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COMMEMORATIVE ARTICLE

The AIDS epidemic in haemophilia patients II: pursuing absolute viral safety of clotting factor concentrates 1985–1988

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> "A man should look for what is, and not for what he thinks should be."
>
> Albert Einstein

Introduction

The primary phase of the AIDS epidemic in the haemophilia population ended abruptly in 1985 [1,2]. Unfortunately, the manner of its ending left unanswered questions destined to affect the haemophilia community until the next decade.

In July 1984, the author [then Director of the Division of Host Factors (DHF; DHF is now known as Division of Blood Disorders, Centers for Disease Control and Prevention), Centers for Disease Control (CDC)] presented data on the effectiveness of heat treatment on inactivation of the AIDS virus at the World Federation of Hemophilia (WFH) Congress in Rio de Janeiro. Upon hearing further confirmatory data by DHF in October 1984, the National Hemophilia Foundation's (NHF) Medical and Scientific Advisory Council (MASAC) issued recommendations that 'treaters using coagulation factor concentrates should strongly consider changing to heattreated products' [3,4]. The haemophilia community widely adopted these recommendations in 1985. The true impact of these recommendations on the epidemic would not be known until DHF's studies of birth cohorts in the United States and Universal Data Collection (UDC) surveillance data retrospectively confirmed, more than a decade later, that US patients were not infected with HIV from heattreated factor subsequent to their adoption as standard of care [2,5]. However, the period from 1985 to 1990 was a period of uncertainty about clinical safety and the haemophilia community, the treating physicians, the manufacturers of coagulation products and regulatory agencies had to make difficult decisions about the reliability of products, manufacturing practices and therapeutic choices with little guidance. Some of these decisions contributed to adverse outcomes.

Lack of clinical data creates uncertainty

In 1985, the use of heattreated products for the prevention of AIDS was in fact an 'off label' application; that is, the heattreated products were not used for the purpose for which they had been licensed by the Federal Drug Administration (FDA). Four US manufacturers – Cutter Biological, Armour Pharmaceutical, Alpha Therapeutics and Hyland Therapeutics of Baxter Healthcare – received licenses for dry heattreated products in 1983 and early 1984 (prior to identification of the HIV virus as the causal AIDS agent) to reduce risk of hepatitis infections in recipients rather than to reduce the risk of AIDS infection [1]. Only subsequently did the *in vitro* (laboratorybased) heating experiments suggest that heattreated products might reduce (if not eliminate) the risk for transmitting HIV, but no actual clinical (*in vivo*) data existed on the efficacy of heattreated factor in reducing HIV infection. Normally, clinical efficacy, determined by prospective clinical trials, would be required before licensing. However, a significant and growing portion of the haemophilia population was being infected in 1984 and the haemophilia community was desperate for any possible preventive measure. Most readily accepted the use of heattreated concentrates based only on the *in vitro* data with evaluation of the level of viral safety by subsequent surveillance [1].

Although DHF established surveillance mechanisms to identify possible HIV seroconversions in patients taking heattreated clotting factors, several problems made the task difficult. Logistically, the surveillance was voluntary and passive, rendering it less sensitive. Second, the majority of infected haemophilia patients were still unidentified, either by clinical symptoms or testing. These patients had to be distinguished from persons seroconverting from the new heattreated products. Patients often used more than one brand of clotting factor concentrate; when these persons were included, identifying an unsafe product depended on statistical analysis of a number of suspected seroconversions. Finally, although most patients in the United States were using heattreated clotting factors in early 1985, some physicians and organizations still objected to its use.

Unfortunately, this resistance caused delay in utilizing the new products in some countries. Large, expensive inventories of nonheattreated clotting factors still existed in manufacturers', distributors', hospitals' and clinics' storage. Although in retrospect, these should have immediately been destroyed, the FDA did not order a formal recall of nonheattreated products, but allowed manufacturers to 'phase in' distribution of the heattreated factors; therefore nonheattreated products continued to be available in many countries for another year [6]. Reportedly, this policy was justified by the lack of clinical effectiveness data for heattreated products and concern in the haemophilia community that the withdrawal of untreated clotting factor would create shortages.

For example, following MASAC's recommendation, the Canadian Bureau of Biologics, in November 1984, issued directives to the Canadian Red Cross and manufacturers to switch to heattreated products 'as soon as possible' [7]. However, the sole Canadian manufacturer of clotting factor, Connaught Laboratories, did not have the equipment or technology to produce heattreated products [7]. In addition, both the Canadian Red Cross, the sole distributor of clotting factor in Canada, and Connaught Laboratories had two other major economic issues. Connaught Laboratories had millions of units of unheated clotting factors in the process of manufacture and the Red Cross had a 2month supply of unheated clotting factors in the inventory. Consequently, though adequate supplies of heattreated products were licensed and available in Canada by the end of January 1985, the Canadian Red Cross made the decision in December 1984 to continue purchasing and distributing 11 million units of nonheattreated factors to haemophilia patients in Canada until July 1985, when Connaught and Red Crossexisting inventories of nonheattreated factors were exhausted. [7,8]. Similarly, other countries, e.g. France and Japan, allegedly delayed licensing the heattreated products in their own countries, in part, to allow their national companies to develop competitive testing or viral inactivation technology [9,10]. Consequently, the nonheattreated products existed in the marketplace well into 1985, thereby infecting additional patients with HIV. Under these circumstances, the availability of both viral inactivated and nonviral inactivated products in the marketplace increased the difficulty of evaluating the residual risk of any single product, created uncertainty in data interpretation and influenced both clinical and corporate decisions.

The manufacturing conundrum: responding to conflicting *in vitro* data

Each of the four manufacturers of clotting factor in the United States used different viral inactivation processes (involving different temperatures and heat durations) – Alpha Therapeutics (wet heat at 60°C for 24 h); Armour Pharmaceutical (dry heat at 60°C for 30 h); Hyland Therapeutics (dry heat at 60°C for 72 h); and Cutter (dry heat at 68°C for 72 h). A few months after DHF completed studies on Cutter and Alpha's processes showing *in vitro* effectiveness of these two processes (the basis for MASAC's recommendations on using heat treated factor), a third manufacturer, Hyland Therapeutics, requested that DHF test the *in vitro* effectiveness of their heat inactivation process [1,11]. The results were similar to that found in the Cutter and Alpha experiments.

However, the fourth manufacturer, Armour, conducted 'in house' studies performed by Dr Alfred Prince, a virologist at New York Blood Center [12]. In January 1985, using different methodology and relatively low titre viral spiking samples, Dr Prince could demonstrate only 2–3 logs of virus inactivation – far short of the 6 logs which would later be considered a theoretical minimum needed for safety by the FDA [13]. For a considerable time, Armour did not disclose the results of its studies to other investigators or governmental agencies, a course of action that possibly affected subsequent regulatory decisions [14].

Meanwhile, several published reports began to clarify some blood safety issues. Only a summary of the heating experiments was published in the October 1984 *MMWR* [4]. The details of these experiments as well as those of other investigators were published in the summer of 1985 [11,15]. Clinical reports suggested a lack of seroconversions in patients receiving heattreated factors compared to other reports of haemophilia patients tested and diagnosed with HIV infection [16–21].

Armour, however, was facing a dilemma. Dr Prince conducted further studies on the Armour technology between January and August 1985, and found results similar to his initial studies. Armour, concerned about these results, requested that DHF also test their viral inactivation process by Dr Stephen McDougal's protocol, but did not disclose results of Dr Prince's studies or the reason for the request. Their request was declined on the basis that *in vitro* studies did not guarantee clinical safety and DHF's mission was not to certify products – it was the responsibility of the manufacturer to demonstrate product safety and efficacy to the FDA, the licensing agency. Armour's subsidiary, Meloy Laboratories, then appealed directly to Dr McDougal to perform inactivation studies for Meloy in DHF's laboratory. Dr McDougal made three attempts to perform these studies in June, August and early autumn 1985. Unfortunately, the titres of virus supplied by Meloy used to spike the samples were so low that these experiments were invalid and results meaningless (author's personal notes; personal communication with J.S. McDougal). During this period, Dr. Prince requested permission to publish results of

his own study, but Armour management refused, first on the grounds that Dr McDougal's experiments were not completed and later on the basis that the 'data taken in isolation could only be confusing to the scientific community, the treatment community and the public…' [22].

In October 1985, FDA and DHF used assumptions drawn from DHF's *in vitro* studies, and published a joint letter in *The Lancet* estimating the level of maximum contamination of clotting factor concentrates that would be produced if the blood donors incubating AIDS were included in the plasma pools used to manufacture the product. This level was estimated to be about 5–6 logs of virus [13] – considerably higher than Dr Prince's results on the inactivation capacity of the Armour process.

With Prince's data, Armour became increasingly concerned about the inability to show *in vitro* effectiveness of their inactivation procedures, and initiated further inactivation studies at Meloy Laboratories from October through December 1985 [22]. These experiments again showed that heating the Armour product at 60°C either at 30 or 60 h inactivated only a few logs of virus, and left 'substantial residual infectious virus'. However, Meloy reported that a temperature of 68°C for 72 h appeared to be much more effective [22].

Possible seroconversions

In January 1986, Dr Gill White, University of North Carolina, Chapel Hill (UNC), reported a suspected seroconversion and DHF assisted with the UNC investigation. The UNC patient, a 31-year old with mild haemophilia, had been treated with the Armour product for a leg injury. He had received no other products since 1975, but had a history of prior drug abuse, including intravenous drugs 7 years prior. Twenty-five days after receiving the Armour product, the patient developed a viral syndrome and was found to be positive for HIV. Retrospective testing showed that he was HIV negative on the initial admission for his leg injury in 1985. Earlier, DHF had developed case definition criteria to assist in the identification of individuals possibly infected by heat-treated products (Table 1). Although highly suspect, the patient's prior drug use prevented a perfect fit with the case definition criteria [23].

Unknown to DHF and UNC investigators in early 1986, Armour, during July–December 1985, had already received reports from the United Kingdom and the Netherlands of several other possible seroconversions in patients receiving Armour's heat-treated products. While some had received other heat-treated products, the patients had all received the Armour product heated at 60°C for 30 h.

When DHF learned of the UNC patient and began to investigate in January 1986, Armour did not volunteer information concerning the European cases to DHF. However, Dr Peter Jones, director of the Newcastle Hemophilia Center in the UK, knew of the Armour-associated cases in Europe. At an AIDS conference held in Newcastle-upon-Tyne in February 1986, Dr Jones voiced concerns about the efficacy of heat treatment methods [24]. Subsequent publication of his remarks in the general circulation newspapers resulted in an uproar in the UK haemophilia community and the British government initiated enquiries directly to Armour about its product.

Table 1. CDC operational criteria for probable association of HIV seroconversion with virus-inactivated factor concentrates.

1. Confirmation of HIV seropositivity
2. Confirmation that the patient was previously HIV seronegative
3. Any use of non-virus-inactivated concentrates must have preceded the last seronegative test by at least 6 months
4. No receipt of other HIV-untested blood components during the relevant period
5. No recognized or suspected gaps in therapy records
6. Patient not known to have practised high-risk behaviours

Almost simultaneously (25 February 1986), Armour met with the FDA to review the possible use the HIV ELISA test to screen donors of source plasma used for Armour's 'Generation I' clotting factor concentrate to improve safety. Armour had been testing donors of source plasma for HIV since May 1985, but considerable Armour concentrate, made from unscreened donors remained in the production sequence or public circulation [22]. At the meeting, Armour reportedly informed the FDA of the possible European cases, but the FDA indicated they did not consider these cases to be 'clear cut' seroconversions associated with Armour's heat-treated products. Unaware of Dr Prince's studies, the FDA reviewed the latest Meloy Laboratory data from December 1985; based on Meloy's report, FDA assumed 5 logs of inactivation by Armour's heat treatment process (3 logs by heating and 2 logs by lyophilization) should be sufficient viral inactivation so that Armour's product manufactured from unscreened plasma did not need to be withdrawn from the market [22]. However, 2 days later, Armour's internal plasma executive committee made a decision to voluntarily withhold products made from unscreened plasma unless it was the only product available to sell. No voluntary or mandatory recall was issued [22].

By early April 1986, the scientific world became aware of possible seroconversions associated with heat-treated factors when UNC's and the Netherland's seroconversion cases were reported in *The Lancet* [25,26]. DHF first learned of the Netherlands case with this publication, and while investigating it, learned of suspected cases in the United Kingdom. By the end of May, DHF's preliminary assessment of these reports was that three of the patients were

compatible with seroconversions associated with the Armour product.

Regulatory actions

The author held discussions on 30 May 1986 with NHF's Medical Director, and representatives of FDA and Armour, and expressed DHF's concern that three known seroconversions indicated a possibility of inadequacy of the Armour viral inactivation process. DHF's concerns were based on several factors. During manufacture, Armour's heattreated lyophilized products had extremely low moisture content and were the least 'pure' factor VIII (FVIII) preparation (contained the largest amount of other plasma proteins) – factors that reduced losses of FVIII during manufacture but also probably reduced the effectiveness of viral inactivation. Of further concern, the Armour product received the least amount of dry heat inactivation (determined by time, temperature and moisture content) compared with the other products [14,23]. Although at least five products were available in both Europe and the United States, only Armour had been used (in some cases exclusively) by all the persons who seroconverted, statistically supporting an association with the Armour product. During these discussions, Armour did not reveal the results of the Prince studies. FDA informed DHF that Armour had agreed to change the heating procedure, but filing a new application was required and the material would not be available on the market for some time (personal notes).

In May, Dr Prince, after learning of the two published seroconversion cases, published his own results in *The Lancet*. These studies were performed at the New York Blood Center (independent of Armour support), but included his earlier Armour experiments without identifying Armour in the article [27]. These studies reported that 'virus inactivation resulting from heating alone was surprisingly modest' at 60°C centigrade. He further indicated that in the light of the two cases of HIV seroconversion, caution should be taken in relying on heat treatment and expressed the need for longterm surveillance.

From 1 to 18 June 1986, the author held further individual discussions with FDA, NHF and Armour briefing them on progress of DHF's investigations of the seroconversions and plans for an *MMWR* article on the topic (personal notes). NHF subsequently held direct discussions with Armour and FDA concerning NHF's positions on the safety of the Armour product, and the FDA discussed directly with Armour the seroconversions relative to regulatory policy and a possible recall of the product. The NHF requested that CDC not report the three patients in the *MMWR*, but inform the haemophilia community through NHF and the Hemophilia Treatment Centers (HTC) in order 'not to cause hysteria in the hemophilia community'. During a MASAC conference on 17 June 1986, Armour proposed the following: '…

1. a direct communication should be sent to the hemophilia community regarding the three [*previously*] unknown cases and their association with the Armour product;
2. a withdrawal of all lots of product manufactured from donors not screened for HTLVIIII antibody should be implemented;
3. any outdated lots should be destroyed or discarded; and
4. a panel of hemophilia professionals should be constituted to discuss any additional steps which need to be taken'. [28]

The FDA accepted the essence of Armour's proposals and did not issue a formal recall of the Armour product; its reasoning was a voluntary recall would be the most expedient method to accomplish removal of the product from the market. However, without a formal recall, the company was not forbidden to export the product.

In late June 1986, Armour sent US HTCs and blood banks a letter voluntarily withdrawing the nonscreened heattreated products while offering to replace it with products manufactured from screened plasma and shortly thereafter notified the Canadian Bureau of Biologics and Red Cross of this policy [22]. An NHF bulletin describing the possible ineffectiveness of the Armour heating process was mailed to the haemophilia community and the Armour recall was announced at the July WFH Congress in Milan [29,30]. By midAugust, DHF, completed a telephone survey of HTCs in the United States and found no other cases of seroconversions associated with clotting factor treatment (personal notes).

Following the publicity engendered by Dr Peter Jones's February 1986 presentation, Armour conducted a similar voluntary exchange of the nonscreened product in the United Kingdom simultaneously with that in the United States [31]. Two months later, the UK treatment centres identified two additional cases implicating unscreened Armour product. Discussions with the UK government quickly followed, and Armour voluntarily withdrew all unscreened and screened products from the United Kingdom at the end of September. On 7 October, the FDA met with Armour to discuss the additional UK cases. The FDA ruled that there was insufficient evidence to issue a formal recall of the product in the United States [31].

The Canadian cases – conditions set for the final HIV infections

In midOctober 1986, Armour applied for modification of the heating process by raising the temperature

to 68°C for 72 h, a method that reduced the viral titre by 7.4 logs of virus. FDA approved this method in January 1987 and the license for the older 60°C/30h treatment was suspended in the United States. However, a month later, in part because existing stocks had not been recalled, the concentrate manufactured by the older method was supplied to Canada by Armour to meet existing contractual requirements as its higher 68°C/72h product was not yet licensed in Canada. The 60°C/30h product continued to be distributed in Canada until the fall 1987 with unfortunate consequences [32]. (Note: An application filed by Armour in Canada in April 1987 for a license of the longer heated material was not granted and Armour's application was withdrawn in January 1988.)

The mini outbreak

In 1987, Dr Chris Tsoukas began a multicentre study to examine haemophilia patients attending Canadian HTCs. By October 5, children attending the Vancouver HTC and an additional child from Edmonton, Canada, had seroconverted to HIV [14]. The patients were treated with factor concentrates manufactured by Armour and Cutter, but all the patients had received one of three lots of Armour products manufactured from a single pool of plasma and distributed in Canada between 20 January 20 and 28 April 1987. A case–control study showed a highly significant association. This pool was later found to contain 11 of approximately 4200 plasma donations from seven donors who later seroconverted to HIV. No manufacturing variances were found in the three implicated lots by either the US or Canadian regulatory authorities [14,23]. No association was found with the patients receiving the Cutter product (heated at 68°C for 72 h), even though it was manufactured from unscreened plasma.

Final recommendations

On 11 January 1988, the DHF hosted a meeting in Atlanta to critically review available clinical and epidemiologic data on the safety of virally inactivated products. Attending the meeting were staff of the FDA, NIH, Canadian Federal Centre for AIDS, other international public health agencies, and experts in haemophilia and infectious diseases. Seventy-five patients, reported worldwide as possible HIV seroconversions associated with heat-treated products from 1985 to 1988, were critically reviewed. Only 18 were considered valid for analysis because no prior negative test existed to substantiate that the other 57 patients had not seroconverted prior to the availability of viral-inactivated products. Fourteen of the 18 valid cases had received the Armour product (highly significant). Six of the 18 of the patients had received only heat-treated products (four Canadian, one US and one European). Because the other 12 had received non-heat-treated products in the past, seroconversions due to non-heat-treated factors could not be absolutely excluded in all these cases [23].

Following this meeting, MASAC recommended that 'products that are heated in aqueous solution (pasteurized), treated with solvent/detergent, purified with monoclonal antibody, heated in suspension in organic media or dry heated at high temperatures for long periods are preferred' to treat haemophilia patients. Armour then ceased production of its implicated product. Subsequently, manufacturers of coagulation factor concentrates continued to improve viral inactivation technology, donor screening and testing, and developed standardized robust methods to test viral inactivation procedures. By 1990, these improvements had also eliminated transmission of hepatitis B and hepatitis C via virally inactivated clotting factor concentrates; the current plasma products have since maintained an exemplary record of safety [2,5].

Discussion

The use of heat-treated clotting factors in patients with haemophilia effectively stopped AIDS transmission; however, all licensed technologies were not equally effective at inactivating HIV. Rare transmissions of HIV occurred globally, most likely by clotting factor concentrates subjected to a single method of viral inactivation. Lacking clinical data and robust validated methods of testing inactivating technology, these seroconversions could not be predicted in advance. Achieving complete safety depended on identifying and investigating sufficient numbers of seroconversions to statistically isolate less effective methods of viral inactivation. A number of factors acted as barriers to identifying and eliminating the residual risk. First, the high frequency of undiagnosed HIV infections already existing in the haemophilia population confused identification of possible new seroconversions due to heat-treated factors. Additional factors were the continued sale of untreated products, the lack of clinical data on the effectiveness of heat-treated factors, the rarity of seroconversions and the delay in sharing vital information. Hopefully, knowledge and recognition of these factors will improve and expedite responses to future unknown epidemics.

Disclosures

The author stated that he has no interests which might be perceived as posing a conflict or bias.

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The observations expressed in this manuscript are solely the responsibility of the author based on his personal experiences. They may or may not reflect the official opinions and policies of the Federal Agencies of the United States Government identified in the manuscript.

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