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APPENDIX
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Predicting the Long-term Risk of HIV Exposure by Cryoprecipitate

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Predicting the Long-term Risk of HIV Exposure by Cryoprecipitate[1]

Bruce Evatt, MD, et al.

Abstract

Most of the world's hemophilia population lives in countries with few medical or financial resources. As such, they cannot easily obtain viral-inactivated clotting product. Many patients are treated with cryoprecipitate made from locally supplied blood. The reasoning for using cryoprecipitate, instead of viral-inactivated products, is based on an unspoken belief that because blood banks can provide reasonably safe products by using modern testing procedures, transmission of HIV and other blood-borne viruses is rare. However, the risk of acquiring a blood-borne infection increases with every exposure, and hemophilia patients treated with cryoprecipitate or fresh-frozen plasma are exposed to hundreds or thousands of donors during their lifetime. The risk that a person infected with HIV will donate blood during the "window period" is directly related to the incidence of HIV in the country where the donation occurs. To demonstrate the extent of this problem, we devised a model for estimating the risk that a person with hemophilia will encounter HIV-contaminated cryoprecipitate based on the years of treatment and the underlying incidence rate of HIV among blood donors. We applied the model to two countries with different incidence rates of HIV: Venezuela and the United States. We found that a person with hemophilia who receives monthly infusions of cryoprecipitate prepared from plasma of 15 donors over a lifetime of treatment (60 years) is at significant risk of being exposed to HIV. In the United States there is a 2% risk of being exposed to HIV-contaminated blood product, and in Venezuela, the percentage of risk is 40%. Given this degree of risk, medical care providers should carefully evaluate the use of cryoprecipitate except in emergencies or when no viral-inactivated products are available.

[1] Adapted from Evatt BL, Austin H, Leon G, Ruiz-Sáez A, and de Bosch N. Hemophilia therapy: assessing the cumulative risk of HIV exposure by cryoprecipitate. *Haemophilia* 1999: 5. For statistical and mathematical formulas, the reader is referred to the original article.

Introduction

People with severe hemophilia usually experience frequent bleeding episodes (as often as every month) that require treatment with clotting factor concentrate. In developed countries, these concentrates are manufactured either from human plasma that is viral inactivated or from cell culture media using recombinant technology. However, for the 80% of the world's hemophilia population living in developing countries, these safe products are often not available. In developing countries, where there are many competing health needs for few resources, people with hemophilia are often treated with cryoprecipitates made from locally supplied blood [1]. Many countries choose to use cryoprecipitates instead of concentrates or recombinant technology, which are thought to be more expensive, based on the belief that current cryoprecipitate technology enables blood banks to provide reasonably safe products. This belief is supported by the observation that the transmission of HIV by blood transfusion in the United States is extremely rare; approximately 1/500,000 to 1/350,000 donors are infected with HIV [2].

Before reaching conclusions on the long-term safety of cryoprecipitate, however, several issues must be considered. One consideration is that the risk of acquiring a blood-borne infection increases with each exposure and accumulates throughout a person's life. During their lifetime, people with hemophilia will receive blood products, such as cryoprecipitate or fresh-frozen plasma, from hundreds to thousands of blood donors. A second consideration is the fact that the incidence rate (the number of new cases per unit of time in a defined population) of infections such as HIV varies greatly among countries. This rate is related directly to the risk that an infected person will donate blood in the "window period", the interval between being infected with HIV and developing antibodies that can be detected by tests. Another consideration is the adequacy and thoroughness of the blood-screening techniques used by various countries and the overall quality of their laboratory procedures. Together, all of these factors strongly affect the risk of acquiring a blood-borne infection for a person receiving a single blood transfusion. Because people with hemophilia receive multiple exposures, they can suffer a serious risk of infection, even when the best blood-banking technology is used.

Below, we estimate the risk that a person with hemophilia will receive HIV-contaminated cryoprecipitate based on the years of treatment and the underlying incidence rate of HIV among blood donors. We applied the method to people with hemophilia in Venezuela, which has a high number of cases of HIV, and the U.S.A., which has a low number of cases of HIV, and compared the results. The total number of cases of a disease per unit of population at a given point in time is called the "prevalence".

Methods

Model development

i) Risk of an HIV Positive Donation in the United States

The probability that a blood donation from an HIV-infected donor would enter the American Red Cross (ARC) blood supply has been estimated recently [2]. The reader is referred to the reference section for details of the method.

The probability that HIV-contaminated blood will enter the ARC supply depends on, among other things, the number of first-time donors and the number of repeat donors giving blood during a defined period. The number of HIV infected people among repeat and first-time volunteer blood donors to the ARC in the United States is shown in Table I.

In the United States, about 80% of volunteer blood donations are obtained from repeat donors. The remaining donations are from first-time donors. As indicated in Table I, the number of cases of HIV is about 9 times higher among first-time donors than among repeat

Table I

The Number and Prevalence* of HIV-Positive Persons among First-time and Repeat Volunteer Blood Donors to the ARC

	Repeat	*First-time*	*Total*
No. HIV-infected	142	349	491
No. Donors	7,148,580	1,898,739	9,047,319
HIV Prevalence	2.0×10^{-5}	18.4×10^{-5}	5.43×10^{-5}

*Prevalence = total number of cases of a disease in a defined population at one point in time.

donors. This difference probably reflects the facts that repeat volunteer donors are a group at low risk for HIV and that HIV-positive persons are not allowed to donate blood again.

Although the prevalence of HIV among donors is important, infected blood is discarded. A greater risk of contamination of the blood supply comes from donors who are infected with HIV, but who have not developed detectable antibodies. This risk is directly related to the incidence rate of HIV infections. Using data from repeat donors (who at their last donation had tested HIV negative), Lackritz et al. estimated that the incidence rate of HIV infection among repeat donors, in one year, was about 2.6 cases per 100,000 donors [2]. The incidence rate of HIV among first-time donors cannot be estimated directly because no previous information on their serostatus is available. However, various scientists have estimated the incidence rate to be between 1.8 and 3 times that of repeat donors [2,3,4]. This means that the number of new cases of HIV, over one year, in first-time donors is about 6.5 per 100,000 donors. Combining the two incidence rate results in an overall incidence rate for all ARC blood donors of 3.4 cases of HIV per 100,000 donors.

However, among these new cases, the ones that are a serious risk to the blood supply are the ones in which antibodies to HIV cannot be detected. Infection in these people will be missed because current screening tests only look for antibodies to the HIV virus. Scientists estimate this window period, where the infection is present but cannot be detected, to be about 25 days [2,5]. When one takes this window period into account as well, then about 2 donations per million will carry undetected HIV infection and will enter the ARC blood supply.

Contaminated blood can also enter the national blood supply because of laboratory errors [6,7,8]. Lackritz et al. estimated that about 0.5% percent of donations from known HIV-infected donors erroneously enter the blood supply [2]. However, these authors also estimate that 15% to 42% of these donations are thrown out due to other problems, such as hepatitis infection. When one considers all this information, one arrives at a final probability that 1 in 659,900 to 1 in 450,300 donations will

be infected with HIV and will enter the ARC blood supply. This is approximately 2 cases per million, which agrees with the first estimate.

ii) ***Estimated Risk of HIV-Infected Blood Donation in Venezuela***

From 1988 and 1997, the Banco Municipal de Sangre in Caracas, Venezuela, collected 269,509 units of plasma. The results of HIV-screening tests performed during this period were examined to determine the number of HIV-infected people among blood donors. The screening tests used varied over this period as improved tests were introduced into the screening program. Testing was carried out with several EIA tests and confirmed by Western blot techniques. There was a slow increase of positive results seen in blood donors, from 0.05% in 1986 to a high of 0.31% in 1992. During the most recent period, 1995 to 1997, HIV prevalence was 0.23-0.24%. We have used 0.23% in the calculations below as our estimation of the prevalence of HIV among Venezuelan blood donors.

Since almost all blood donations in Venezuela are obtained from first-time donors, it is not possible to estimate the incidence rate of HIV based on data collected at blood banks in Venezuela [9,10]. For the purpose of this study, we have assumed that the ratio of the incidence rates of HIV in Venezuela and the United States is equal to the ratio of the prevalence of HIV in the two countries. Among first-time donors, the ratio of the prevalence of HIV in Venezuela to that in the United States is about 12.5. Thus, the number of new cases of HIV in Venezuela can be calculated to be 12.5 * 6.5 per 100,000 donors, or 81 new cases per 100,000 donors. When we take into account other factors, such as the window period, laboratory errors and other infections, we find that between 1 in 25,700 and 1 in 17,500 donations will be missed HIV-infected units which are added to the national blood supply. The average is about 1 in 21,200 donations.

iii) ***Observed Risk for HIV-Infected Donation in Venezuela***

The Banco Municipal de Sangre in Venezuela is certified by the American Association of Blood Banks and uses blood-screening procedures and testing identical to those used in the United States. About 70% of the 269,509 units of plasma collected between 1988 and 1997 was used to treat hemophilia patients either as cryoprecipitate or fresh-frozen plasma made from the plasma. The hemophilia patients receiving plasma or cryoprecipitate from this blood bank are routinely tested every year for anti-HIV antibodies. Other people treated with plasma produced by the blood bank are not routinely tested for anti-HIV antibodies by the blood bank, unless they develop symptoms of HIV infection. Thirteen cases of HIV seroconversions (a change from HIV-negative to HIV-positive test) were observed among hemophilia patients who received cryoprecipitate or plasma during this period and were attributed to HIV-contaminated blood products. Thus, the overall observed rate of seroconversion per unit of plasma collected is 1/20,700. This figure agrees with our estimate that between 1/25,700 to 1/17,500 donations entering the Venezuelan blood bank may be infected. However, it is a very conservative estimate because of the incomplete testing of plasma recipients other than those with hemophilia.

Results[2]

We used the information above to estimate the risk that a person with hemophilia in Venezuela would be exposed to HIV-contaminated blood products. We assumed that a typical Venezuelan with hemophilia receives 12 cryoprecipitate treatments per year, each of which is obtained from 15 different blood donors. During 10 years of treatment, a typical

[2] For statistical and mathematical formulas, refer to: Evatt BL, Austin H, Leon G, Ruiz-Sáez A, and de Bosch N. Hemophilia therapy: assessing the cumulative risk of HIV exposure by cryoprecipitate. *Haemophilia* 1999: 5.

person with hemophilia will have received about 120 factor treatments obtained from about 1,800 donors. Using standard statistical methods, we estimate that the probability of exposure of people with hemophilia to HIV during a 10-year period is 0.08.

Table II displays the risk that a person with hemophilia in Venezuela will encounter HIV-contaminated blood based on both years of exposure and the risks described above. As we mentioned before, purified concentrates and recombinant factor are used in the United States. However, for comparison, we applied the calculation to people with hemophilia in the U.S., assuming that they received cryoprecipitate which had been prepared from the ARC blood using the same procedures as those used in Venezuela.

We found that over a lifetime of treatment (60 years), a Venezuelan person with hemophilia receiving monthly infusions of cryoprecipitate prepared from the plasma of 15 donors has a 40% risk of being exposed at least once to HIV-contaminated product.

Discussion

The risk of acquiring HIV from contaminated blood varies widely among countries. The risk depends on several factors, such as:

- background incidence rate of HIV among blood donors, including rates of co-infection (e.g., hepatitis B virus and HIV), which also directly influence the probability of collecting and using HIV-contaminated blood products;
- quality of the HIV-screening tests, which will also affect the length of the window period (a minimum of 25 days with current technology);
- overall quality of the laboratory (errors in the laboratory are an obvious source of contaminated blood);
- number and thoroughness of other screening tests that could lead to rejection of a donor's blood; and
- total number of transfusions, or exposures, received throughout a person's life.

Our risk model predicts that extended use of cryoprecipitate by people with hemophilia in Venezuela results in considerable risk for exposure to HIV. The predicted risk is

Table II

Risk (%) that a person with hemophilia in Venezuela or U.S.A. will be exposed to HIV-contaminated blood product based on years of treatment and risk of an HIV-infected donation

Years of treatment	Venezuela			U.S.
	Lower (1/25,700)*	Mid (1/21,200)*	Upper (1/17,500)*	Mid (1/545,100)*
5	3.4	4.2	5.0	0.16
10	6.8	8.1	9.8	0.33
15	10.0	12.0	14.3	0.49
20	13.1	15.6	18.6	0.66
30	19.0	22.5	26.6	0.99
40	24.4	28.8	33.7	1.3
50	29.5	34.6	40.2	1.6
60	34.3	39.9	46.0	2.0

* Estimated risk for HIV-infected donation.

supported by the observation that HIV transmissions by blood products occurred in Venezuela despite high quality testing and screening procedures. The situation will be notably worse in developing countries where the incidence of HIV may be considerably higher and where lack of resources may interfere with the application of modern HIV-screening tests and the maintenance of high quality control in laboratories. In Venezuela, the incidence rate of HIV is 12 times higher than that in the United States. This increases the lifetime risk that a person with hemophilia who is receiving cryoprecipitate treatment will be exposed to HIV-contaminated blood product from 2% in the U.S. to 40% in Venezuela.

If the assumptions used in this model are valid, then the model is likely to produce satisfactory estimates that a person with hemophilia will encounter HIV-contaminated blood. However, we must admit that there is uncertainty about these assumptions and therefore uncertainty about the strength of our estimates. For example, although we observed the prevalence of HIV among Venezuelan blood donors to be 12 times higher than that among U.S. donors, the incidence rate of HIV may not be 12 times higher among Venezuelan blood donors. Blood-screening procedures for HIV and other pathogens in Venezuelan blood banks are believed to be equivalent to those used at U.S. blood banks. However, this does not mean that quality control in the laboratories is equivalent or that the tests are performed with the same skill in the two countries. Since the lack of adequate resources is a larger problem in Venezuela than in the United States, our model would *underestimate* the risk that a person with hemophilia in Venezuela will be infused with HIV-contaminated factor.

The risk also clearly depends on the number of infusions and the number of source donors. We assumed 12 infusions per year, each of which is derived from 15 donors. More frequent infusions would increase the risk. On the other hand, the use of products derived from fewer donors would decrease the lifetime risk.

Finally, it is important to recognize that our model predicts the risk that a person with hemophilia will be exposed to HIV-contaminated factor, not the risk that the individual actually will become infected with HIV. The risk of HIV seroconversion is necessarily smaller. The model also assumes that the blood product is "contaminated" if only one of the 15 donors is infected with HIV. It is reasonable to think that the level of HIV virus in cryoprecipitate prepared from 14 normal and 1 HIV-infected donor may be too low to result in seroconversion in the treated patient. However, the 60% HIV-infection rate among people with hemophilia in the U.S. who received clotting factor treatments before adequate HIV inactivation procedures against HIV were started suggests that repeat exposure to contaminated blood product, even a low HIV viral load, can transmit HIV. Hence, the risks described probably will result in high HIV seroconversion rates, as the limited available experience of Venezuelan blood recipients suggests.

The model also shows that even in the United States, a country with a fairly low prevalence of HIV, a lifetime of treatment with cryoprecipitate would result in an important risk of encountering HIV-contaminated product (about 2%). In well-developed countries, such as those in Europe and North America, the assumption that the accuracy and sensitivity of donor-screening testing will remain unchanged is obviously unrealistic for a 60-year lifespan. Blood banks have already added HIV-antigen testing to donor screening and the ARC will introduce DNA testing for HIV for donors by the end of 1999. These changes will certainly reduce the chance that blood contaminated with HIV will enter the blood supply and thus reduce the overall high risk to people who use blood components often. On the other hand, the likelihood of rapid improvement in blood-banking safety in developing countries is far less certain. If

today's technology is continued in these developing countries, the lifetime risk to persons receiving multiple exposures to blood components will remain high. Long-term solutions, such as encouraging voluntary donor programs using higher numbers of repeat donors, better donor screening, using the latest blood banking technology, and developing techniques for viral inactivation in blood components, will eventually reduce the risk. However, any decrease produced by improvement in the blood-banking system could be offset by a rise in the incidence of HIV infections in the donor pool. For people with hemophilia in many developing countries, there is an immediate need to reduce the risk of HIV. The best approach for people with hemophilia is switching to viral-inactivated products.

Modern concentrates are safe because of very effective viral inactivation techniques and strictly regulated quality control procedures. Similar viral inactivation techniques have not been applied successfully to cryoprecipitate, because they cause a considerable loss of clotting factor activity. Cost of production of cryoprecipitate has been estimated to be between US$0.10 and US$0.20 per international unit (i.u.) [12]. Viral-inactivated intermediate (between unpurified and completely purified) purity concentrates have been reported to be widely available at US$0.20 per i.u.

Considering the lifetime risk of transmitting HIV to people with hemophilia through cryoprecipitate, the inferior therapeutic results obtained using cryoprecipitate, the inability to collect enough plasma to provide sufficient treatment for these people, and the fairly small difference in costs between viral-inactivated concentrates and cryoprecipitate, health care providers should carefully evaluate the use of cryoprecipitate except in emergencies or when no viral-inactivated products are available and lack of treatment means disability or death for people with hemophilia. In countries where cryoprecipitate is the only available option, the short-term goal should be to improve donor screening and testing as much as possible while working to introduce the use of viral-inactivated products.

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