Administration which were made on March 24th 1983 to American plasma collecting agencies...." "The evidence to incriminate Factor IX concentrates in AIDS is even less than with Factor VIII and it seems logical to continue to use our normal

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			supplies of NHS concentrate...."
34	28 June 1983	**UK Document**: Committee on Safety of Medicines [CSM], "Suggested 'Agenda' for Discussion on AIDS in Relation to Licensed Blood Products."	"The advantages of requiring more stringent procedures than those now adopted in the US are questionable and the practicalities of doing so are clearly difficult and beyond the sub-committee's expertise...additional measures are not at present feasible on the scale needed. Tests, which need to be speedy and simple, for known agents may become available which could be introduced into the requirements for source plasma, but only a test to detect the presence of an identified etiological agent(s) could be expected to control AIDS."
35	30 June 1983	**UK Document**: World Federation of Hemophilia, "Resolutions by the World Federation of Hemophilia [WFH] General Assembly regarding Acquired Immune Deficiency Syndrome (AIDS)."	"There is insufficient evidence to recommend at the present any change in treatment; therefore present treatment of hemophilia should continue with whatever blood products are available, according to the judgment of the individual physicians."
36	July 1983	Public Health Service, US DHHS Pamphlet: "Facts About AIDS."	This information bulletin contains facts about AIDS. Topics discussed include the definition of AIDS, symptoms, causes, at-risk populations, transmission, treatment and prevention.
37	11 July 1983	**UK Document**: UK Haemophilia Centre Directors Hepatitis Working Party, "Factors to Be Considered in the Selection of Hepatitis Reduced Products for Clinical Trial – Evaluation of Residual Infectivity for Hepatitis Viruses."	This report considers the ethical problems associated with the assessment of heat treated products in clinical trials. "Since the only way of ensuring the susceptibility to non-A, non-B viruses is by using patients who have not previously received Factor VIII or IX concentrate, a choice will have to be made between using heat treated products from commercial sources, which might carry a small risk of AIDS transmission, or using National Health Service (NHS) concentrate which appears to carry a 100% chance of transmitting non-A, non-B Hepatitis."
38	15 July 1983[†]	**UK Document**: Committee on the Safety of Medicines, "Summary of Main Points from a Consideration of AIDS and Licensed Blood Products," CSM/83/7[th] Meeting, Tabled Paper 4.	"The possibility was considered of withdrawing US preparations from the UK. It was concluded that this is not at present feasible on grounds of supply. Moreover, the perceived level of risk does not at present justify serious consideration of such a solution."

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39	19 July 1983[†]	Summary Minutes – Meeting 8, Blood Products Advisory Committee [BPAC, FDA].	These minutes present a summary of discussions regarding US factor concentrate recall policy and related supply concerns. "It was very clear that confronted with this complex problem the Committee felt that a balance must be struck between theoretical risk of the product to recipients against the need for an uninterrupted supply of a life-sustaining therapy. As several members of the panel stressed, it would be undesirable to distribute and use a lot of product which incorporated plasma from a donor with a definite diagnosis of AIDS. However, signs and symptoms suggestive of AIDS (e.g., persistent lymphadenopathy, night sweats, etc.) would not be persuasive enough to dictate a recall of product."
40	21 July 1983	Memorandum from Dennis M. Donohue, Director of the Division of Blood and Blood Products [DBBP, FDA], to John C. Petricciani, Director of Office of Biologics [OoB, FDA], regarding "Results of the Blood Products Advisory Committee Meeting Related to the Safety of Plasma Derivatives."	This memorandum includes an interpretation of the Advisory Committee's review of Factor VIII safety in relation to AIDS and states: "[r]isk of transmitting AIDS to an individual hemophiliac from a specific lot of Factor VIII is very, very small if it exists."
41	28 July 1983	**UK Document**: Letter regarding "AIDS." [Author and Source Unknown.]	This letter notes that at the 19 July 1983 FDA meeting, "banning all products made before the implementation of the March '83 regulations was discussed but was rejected on a majority vote. The hiatus in supplies which such action would cause was the deciding factor."
42	23 August 1983	NHF, "AIDS and Hemophilia: Questions & Answers," *Hemophilia Information Exchange: AIDS Update.*	This newsletter lists questions and answers about AIDS, including the definition of AIDS, the risks of AIDS, treatment issues and current research.
43	23 August 1983	**UK Document**: Letter regarding "Use of Blood from Prisons." [Author and Source Unknown.]	"Transfusion Directors have been aware of the dangers of relying too heavily on prisons as a source of donation for some time.…There is at least one [region] which has to view them as a major source of donations in order to meet targets…AIDS has now called the wisdom of continuing to view prisons as a source of blood even further into question…in the past [the

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			Home Office] have been very much in favour of blood donations by prisoners."
44	9 September 1983	CDC, "Update: Acquired Immunodeficiency Syndrome (AIDS) – United States," *MMWR*, Vol. 32, No. 35, pp. 465-67.	"As of 2 September 1983, physicians and health departments in the United States and Puerto Rico had reported 2,259 persons with Acquired Immunodeficiency Syndrome (AIDS) who met the surveillance case definition." This report states that 1% of these persons were haemophiliacs.
45	22 October 1983	NHF, "The National Hemophilia Foundation Medical and Scientific Advisory Council Recommendations to Prevent AIDS in Patients With Hemophilia," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 9, Chapter Advisory No. 12.	These "Recommendations to Prevent AIDS in Patients with Hemophilia" addressed which patients should be treated with cryoprecipitate, the exclusion of high-risk donor groups and research in surrogate AIDS testing. The recommendations also encouraged continued development of viral inactivation processes and urged manufacturers to recall any lot of concentrate with plasma from a donor later identified as having AIDS.
46	1 November 1983	Sonnabend, J.A., "The Etiology of AIDS," *AIDS Research*, Vol. 1, No. 1, pp. 1-12.	"Despite vigorous attempts to isolate a new agent from clinical isolates by a variety of techniques including animal inoculation experiments, the AIDS agent remains elusive." "The first issue of this new journal is an appropriate occasion to review an alternative hypothesis regarding the genesis of AIDS. This hypothesis proposes that there is no specific etiologic agent of AIDS, and suggests that the disease arises as a result of a cumulative process following a period of exposure to multiple environmental factors."
47	25 November 1983	CDC, "Acquired Immunodeficiency Syndrome (AIDS) – Europe," *MMWR*, Vol. 32, No. 46, pp. 610-11.	As of 20 October 1983, Europe had 267 cases of AIDS "reported by member countries of the European Region of the World Health Organization (WHO)."
48	10 December 1983	Jones, P., "Acquired Immunodeficiency Syndrome [AIDS], Hepatitis, and Haemophilia," *British Medical Journal*, Vol. 287, pp. 1737-38.	"People with haemophilia, their families, and their doctors feel threatened by the deluge of speculation about the possible side effects of treatment with blood products. Two topics hold their attention: the risk of contracting the acquired immunodeficiency syndrome (AIDS) and the risk of developing hepatitis and subsequent chronic liver disease."

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49	15 December 1983†	Blood Products Advisory Committee [BPAC, FDA] Meeting Transcript, Vol. 1.	This meeting's objective was to review the results of research to define tests which could be applied to blood, plasma or donors that would indicate an increased risk of the transmission of AIDS. Topics discussed included donor characteristics, test sensitivity and specificity, and a summary of tests performed for anti-Hepatitis B core antibody at the New York Blood Center.
50	21 December 1983	NHF, "Revised Medical and Scientific Advisory Council Recommendations to Prevent AIDS in Patients with Hemophilia," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 9, Advisory No. 12.	This newsletter reports revisions to MASAC "Recommendations to Prevent AIDS in Patients with Hemophilia" as follows: "1) Modification of donor screening language…to make it explicit that our intent is for screening to be conducted in a discreet and sensitive fashion; 2) An added recommendation…that donors be screened for symptoms; and 3) Specific reference to the need for additional data in regard to modified Factor VIII products…" (internal references omitted). All other recommendations were unchanged.
51	6 January 1984	CDC, "Update: Acquired Immune Deficiency Syndrome (AIDS) – United States," *MMWR*, Vol. 32, No. 52, pp. 688-91.	As of 19 December 1983, the United States and its territories have a total of 3,000 patients who meet the surveillance definition for AIDS. Patients with haemophilia represent 1% of all cases.
52	9 January 1984	**UK Document:** The Haemophilia Society Blood Products Sub-Committee [UK] Minutes regarding the supply of blood products in the UK.	"[T]here is no reason to suppose that the use of paid donors by commercial companies results in a product of poorer quality than that from the UK…. Recent work suggests that British material is no better (and may be worse) than imported material with respect to hepatitis."
53	3 February 1984	NHF, "Questions Raised About Sexual Relations and AIDS," *Hemophilia Information Exchange: AIDS UPDATE*, Chapter Advisory No. 14.	This newsletter discusses CDC's suspicion that AIDS was sexually transmitted from a haemophiliac to his wife and lists recommendations concerning the use of condoms.
54	29 March 1984†	**UK Document:** Memorandum from the [UK] Haemophilia Centre Directors Hepatitis Working Party to	"All products except those derived from NHS Factor VIII are made from plasma imported from the US, and, therefore, they carry a putative risk of transmission of AIDS…It is evident that 8 [heat treated] products will shortly

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		All UK Haemophilia Centre Directors regarding "Trials of 'Hepatitis Reduced' Factor VIII – An Update." [Author Unknown.]	be available on the market and, unless these are coordinated, there will not be enough patients available to evaluate each product carefully....It is important to ensure that each Company obtains an exemption from a clinical trial certificate from the UK Licensing Authority. Studies conducted on a named patient basis carry no protection under the Medicines Act, as the patient's doctor and not the Pharmaceutical Company carries the liability for compensation arising out of unexpected hazards which come to light as part of the trial."
55	16 April 1984†	NHF, "AIDS Status Report, DDAVP Available, Core Testing of Donors Initiated, NHF MASAC to Meet," *Hemophilia Information Exchange: AIDS UPDATE*, Chapter Advisory No. 15.	"During the first quarter (January-March) of 1984, 9 new cases of AIDS among hemophiliacs were reported by the Centers for Disease Control (CDC). The total number of hemophiliacs now affected with AIDS is 33 (three of those affected have other risk factors besides hemophilia)." "THE NHF REAFFIRMS ITS RECOMMENDATION THAT PATIENTS CONTINUE TO TREAT BLEEDING EPISODES WITH CONCENTRATE, OR CRYOPRECIPITATE AS PRESCRIBED BY THEIR PHYSICIANS. THE LIFE AND HEALTH OF HEMOPHILIACS DEPENDS UPON THE APPROPRIATE USE OF BLOOD PRODUCTS."
56	4 May 1984†	Gallo, R.C., Salahuddin, S.Z., Popovic, M. et al., "Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS," *Science*, Vol. 224, pp. 500-03.	"These studies of HTLV-III isolates from patients with AIDS and pre-AIDS and from some healthy individuals at risk for AIDS provide strong evidence of a causative involvement of the virus in AIDS."
57	9 May 1984	NHF, "Lymphotropic Cytopathic Viruses and AIDS, Genetic Engineering Breakthrough for Factor VIII," *Hemophilia Information Exchange: AIDS UPDATE*, Chapter Advisory No. 16.	This newsletter discusses the discovery of Human T-Lymphotropic Virus III (HTLV-III) and Lymphadenopathy-Associated Virus (LAV) and "their probable causative role in AIDS" and reports Genentech's announcement on 25 April 1984 of the production of genetically engineered Factor VIII – an important discovery because of the association between AIDS transmission and the use of blood products.
58	9 May 1984	Michela Reichman, Assistant Chancellor, University of California, San Francisco, Press Release: "UC-	"A study by Jay Levy, MD,...confirms findings by French scientists that a retrovirus – LAV – could be the primary cause of AIDS....The study by Levy and his coworkers indicate that the heating procedure used now by

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		San Francisco Studies Confirm French Finding of Retrovirus in AIDS and Demonstrate a Retrovirus Could Be Passed through Blood Clotting Factor."	Cutter eliminates the retrovirus effectively."
59	20 June 1984	US Department of Health and Human Services Press Release, *HHS News*.	"Five private pharmaceutical firms have been chosen to develop and distribute a blood test for AIDS."
60	30 June 1984	Bloom, A.L., "Acquired Immune Deficiency Syndrome and Other Possible Immunological Disorders in European Haemophiliacs," *The Lancet*, Vol. 8392, pp. 1452-55.	"Therefore the role of American concentrates in the causation of AIDS in European haemophiliacs must be regarded as unproven."
61	13 July 1984	CDC, "Antibodies to a Retrovirus Etiologically Associated with Acquired Immunodeficiency Syndrome (AIDS) in Populations with Increased Incidences of the Syndrome," *MMWR*, Vol. 33, No. 27, pp. 377-79.	"The isolation of retroviruses antigenically identical to LAV from a blood-donor-recipient pair, each of whom developed AIDS, provides further evidence that this virus is the etiologic agent of AIDS and may be transmitted through blood transfusion....Seventy-two percent of asymptomatic persons with Hemophilia A in a home-care treatment program demonstrated antibody to LAV antigens utilizing the Western blot technique. All had used Factor VIII concentrates from 1980 to 1982...Until the usefulness of positive and negative serologic tests is fully established, all individuals in populations with increased incidences of AIDS, as well as those outside such groups with positive tests, should comply with the March 1983 PHS recommendations for the prevention of AIDS to minimize the transmission of the syndrome."
62	August 1984	NHF, "AIDS and Hemophilia: Questions & Answers," *Hemophilia Information Exchange: AIDS UPDATE*.	"To date, there is no specific evidence indicating that there is greater risk with concentrate than with cryoprecipitate or fresh frozen plasma.... Hemophiliacs are urged not to withhold treatment if it is medically indicated....It is not known if heat treatment of concentrates has any effect on their potential to transmit AIDS."
63	1 August 1984	NHF, "HTLV-III/LAV Testing Update," *Hemophilia Information Exchange: AIDS UPDATE*, Chapter Advisory No. 17, Medical Bulletin No. 12.	"As expected, the majority of hemophiliacs tested positive for HTLV-III/LAV antibodies." (This statement refers to 72% of a small sample in a CDC study and approximately two-thirds of a larger sample in a study reported by NHF Medical Co-Director, Peter Levine).

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64	24 August 1984	Levy, J. et al., "Isolation of Lymphocytopathic Retroviruses from San Francisco Patients with AIDS," *Science*, Vol. 225, pp. 840-42.	"Although no conclusion can yet be made concerning [HTLV-III and LAV's] etiologic role in AIDS, their biologic properties and prevalence in AIDS patients certainly suggest that these retroviruses could cause this disease."
65	September 1984	Simon, T.L. and Bankhurst, A.D., "A Pilot Study of Surrogate Tests to Prevent Transmission of Acquired Immune Deficiency Syndrome by Transfusion," *Transfusion*, Vol. 24, No. 5, pp. 373-78.	"The surrogate tests [for AIDS] studied were nonspecific and did not appear worthy of future investigation."
66	8 October 1984	NHF, "NHF Reaffirms Position that Product Withdrawal Should Not Change Use of Clotting Factor," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 14, Chapter Advisory No. 19.	"On Friday, October 5, 1984, American Red Cross initiated a voluntary market withdrawal of one lot of AHF in the United States. The withdrawal was based on identification of a donor who was confirmed as having AIDS." Noting the precautionary nature of the withdrawal, the NHF advised: "AND MOST IMPORTANT, DESPITE THE CONCERN THAT MAY BE RAISED BY THE WITHDRAWAL OF PLASMA PRODUCTS, THE NHF REAFFIRMS ITS RECOMMENDATION THAT PATIENTS MAINTAIN THE USE OF CONCENTRATE, OR CRYOPRECIPITATE AS PRESCRIBED BY THEIR PHYSICIANS. THE LIFE AND HEALTH OF HEMOPHILIACS DEPENDS UPON THE APPRORIATE USE OF BLOOD PRODUCTS."
67	November 1984	Kasper, C.K., "Viral Transmission in Plasma Products," *The Hemophilia Bulletin* (Notes from the XXX Meeting, International Society on Thrombosis and Hemostasis, Miami Beach, Florida, November 15-17, 1984, Subcommittees on Factors VIII and IX).	"The viruses known to be transmitted in plasma products include Hepatitis B, NANBH the AIDS agent and human parvoviruses."
68	2 November 1984	CDC, "Update: Acquired Immunodeficiency Syndrome – Europe," *MMWR*, Vol. 33, No. 43, pp. 607-09.	In Europe, a total of 421 AIDS cases were diagnosed in ten countries (Denmark, France, the Federal Republic of Germany, Greece, Italy, the Netherlands, Spain, Sweden, Switzerland and the UK) as of 15 July 1984. The same countries reported 215 cases in October 1983. Twelve

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			out of 421 AIDS cases were haemophiliacs.
69	5 November 1984	NHF, "CDC Issues Update on AIDS & Hemophilia and Supports NHF's Medical and Scientific Council Recommendations Concerning Heat-Treated Clotting Factor," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 16, Chapter Advisory No. 21.	A 26 October 1984 CDC special report stated that "preliminary evidence concerning the effects of heat-treatment on the viability of the AIDS virus is strongly supportive of usefulness of heat-treatment in reducing the potential for transmission of the AIDS virus in factor concentrate products." NHF advised that: "Heat treated products are available in the United States from Alpha Therapeutics Corporation, American Red Cross, Armour Pharmaceutical Company, Cutter Biological and Hyland Therapeutics."
70	December 1984	**UK Document**: Research and Development Department, BPL Plasma Fractionation Laboratory [UK], *Annual Report to December 1984, R & D Estimates 1985/6.*	"It is well established that almost all previously untreated patients with no prior immunity to hepatitis viruses acquire NANBH after their first one or two infusions of either Factor VIII or Factor IX. The infection is often apparently trivial or sub-clinical but it is feared that more serious chronic liver damage may develop in later life. Heating coagulation factor concentrates in either the lyophilized state or in protective solutions is thought to be an effective action against NANBH viruses, HTLV-III and other retroviruses."
71	7 December 1984	**UK Document**: "AIDS: Newcastle Policy December 1984." [Author and Source Unknown.]	This document states that haemophilia policy requires "that all commercial concentrate used is to be heat treated." This decision was subjected to peer-review and was agreed upon based on recent CDC and NHF treatment recommendations. "Three companies (Alpha, Armour and Cutter) agreed to change stock without financial penalty."
72	11 December 1984	NHF, "AIDS Cases and Surveillance," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 19.	"As of December 10, 1984, fifty-eight cases of AIDS have been confirmed among patients with hemophilia and related bleeding disorders. Thirty-one have died."
73	12 December 1984	**UK Document**: Notes of the [UK] Haemophilia Reference Centre Directors Meeting, Blood Products Laboratory, Elstree.	"Directors felt they should use commercial heat treated Factor VIII in preference to commercial non-heat treated Factor VIII. Most agreed that untreated BPL Factor VIII could continue to be used until heat treated Factor VIII was available from Elstree."
74	14 December 1984[†]	Letter from Elaine Esber, Acting Director of the Office of Biologics Research and Review, [OBRR,	"Recently the HTLV-III virus has been reported as the etiologic agent of AIDS, and government and industry are proceeding as rapidly as possible with the development of a laboratory screening test for antibody to the

TAB #	DATE	PUBLICATION	EVENT
		FDA] to All Establishments Collecting Blood, Blood Components or Source Plasma and all Licensed Manufacturers of Plasma Derivatives regarding "Revised Recommendations to Decrease the Risk of Transmitting Acquired Immunodeficiency Syndrome (AIDS) from Blood and Plasma Donors."	virus…All of the basic principles of donor screening remain unchanged; only minor alterations in operating procedures will be required." Interim procedures to minimize the risk of transmitting AIDS through blood products or plasma derivatives include educational materials, medical questioning, self-exclusions and quarantine of product if AIDS is discovered.
75	20 December 1984	**UK Document**: The Haemophilia Society [UK] Press Release regarding the contamination of Scottish Factor VIII with HTLV-III virus.	The Society has been urging the DHSS for introduction of heat-treated concentrates. "Treatment by prescribed medication is the first priority for anyone with haemophilia, based on the firm conviction that haemophilia itself, is more dangerous than AIDS, in the light of the recent development of heat-treated product we urge members to press for these concentrates…we are not dissuaded from our view by statements that heat-treated concentrates should be further scientifically evaluated before they are introduced on a wider scale…."
76	22 December 1984	Editorial, "Blood Transfusion, Haemophilia and AIDS," *The Lancet*, Vol. 2, pp. 1433-35.	This editorial states that HTLV-III is relatively heat-labile or susceptible to destruction by heat, and therefore concentrates can be heat treated to reduce the risk. "In the UK unheated large-pool concentrates, even those prepared from voluntary donations, have transmitted non-A, non-B Hepatitis…Meanwhile we must not forget that by far the commonest cause of haemophilic death is bleeding."
77	1985	Kernoff, P.B.A., Lee, C.A., Karayiannis, P. and Thomas, H.C., "High Risk of non-A, non-B Hepatitis After First Exposure to Volunteer or Commercial Clotting Factor Concentrates: Effects of Prophylactic Immune Serum Globulin," *British Journal of Haemotology*, Vol. 60, pp. 469-79.	"Whether prepared from volunteer or commercial donor plasma, clotting factor concentrates carry a very high risk of acute NANBH in first exposure patients."
78	January 1985	**UK Document**: National Blood	"AIDS is a serious disease. Please do not give blood: if you are a

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		Transfusion Service [UK], "A.I.D.S.: Important New Advice for Blood Donors."	practicing homosexual or bisexual man, if you are a drug abuser who injects drugs, if you are a sexual contact of any of these people."
79	3 January 1985	**UK Document:** Notes of the [UK] Haemophilia Reference Centre Directors Meeting, Blood Products Laboratory, Elstree.	"Availability of tests: Dr. Craske advised that currently, the reagents were only available on a research basis, and that substantial resources would be required to enable the proposed workload to be undertaken. It was considered that to know the antibody status of every hemophiliac would be advantageous in determining the regime for treatment. However, the limited resources made it impossible to do routine tests at the moment." "Factor VIII Concentrates: It was agreed that heat-treated (HT) product should be given to all patients, if freely available, to include those found to be antibody +ve (positive). In the case of antibody –ve (negative) patients, it was agreed that from now on, treatment must be with HT material."
80	11 January 1985[†]	CDC, "Provisional Public Health Service Inter-Agency Recommendations for Screening Donated Blood and Plasma for Antibody to the Virus Causing Acquired Immunodeficiency Syndrome," *MMWR*, Vol. 34, pp. 1-5.	Two percent of all reported AIDS cases in the US are associated with the administration of blood or blood products. "Evidence has shown that a newly recognized retrovirus is the cause of AIDS…Tests to detect antibody to HTLV-III will be licensed and commercially available in the US in the near future to screen blood and plasma for laboratory evidence of infection with the virus….All blood or plasma should be tested for HTLV-III antibody by Enzyme-Linked ImmunoSorbent Assay (ELISA)."
81	18 January 1985	CDC, "Update: Acquired Immunodeficiency Syndrome – Europe," *MMWR*, Vol. 34, pp. 21-31.	In Europe, as of 15 October 1984, 559 cases of AIDS had been reported to the World Health Organization (WHO). The report states that 4% are haemophiliacs.
82	19 January 1985	Bird, A.G., Codd, A.A. and Collins, A., "Haemophilia and AIDS," *The Lancet*, Vol. 1, pp. 162-63.	"…We do not agree with the advice to switch completely to heat-treated Factor VIII for the treatment of Haemophila A. This decision would involve a probably irreversible change of policy and, as the editorial makes clear, would be based on inadequate evidence. Moreover the policy would expose all haemophiliacs to a new series of risks and difficulties. Our major concern stems from the very preliminary and mostly unpublished data on the heat sensitivity of the AIDS virus and the unknown but very real dangers of heat treatment of impure protein fractions. Even mild heat treatment will aggregate protein and the subsequent product will not only predispose to the phlogistic reactions

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			seen with intravenous gammaglobulin but also enhance the immunogenicity of native Factor VIII and thus the propensity to antibody formation".
83	14 February 1985	**UK Document:** Letter from the Public Health Laboratory, Withington Hospital, Manchester, UK, regarding HTLV-3 positive patients. [Author and Recipient Unknown.]	"If our suspicions that HTLV-3 infection is transmitted via Factor IX are confirmed, then it is likely that this infection in haemophiliacs resulting from NHS blood products may have occurred at a much earlier date than we thought."
84	2 March 1985[†]	Statement from Margaret M. Heckler, US Secretary of Health and Human Services, on FDA's approval of an HIV antibody screening test.	"The Food and Drug Administration has approved a test to screen blood supplies for antibodies indicating exposure to HTLV-III, the virus identified just last year as the cause of AIDS." "The test we are licensing today is not meant as a diagnostic tool for AIDS; it is designed to screen blood....The test we are approving today will be performed later in the laboratory, using a sample of the donated blood itself – it will not be performed on the individual....Never before in the history of medicine have we learned so much about an entirely new disease in so short a time. AIDS was first identified in 1981; we discovered its cause, the HTLV III virus, three years later in 1984. Today we are licensing a blood test which will identify the antibodies to the AIDS virus which will protect the blood supply for all Americans."
85	20 March 1985	"Dear Doctor" Letter from Frank Young, Commissioner of Food and Drugs, Public Health Service [PHS, FDA], regarding PHS' donor screening recommendations.	This letter notes that the first test to determine the presence of the HTLV-III antibodies in donors has been licensed by the FDA. "It is vital that both physicians and patients understand that the antibody test is NOT a test for AIDS....As with any serologic test, there will be some false positives, even in samples which are repeatedly reactive....The natural history of the disease is not completely understood at the present time, the medical significance of a positive result is unknown...."
86	22 March 1985	CDC, "Update: Acquired Immunodeficiency Syndrome – Europe," *MMWR*, Vol. 34, pp. 147-56.	In Europe, as of 31 December 1984, 762 cases of AIDS have been reported to the WHO. Of these, 3%, or 20, are haemophiliacs.
87	29 March 1985	NHF, "HTLV-III Antibody Testing for	"On March 2, 1985, Margaret M. Heckler, Secretary of the United States

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		Blood Donors Begins," *Hemophilia Information Exchange: AIDS UPDATE*, Chapter Advisory No. 25.	Department of Health and Human Services, announced the approval of a blood test which will screen donated blood for presence of the antibody to the HTLV-III virus, that is suspected of causing AIDS....The National Hemophilia Foundation has urged that the HTLV-III antibody test be used for all donors at all blood and plasma collection sites. The US Public Health Service has also taken this position which is being followed by volunteer and commercial blood collection centers. All blood samples showing a positive reactive test result will not be distributed for transfusion or further manufacturing into injectable products." "The Foundation's AIDS Task Force does not recommend that HTLV-III antibody testing be universally given to all persons with hemophilia, because whatever the results of these tests, there would not be a resultant change in treatment."
88	12 April 1985	NHF, "Revised Medical and Scientific Advisory Council Recommendations Concerning AIDS and the Treatment of Hemophilia," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 21, Chapter Advisory No. 26.	Revised recommendations now encourage patients with severe haemophilia to receive heat treated product due to "the accumulating evidence for the heat sensitivity of HTLV-III....We reaffirm our position that patients continue to treat bleeding episodes with clotting factor as prescribed by their physicians, as the risks of withholding treatment far outweigh the risks of treatment."
89	8 May 1985	NHF, "MASAC Revises Product Withdrawal Policy in Response to New Data on Heat Treatment, Product Withdrawal Announced," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 22, Chapter Advisory No. 27.	"Based on current information on the issue of heat treatment and HTLV-III, and on the recall of lots of Factor VIII and Factor IX concentrates to which a person subsequently found to have AIDS had donated, the MASAC no longer recommends that heat treated product be withdrawn." "The reason that MASAC revised its position concerning the withdrawal of heat treated product is because HTLV-III appears to be adequately killed under currently licensed heat treatment procedures at the number of infectious doses likely to be present in the final blood product."
90	10 May 1985	NHF, "The Potential Spread of HTLV-III to Sexual Partners of Persons with Hemophilia," *Hemophilia Information Exchange: AIDS UPDATE*, Medical	This newsletter reports on a study of ten HTLV-III antibody positive haemophiliacs and their spouses. The NHF emphasized that the "findings are very preliminary and will require confirmation with an appropriate number of negative controls as well as more spouse pairs....However, if

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		Bulletin No. 23.	confirmed, results suggest that the virus may be transmitted sexually from some healthy hemophiliacs to their spouses, and that an antibody negative virus positive carrier state might persist in these healthy spouses for years."
91	17 May 1985	CDC, "World Health Organization [WHO] Workshop: Conclusions and Recommendations on Acquired Immunodeficiency Syndrome," *MMWR*, Vol. 34, pp. 275-76.	"Member countries should inform the public that LAV/HTLV-III infection is acquired through heterosexual and homosexual intercourse, needle-sharing by IV drug abusers, transfusion of contaminated blood and blood products, transmission by infected mothers to their babies, and probably repeated use of needles and other unsterile instruments used for piercing skin/mucous membranes...Screen, where feasible, potential donors of blood and plasma [they] should be tested for antibody to LAV/HTLV-III and [treaters and manufacturers should] not use positive units for transfusion or for the manufacture of products where there is a risk of transmitting infectious agents...Reduce the risk of transmission of LAV/HTLV-III by FVIII and FIX concentrates by treating them by heat or other proven methods of inactivation. The use of such products is recommended."
92	17 May 1985	NHF, "News from Atlanta," *Hemophilia Information Exchange: AIDS UPDATE,* Chapter Advisory No. 28.	"During the past year it has become clear that sexual partners of bisexual men and IV drug abusers have a small but real risk of AIDS. In addition, several cases of AIDS or so-called AIDS-related complex have occurred in sexual partners of apparently healthy persons in high risk groups....There are now two documented cases of AIDS of [sic] sexual partners of persons with hemophilia in the United States." "Several studies have now shown convincingly that heat treatment of Factor VIII and IX concentrates kills live HTLV-III virus which had been added to the concentrate. The amount of virus added in these experiments appears to be much in excess of what could be present in factor concentrates, even if good donor screening were not used. Further, the virus was killed after only a few hours of heating, whereas many hours of heating are used by commercial manufacturers."
93	17 May 1985	NHF, "Stabilization of the Incidence of AIDS in Hemophilia Reported," *Hemophilia Information Exchange: AIDS UPDATE*, Chapter Advisory No. 29, Medical Bulletin No. 24.	"While the majority of persons with hemophilia have developed the HTLV-III antibody, less than 1% have contracted AIDS. As of May 3, there were 73 persons with hemophilia and AIDS in the US." A "levelling [sic] off or slight drop in the increase of new cases suggests that there may be a limited number of persons with hemophilia who after acquiring viral exposure are

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			susceptible to the development of the clinical syndrome we call AIDS, and that the remaining susceptibles may be relatively few in number. This is very hopeful information."
94	11 June 1985	**UK Document:** World Health Organization Meeting Minutes regarding "Viral Hepatitis in Europe: Report on a WHO Meeting, Held on 11-13 June 1985, Munich, Federal Republic of Germany."	These minutes note that the WHO has been actively involved in the field of viral hepatitis for thirty years. "There is currently no reliable serological marker for the different types of non-A, non-B Hepatitis…diagnosis is based on exclusion of other factors causing similar types of liver damage….However, acute hepatitis occurring without these serological markers [for Hepatitis A, B or D] is not necessarily NANBH. A clinical syndrome indistinguishable from acute viral hepatitis can be caused by other viruses, some bacteria, a variety of drugs and several non-infective diseases of the liver….There is an urgent need for a reliable serological test for the diagnosis of NANBH…."
95	18 June 1985	NHF, "On the Treatment of Infants and Young Children with Severe Hemophilia: A Follow-up," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 25.	This newsletter reprints earlier guidance that: "The accumulating evidence for the heat sensitivity of HTLV-III suggests that heat treated Factor VIII and Factor IX are the preferred products for the treatment of patients in groups for which it was previously recommended that cryoprecipitate or plasma be used: - newborn infants and children under 4 with severe hemophilia; - newly identified patients with severe hemophilia never treated with Factor VIII or Factor IX concentrates. It is emphasized that Hepatitis B vaccination is essential when these patients are treated in this way, and it is recommended that this be administered shortly after birth. Moreover, as the transmission of non-A, non-B Hepatitis may be greater with these products, even if heat treated, it may be preferable in some cases to treat patients in these groups with cryoprecipitate (Hemophilia A) or fresh frozen plasma (Hemophilia B), especially in those areas in which there is a low incidence of patients with AIDS in the general population."
96	August 1985	McDougal, J.S. et al., "Thermal Inactivation of the Acquired Immunodeficiency Syndrome Virus, Human T Lymphotropic Virus-III/Lymphadenopathy-Associated	This study reports that a study of HTLV-III/LAV in liquid Factor VIII and IX lyophilized and heated according to unnamed commercial manufacturers' specifications has led to the conclusion that heat treatment should reduce or stop transmission of HTLV-III/LAV by commercial AHF or Factor IX.

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		Virus, with Special Reference to Antihemophilic Factor," *Journal of Clinical Investigation*, Vol. 76, pp. 875-77.	
97	2 August 1985	CDC, "Update: Acquired Immunodeficiency Syndrome – Europe," *MMWR*, Vol. 35, pp. 471-75.	In Europe, "as of 31 March 1985, 940 cases of AIDS have been reported to the WHO Collaborating Centre on AIDS." Twenty-eight of these, or 3.0%, are haemophiliacs.
98	29 August 1985	**UK Document**: The Haemophilia Society, "A.I.D.S.," *Haemofact*, Release No. 8.	This pamphlet recommends that patients: "Continue to treat bleeding episodes wherever possible with HT material, be that imported or British." It also states: "No one knows the precise meaning of HTLV-III antibody tests, their value is scientific, and for this reason we recommend that you continue to co-operate with your doctors. These tests may have greater meaning in the future."
99	September 1985	**UK Document**: National Blood Transfusion Service [UK], "Important Information for Blood Donors."	"AIDS is a serious disease. Please do not give blood [if you are]: a practicing homosexual or bisexual man, a drug abuser who injects drugs, a haemophiliac who has been treated with blood products or have had sexual contact with any of these people."
100	6 September 1985	CDC, "Update: Revised Public Health Service Definition of Persons Who Should Refrain from Donating Blood and Plasma – United States," *MMWR*, Vol. 34, pp. 547-48.	"To further reduce the risk of HTLV-III infection from blood and plasma, the US FDA has reworded the donor deferral recommendation to state that any man who has had sex with another man since 1977 should not donate blood or plasma."
101	27 September 1985	CDC, "Update: Acquired Immunodeficiency Syndrome – Europe," *MMWR*, Vol. 34, pp. 583-89.	In Europe, "as of 30 June 1985, 1,226 cases of AIDS have been reported to the WHO European Collaborating Centre on AIDS." Thirty-nine of these, or 3%, are haemophiliacs.
102	October 1985	**UK Document**: The Haemophilia Society [UK], "Advice on Safer Sex: Special Issue," *Haemofact*.	"People with haemophilia are in the at-risk group for exposure to HTLV-III." The pamphlet states that few of those exposed will develop symptoms of AIDS. The significance of HTLV-III antibody positivity or negativity is not

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			yet known. Intercourse without the use of a condom is considered a high risk activity. "Continue to treat bleeding episodes to avoid long term joint damage, etc. By now you should ONLY be receiving heat treated materials, whether imported or British."
103	1 October 1985	**UK Document**: UK DHSS, "AIDS Booklet 2: Information for Doctors concerning the Introduction of the HTLV III Antibody Test."	All blood donations will be screened for HTLV-III. Alternative test sites providing confidential tests will also become available. Alternative sites are necessary, "to ensure that people who believe themselves at risk of infection do not donate blood in order to be tested. This is crucial because even a reliable test cannot detect very early infections to which an antibody response has not yet been generated."
104	8 October 1985	**UK Document**: "Briefing for CMO's Meeting, Luxembourg 14-15 October: Agenda Item 5, Control of Blood and Products of Human Origin." [Author and Source Unknown.]	"All blood and other products of human origin which are sold by commercial companies and used in medications are subject to product licenses by the CSM. Licenses are approved on the basis that three requirements are satisfied: a) the source of the blood/other product is acceptable and can be traced to the individual from whom it was derived…b) there is evidence that processes used to inactivate any microbiological contamination are effective…and c) satisfactory long term follow up of patients who have received the product in clinical trials."
105	19 October 1985	Petricciani, J.C., McDougal, J.S. and Evatt, B.L., "Case for Concluding that Heat-treated, Licensed Anti-Haemophilic Factor [AHF] is Free from HTLV-III," *The Lancet*, pp. 890-91.	This case study states that "there still seems to be enough of a safety factor afforded by AHF heat treatment to permit the conclusion that infectious LAV/HTLV-III is unlikely to be present in currently licensed heat-treated AHF, and that the use of such products should not result in additional cases of AIDS in persons with haemophilia."
106	November 1985	NHF, "The National Hemophilia Foundation Medical and Scientific Advisory Council Recommendations Concerning AIDS and the Treatment of Hemophilia," *Hemophilia Information Exchange, AIDS UPDATE*.	"In view of the accumulating evidence for the heat sensitivity of HTLV-III, and the apparent lack of untoward effects attributable to the heat treatment, we recommend that physicians who prescribe clotting factor concentrates should prescribe only heat treated or otherwise viral-attenuated coagulation factor concentrates for the treatment of patients with severe hemophilia who do not have inhibitors, with the understanding that protection against AIDS is yet to be absolutely proven; heat treated, or otherwise viral-attenuated Factor VIII and Factor IX may be the preferred products for the treatment of patients in groups for which it was previously recommended that cryoprecipitate or plasma be used: newborn infants and children under

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			4 years of age with severe hemophilia and newly identified patients with severe hemophilia never treated with Factor VIII or Factor IX concentrates." "It is emphasized that Hepatitis B vaccination is essential when these patients are treated in this way, and it is recommended that this be administered shortly after birth. Moreover, as the transmission of non-A, non-B Hepatitis may be greater with these products, even if heat treated, it may be preferable in some cases to treat patients in these groups with cryoprecipitate (Hemophilia A) or fresh frozen plasma (Hemophilia B). A decision as to the risks and benefits of these alternatives will vary depending on the circumstances of the particular patient and the latest data on various blood products, and the treating physician's best judgement will be important in each case. Desmopressin (DDAVP) should be used whenever possible in patients with mild or moderate Hemophilia A. When desmopressin does not provide adequate treatment, these patients should usually be treated with cryoprecipitate. Similarly, for patients with mild or moderate Factor IX deficiency, plasma is usually the preferred product. It is recognized, however, that there are some circumstances in which viral attenuated (heat treated) Factor VIII or Factor IX may be the more appropriate therapy."
107	1 November 1985	The National Hemophilia Foundation, "General Information on HTLV-III Infections: Frequently Asked Questions."	This pamphlet uses a Q & A format to provide general information on AIDS.
108	8 November 1985	CDC, "Acquired Immunodeficiency Syndrome: Meeting of the WHO Collaborating Centres on AIDS," *MMWR*, Vol. 34, pp. 678-79.	"Although it is expected that additional AIDS cases may develop in recipients of blood and blood products who are already infected with the causative virus of AIDS, LAV/HTLV-III, future infections from blood and blood products can now virtually be considered preventable by screening blood donations for evidence of antibodies to the virus." "The group concurred on the following....For routine, large-scale testing for AIDS, the only practical methods currently available involve tests for antibodies to LAV/HTLV-III."
109	8 November 1985	**UK Document:** Letter to the UK DHSS from the UK NBTS, Newcastle	The NBTS has been screening all donations for HTLV-III. It has "instructed all hospitals not to use material issued before 29th September

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		upon Tyne. [Author Unknown.]	1985 when we commenced testing. The cryoprecipitate returned will be destroyed but the plasma after pooling will, I understand, be accepted by BPL for preparation of heat-treated products."
110	4 December 1985†	NHF, "Revised Medical and Scientific Advisory Council Recommendations Concerning AIDS and the Treatment of Hemophilia," *Hemophilia Information Exchange, AIDS UPDATE*, Medical Bulletin No. 32, Chapter Advisory No. 37.	These revised recommendations "essentially represent an update of NHF's policy with respect to the significant improvement in the safety of blood products for people with hemophilia and related clotting disorders, and a response to the increasing data available in this regard." "The MASAC reaffirms its position that PATIENTS CONTINUE TREATING BLEEDING EPISODES WITH CLOTTING FACTOR AS PRESCRIBED BY THEIR PHYSICIANS AS THE RISKS OF WITHHOLDING TREATMENT FAR OUTWEIGH THE RISKS OF TREATMENT."
111	2 August 1986	Editorial, "Safer Factor VIII and IX," The Lancet, Vol. 2, pp. 255-56.	"The risk of contracting non-A, non-B Hepatitis from Factor VIII and IX concentrate was first recognised ten years ago. The requirement for large pools of plasma…as starting materials in manufacture…has produced attack rates approaching 100% in recipients after exposure to unheated Factor VIII. The acute illness was often mild….Unfortunately it is now clear that there is a substantial risk of chronic sequelae…"
112	September 1986	NHF, "The National Hemophilia Foundation Medical and Scientific Advisory Council Recommendations Concerning AIDS and the Treatment of Hemophilia," *Hemophilia Information Exchange, AIDS UPDATE.*	"In view of the accumulating evidence for the heat sensitivity of HIV, and the apparent lack of untoward effects attributable to the heat treatment, we recommend that physicians who prescribe clotting factor concentrates should prescribe only heat treated or otherwise viral-attenuated coagulation factor concentrates for the treatment of patients with severe hemophilia who do not have inhibitors, with the understanding that protection against AIDS is yet to be absolutely proven. Heat treated, or otherwise viral-attenuated Factor VIII and Factor IX may be the preferred products for the treatment of patients in groups for which it was previously recommended that cryoprecipitate or plasma be used: newborn infants and children under 4 years of age with severe hemophilia and newly identified patients with severe hemophilia never treated with factor VIII or factor IX concentrates." "It is emphasized that Hepatitis B vaccination is essential when these patients are treated in this way, and it is recommended that this be

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			administered shortly after birth. Moreover, as the transmission of non-A, non-B Hepatitis may be greater with these products, even if heat treated, it may be preferable in some cases to treat patients in these groups with cryoprecipitate (Hemophilia A) or fresh frozen plasma (Hemophilia B). The decision may also be influenced by the availability of cryoprecipitate prepared from, for example, a small number of well-screened and carefully tested repeat donors. A decision as to the risks and benefits of these alternatives will vary depending on the circumstances of the particular patient and the latest data on various blood products, and the treating physician's best judgement will be important in each case. Desmopressin (DDAVP) should be used whenever possible in patients with mild or moderate Hemophilia A. When desmopressin does not provide adequate treatment, these patients should usually be treated with cryoprecipitate. Similarly, for patients with mild or moderate Factor IX deficiency, plasma is usually the preferred product. It is recognized, however, that there are some circumstances in which viral-attenuated (heat treated) Factor VIII or Factor IX may be the more appropriate therapy."
113	6 January 1987	NHF, "Seroconversion Update: Coagulation Product Exchange," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 45, Chapter Advisory No. 50.	"It is clear that optimum safety requires a triple 'safety net,' including: the screening out of donors from high risk groups; the testing of each and every unit of donated plasma for antibody to human immunodeficiency virus (HIV), in order to minimize the quantity of HIV virus before heat treatment is applied; and heat treatment or other viral attenuation methods. The use of all three safety measures provides the best protection available at this time."
114	25 March 1987	NHF, "Blood Product Safety Update," *Hemophilia Information Exchange: AIDS UPDATE*, Medical Bulletin No. 48, Chapter Advisory No. 53.	According to the 13 March 1987 issue of the CDC's MMWR, "the risk associated with unscreened*, heat-treated product is so low that several more months of surveillance will be required before a statistically significantly [sic] further reduction of risk can be substantiated." A footnote clarifies that "* *Screening in the context of the MMWR report refers to testing each unit of donated plasma for the HIV antibody.*"
115	25 June 1987	Letter from Bruce L. Evatt, Director of Division of Host Factors [DHF, CDC].	"Our laboratories, which are very well experienced with testing all sorts of materials for human immunodeficiency virus (HIV) antibody have been

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			unable to reliably test factor concentrate products for HIV antibody. This is primarily because these products are non-specifically reactive, probably due to their high protein content. Thus, direct testing of factor products for HIV antibody is not reliable and should not be used in assessing whether these are safe for patient usage."
116	18 December 1987	CDC, "Human Immunodeficiency Virus Infection in the United States," *MMWR*, Vol. 36, No. 49, pp. 801-04.	"HIV antibody prevalence among persons with coagulation disorders requiring clotting factor concentrates (hemophiliacs) has varied according to the type and severity of the disorder. The overall prevalence among Hemophilia A patients has been approximately 70%; for Hemophilia B patients, it has been 35%."
117	February 1988	NHF, "The National Hemophilia Foundation Medical & Scientific Advisory Council (MASAC) Recommendations Concerning HIV Infection, AIDS and the Treatment of Hemophilia," *Hemophilia Information Exchange: AIDS UPDATE.*	In regards to HIV, this newsletter states that: "Products that are heated in aqueous solution (pasteurized), detergent-solvent treated, monoclonal antibody purified, heated in suspension in organic media, or dry heated at high temperatures for long periods of time are preferred products for treatment of Hemophilia A for substantially reduced risk of HIV transmission." In regards to hepatitis, it states: "Preliminary available data suggest that some improved methods of viral inactivation may result in a reduced risk of hepatitis transmission. These products are those that are heated in aqueous solution (pasteurized), detergent-solvent treated, or monoclonal antibody purified. Products heated in suspension in organic media or dry heated at high temperatures for long periods of time may not be as efficient in attenuating or eliminating hepatitis viruses as the products mentioned in the previous sentence. It is recognized that these data are extraordinarily preliminary and more clinical data are urgently needed."
118	16 May 1988	**UK Document:** [UK] Haemophilia Reference Centre Directors, "Recommendations on Choice of Therapeutic Products for the Treatment of Non-Inhibitor Patients with Haemophilia A, Haemophilia B or Von Willebrand's Disease."	"All the products listed below are considered to have a negligible risk of HIV transmission." The list includes Koate HT and Koate HS.

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119	22 July 1988	NHF, "World Federation Issues 'Urgent Bulletin' Concerning Factor VIII Shortage," *Hemophilia Information Exchange: Network Report*, Supply Watch Bulletin No. 4.	"On June 27, 1988, the World Federation of Hemophilia issued the attached medical bulletin concerning the potential world-wide shortage of the supply of lyophilized clotting factors. This is a representation of the crisis we are now facing regarding the supply of concentrates....It is important that health professionals, patients, and families work cooperatively towards efforts to conserve clotting factor during this period."
120	October 1988	Kasper, C.K., "A Shortage of Concentrate: News from the Annual Meeting of the National Hemophilia Foundation, and Other Sources," *The Hemophilia Bulletin*, No. 3.	This bulletin notes that increasing cost and serious shortages of factor concentrate were plaguing the haemophilia community in the US and were expected to last another nine months. One reason for the shortages was new purification and viral inactivation methods adopted by the fractionators that reduce concentrate yield.
121	21 April 1989	CCBC Newsletter, "Current Events & Trends Relevant to Blood Services."	"Scientists at Chiron Corporation today published results of their research on a viral agent that they believe causes the majority of [NANB]...what they call the Hepatitis C virus (HCV)."
122	12 May 1989	CDC, "AIDS and Human Immunodeficiency Virus Infection in the United States: 1988 Update," *MMWR*, Vol. 38, pp. 1-14.	"The risk of new infection in persons with hemophilia and in persons receiving blood transfusions has declined dramatically because of the screening of donated blood and the heat treatment of clotting factor concentrates."
123	31 July 1989	NHF, "Factor VIII Supply Continues to Improve," *Hemophilia Information Exchange: Network Report*, Supply Watch Bulletin No. 17.	Under the title "FACTOR VIII SUPPLY CONTINUES TO IMPROVE," the NHF reported that: "Based on anecdotal reports, ample supplies exist in most parts of the country. Shortages persist for some specific products and vial sizes. NHF cannot predict the impact on the future supply of the backlog of deferred surgery, prophylactic care or of increasing home care inventories. For these reasons NHF cannot claim that the shortage is over."
124	26 October 1989	Schimpf, K., Brackmann, H.H., Kreuz, W. et al., "Absence of Anti-Human Immunodeficiency Virus Types 1 and 2 Seroconversion after the Treatment of Hemophilia A or Von Willebrand's Disease with Pasteurized Factor VIII Concentrate," *The New England Journal of*	"It appears that pasteurization [60°C for 10 hours] effectively inactivates HIV, even in plasma that is likely to be highly contaminated with the virus."

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		Medicine, Vol. 321, No. 17, pp. 1148-52.	
	Retrospective Articles:		
125	1990	Aronson, D.L., "The Development of the Technology and Capacity for the Production of Factor VIII for the Treatment of Hemophilia A," *Transfusion*, Vol. 30, No. 8, pp. 748-58.	"In the last 25 years, there has been a progressive improvement in the amount and quality of materials available for the treatment of Hemophilia A. The supply of Factor VIII and the system for its delivery have developed concurrently. This progress has resulted from a positive cooperation between academia and industry even at a time when it was not perceived that [Factor VIII] would be a commercially viable product."
126	1992	Kasper, C.K. et al., "Recent Evolution of Clotting Factor Concentrates for Hemophilia A and B," *Transfusion*, Vol. 33, No. 5, pp. 422-34.	"This report describes the changes in concentrates used for the treatment of Hemophilia A and B during the 1980s, the rationale for those changes, the nomenclature for the various concentrates, and the concentrates available today."
127	1994	Kroner, B.L., Rosenberg, P.S., Aledort, L.M., Alvord, W.G. and Goedert, J.J., "HIV-1 Infection Incidence Among Persons with Hemophilia in the United States and Western Europe, 1978-1990," *Journal of Acquired Immune Deficiency Syndromes*, Vol. 7, No. 3, pp. 279-86.	"Median seroconversion dates for subgroups of all seropositives ranged from July 1980 to December 1983, depending on the dose and type of factor concentrate....Median dates in Europe ranged from September 1981 to March 1983....Infection incidence apparently peaked about the same time that public health interventions were introduced to reduce transmission."
128	2003	Mannucci, P.M., "AIDS, Hepatitis and Hemophilia in the 1980s: Memoirs from an Insider," *Journal of Thrombosis and Haemostasis*, Vol. 1, pp. 2065-69.	"[T]he 1970's had witnessed dramatic improvements in the management of hemophilia. Whereas before patients had to endure a life threatening and crippling scourge, the increased availability of plasma concentrates of coagulation factors made from plasma pooled from thousand of donors and the widespread adoption of home care ('treatment at the doorstep') transformed hemophiliacs into individuals able to take full advantage of their talents and opportunities. Hemophilia care became one of the gratifying examples of successful secondary prevention of a chronic disease. It was known that coagulation factor concentrates were contaminated with the virus causing [NANB] (later identified as the

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			Hepatitis C virus). At that time, the peculiar epidemiology of Hepatitis C, with the long time interval between infection and the occurrence of severe consequences…was not well established and chronic hepatitis appeared mild, with little negative effects on the well-being and life style of hemophiliacs." "Although some extreme views were held that hemophiliacs should not receive concentrates, there was in my view little alternative during that period but to continue treating. I certainly told hemophiliacs under my care of the risk of AIDS from the early stages, but if one balances the risks that were known at the time against the substantial, well-perceived benefits of concentrate treatment, it is not surprising that very few of them elected to discontinue the use of factor concentrates."