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Retroviral Infections Transmitted by Blood Transfusion

S. GERALD SANDLER, M.D.,[a] CHYANG FANG, Ph.D.,[b] AND ALAN WILLIAMS, Ph.D.[c]

[a]*Clinical Professor, Georgetown University School of Medicine, and Medical Director, National Headquarters, Blood Services, American Red Cross, Washington, DC;* [b]*Director, National Reference Laboratory for Infectious Diseases, National Headquarters, American Red Cross, Rockville, Maryland;* [c]*Epidemiologist, Transmissible Diseases Laboratory, Jerome H. Holland Laboratory, American Red Cross, Rockville, Maryland*

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Modifications in donor screening and the introduction of laboratory testing of donated blood for anti-HIV-1 and anti-HTLV-I have resulted in a significant reduction in the risks of retroviral infections from blood transfusion. Presently, the American Red Cross detects an average of eight carriers of human immunodeficiency virus, type 1 (HIV-1) per 100,000 otherwise acceptable blood donors (0.008 percent), compared with an average of 35 per 100,000 (0.035 percent) when testing for HIV-1 antibodies began in 1985. Surveillance studies in the United States indicate a small likelihood that HIV-2 carriers will pass current screening procedures and be accepted as blood donors. Even if an HIV-2-infected person were to be accepted as a blood donor, there is a 42–92 percent likelihood that this person's blood would be detected as infective for HIV-2 and excluded because of serological cross-reactions that occur in the EIA for HIV-1 antibodies. During 1989, which was the first year that donated blood was routinely tested for antibodies to human T-lymphotropic virus, type I (HTLV-I) in the United States, approximately nine in 100,000 donors (0.009 percent) were confirmed positive for antibodies to HTLV-I, and their donated blood was excluded. Subsequent testing has revealed that a significant number of these persons whose sera was reactive by the HTLV-I EIA were, in fact, infected by HTLV-II. Epidemiological studies of human retroviral infections (HIV-1, HIV-2, HTLV-I, and HTLV-II) continue to provide important data and direction for improving criteria for qualifying blood donors.

INTRODUCTION

An understanding of the unique biology of human retroviral infections—specifically, the prolonged carrier state that has resulted in multiple blood donations and transfusions from persons with undetected infections—has led to major revisions in blood donor screening and laboratory testing procedures. Beginning with the "Joint Statement on Acquired Immune Deficiency Syndrome Related to Transfusion" issued on January 13, 1983 [1], the American Association of Blood Banks, American Red Cross, and the Council of Community Blood Centers have developed a series of revisions to update standard operating procedures in order to address the special challenges posed by human retroviral infections.

Abbreviations: AIDS: acquired immunodeficiency syndrome EIA: enzyme immunoassay HIV-1: human immunodeficiency virus, type 1 HIV-2: human immunodeficiency virus, type 2 HIV-Ag: HIV-1 antigen HTLV: human T-lymphotropic viruses HTLV-I: human T-lymphotropic virus, type I HTLV-II: human T-lymphotropic virus, type II PCR: polymerase chain reaction rr: relative risk

Address reprint requests to: S. Gerald Sandler, M.D., National Headquarters, American Red Cross, Washington, DC 20006

Following the discovery in 1984 that a human retrovirus was the cause of the acquired immunodeficiency syndrome (AIDS) [2], the national blood collection organizations introduced new operational procedures to protect transfusion recipients from infection by this agent, currently known as the human immunodeficiency virus, type 1 (HIV-1) [3]. Following the Food and Drug Administration's issuance of the first license to a manufacturer of test kits for HIV-1 antibodies on March 2, 1985, blood collectors began to test all donated blood in the United States for HIV-1 antibodies [4]. Additional information about donor screening [5], laboratory testing for HIV-1 antibodies [6], and criteria for confirmatory testing [7] are summarized elsewhere.

The identification of HIV-2, a second human retrovirus capable of causing AIDS [8], has led to efforts to assess the risk of its transmission by blood transfusion and to plan for additional measures, if appropriate, to protect transfusion recipients in the United States [9]. Also, based on studies in Japan, the Caribbean, and the United States, blood services in the United States began testing all donated blood for antibodies to the human T-lymphotropic virus, type I (HTLV-I) in January 1989 [10–14].

The American Red Cross Blood Services, which collects approximately half of the blood donated for transfusion in the United States, maintains standardized procedures of laboratory testing for infectious diseases in its 54 regional blood centers. The results of these laboratory tests are reported to Red Cross national headquarters monthly, where they are reviewed as part of a systemwide surveillance and quality control program. Also, these test results provide important data on the prevalence of hepatitis B [15], HIV-1 [16], and HTLV-I [17] infections in the blood donor population.

The following review is based, in part, on these Red Cross data and is intended to address selected topics that relate to human retroviral infections as these relate to the safety of blood transfusions.

HUMAN IMMUNODEFICIENCY VIRUS, TYPE 1 (HIV-1)

Seronegative Window Period

One of the most important unresolved scientific issues related to transfusion-transmitted HIV-1 infection is the definition of the seronegative window period that follows HIV-1 infection. Investigators studying early HIV-1 infection in male homosexuals, and using *in vitro* amplification techniques and/or assays for antibodies to non-structural HIV-1 antigens, have reported the detection of HIV-1 infection as early as 42 months before standard FDA-licensed enzyme immunoassays (EIAs) for HIV-1 antibodies were reactive [18–22]. These findings suggest that, after infection by HIV-1, some persons enter a prolonged phase of low viral expression without an antibody response that is detectable by conventional enzyme immunoassays. Assuming that these observations are substantiated, the most critical questions that follow are *(1)* how often do such prolonged seronegative latency periods occur and *(2)* are such HIV-1-infected EIA-seronegative persons capable of transmitting HIV infection via blood transfusion? As of June 30, 1990, the Centers for Disease Control listed only 11 cases of transfusion-associated acquired immunodeficiency syndrome (AIDS) that were reported during the five years (since spring 1985) that blood services in the United States have tested donated blood by EIA for HIV-1 antibodies [23]. This relatively low number of AIDS cases, within a total of 136,204 cases of AIDS reported to the Centers for Disease Control as of June 30, 1990, would be increased significantly if asymptom-

TABLE 1
Results of Testing American Red Cross Blood Donors for HIV-1 Antibodies[a]

Testing Period	Enzyme Immunoassay Repeat Reactive (%)	Western Blot—Positive (%)
12-Month Average (10/1/88–9/30/89) (n = 6,269,300)	0.038	0.011
Most Current Results (9/1/89–9/30/89) (n = 510,800)	0.029	0.008

[a]Results from 55/56 American Red Cross regions reporting test results

atic HIV-1-infected transfusion recipients, such as those detected in lookback studies, were listed also. Answers to the questions of how often prolonged seronegative latency periods occur and whether blood donated during this period is infective remain unanswered, and research on these issues remains a priority. Current blood donor deferral practices are based on the assumption that virtually all healthy persons who become infected by HIV-1 will develop detectable antibodies within six months.

Statistics

The results of current testing for HIV-1 in American Red Cross blood donors are summarized in Table 1. During the most recent month for which complete test results are available (September 1989), 0.008 percent of 510,800 donors had positive tests for HIV-1 antibodies that were confirmed by Western blot.

A study of over 17 million American Red Cross blood donors revealed that the relative risk (rr) of HIV-1 infection continues to be lowest in repeat female donors (rr = 1), compared to first-time female donors (rr = 2.4), repeat male donors (rr = 3.4), and first-time male donors (rr = 9.1) [24]. From the results of this study, and others, it is estimated that the risk of a transfusion recipient contracting HIV infection is approximately 1:150,000 per unit transfused, or 1:28,000 for a recipient of the average transfusion (5.4 units) [24].

HIV Antigen

In November 1989, the Food and Drug Administration issued a license for a diagnostic test kit for HIV-1 p24 antigen (HIV-Ag), raising the possibility that HIV-Ag testing could be added to current tests of donated blood to reduce further the risk of transfusion-transmitted HIV-1 infection. A multi-organizational study to evaluate HIV-Ag screening of blood donors was conducted in 12 community blood centers in the United States. More than 500,000 donors were tested, and none tested positive for HIV-Ag in the absence of anti-HIV-1 [25].

Also, addressing the HIV-Ag testing issue from a different perspective, investigators at Harvard University's John F. Kennedy School and the American Red Cross used a probabilistic model to estimate the probability that HIV-Ag testing would detect an additional HIV-infective blood component was approximately 1 in 4,860,000 [26]. This figure projects to an estimate that adding HIV-Ag testing would prevent

approximately four cases of primary transfusion-transmitted HIV infection annually in the United States, which would represent approximately one case of AIDS per year. For these reasons, neither the Food and Drug Administration nor the national blood services organizations recommend testing of donated blood for HIV-Ag.

HIV-2 (HUMAN IMMUNODEFICIENCY VIRUS, TYPE 2)

Epidemiology

HIV-2, the second human retrovirus identified that is capable of causing AIDS, has been detected primarily in West Africa [27]. Although there is some evidence that HIV-2 is less pathogenic than HIV-1 [28], HIV-2 infection has caused severe immunodeficiency and AIDS in a substantial proportion of infected persons [29,30]. An increasing number of cases of HIV-2 infection in West African immigrants or their sexual contacts have been identified in the United States, Central Africa, South America, Canada, and Europe [31,32]. In the United States, the Centers for Disease Control and the Food and Drug Administration tested samples form 8,500 random blood donors and 16,000 individuals at risk for HIV infection. None of the samples tested positive for HIV-2 antibodies [33]. Using an EIA for HIV-2 antibodies, the American Red Cross has retested over 20,000 donor sera that tested repeatedly reactive for HIV-1 antibodies from 1987–1989, and none contained confirmed HIV-2 antibodies [Fang C: personal communication, May 1, 1990].

Serological Cross-Reactivity

There is considerable serological cross-reactivity between HIV-1 and HIV-2 as a consequence of the homology of HIV-1 and HIV-2 in the *gag* (77.5 percent), *pol* (67.5 percent), and *env* (45.0 percent) regions [34]. Thus, it is not unexpected that FDA-licensed EIAs for *HIV-1* antibodies detect as many as 42–92 percent of sera from persons infected by *HIV-2* [35,36]. Attempts have been made to utilize this cross-reactivity to prepare combination HIV-1/HIV-2 enzyme immunoassays. One method has used an immunoassay employing an epitope of the transmembrane glycoprotein that is common to both HIV-1 and HIV-2 [37]. Another method has tried to use whole virus lysates from both retroviruses in one EIA [38]. In addition, the differences between HIV-1 and HIV-2 have been utilized to distinguish HIV-1 and HIV-2 by serological methods [39].

HUMAN T-LYMPHOTROPIC (LEUKEMIA) VIRUS, TYPE I, AND TYPE II (HTLV-I AND HTLV-II)

Several factors led to the decision to test all donated blood for HTLV-I infection, even before a case of transfusion-transmitted HTLV-I-related disease had been reported in the United States and before the FDA-licensed test kits were available [40,41]. Probably the most important factor in the decision to test donated blood for HTLV-I infectivity was evidence that persons infected by HTLV-I were donating blood in the United States, and, as a result, an estimated 2,800 transfusion recipients would be infected by HTLV-I annually [42].

Statistics

The results of current tests for HTLV-I antibodies in American Red Cross blood donors are summarized in Table 2. During the most recent month for which complete

TABLE 2
Results of Testing American Red Cross Blood Donors for HTLV-1 Antibodies[a]

Testing Period	Enzyme Immunoassay Repeat Reactive (%)	Confirmed Positive (%)[b]
6-Month Average (4/1/89–9/30/89) (n = 2,869,400)	0.070	0.010
Most Current Results (9/1/89–9/30/89) (n = 467,400)	0.083	0.009

[a] Data from 51/56 American Red Cross regions reporting test results
[b] Western blot and/or radioimmunoprecipitation assay

test results are available, 0.009 percent of 467,400 donors had positive tests for HTLV-I antibodies confirmed by Western blot and/or radioimmunoprecipitation assay.

Donor Risk Factors

As part of the effort to identify risk factors associated with retroviral infections in potential blood donors, the American Red Cross conducted interviews with donors whose blood was tested and found to contain HTLV-I antibodies. A preliminary report of these findings was presented at the 1989 Annual Meeting of the American Association of Blood Banks [43]. These data have been updated for inclusion in this review. As of Februaruy 1, 1990, 482 American Red Cross blood donors with Western blot or radioimmunoprecipitation assay-confirmed HTLV-I/II infections have been interviewed for additional information concerning risk factors for HTLV-I/II. For these donors, the hierarchical risk of infection was greatest for sex with an intravenous drug user (21.2 percent), followed by birth/sexual contact in the Caribbean (18.9 percent), history of blood transfusion (11.3 percent), intravenous drug use (8.3 percent), birth/sexual contact in Japan (8.1 percent), history of sexually transmitted disease (6.4 percent), and birth/sexual contact in Africa (1.0 percent). No overt risk factor was identified for 24.7 percent of the persons interviewed.

HTLV-II

Studies of blood donors in American Red Cross regional blood centers, who tested repeatedly reactive by FDA-licensed HTLV-I enzyme immunoassays, reveal that a significant number are, in fact, infected by HTLV-II. As of February 1, 1990, genome amplification studies in 135 Red Cross donors who tested repeatedly reactive by Abbott Laboratories HTLV-I EIA revealed that the infective agents were HTLV-II in 49.1 percent; HTLV-I in 48.3 percent; and HTLV-I and -II in 2.6 percent. There were 14.7 percent with negative or unresolved test results [Williams A, et al: unpublished data]. These findings are consistent with evidence that HTLV-II is spreading rapidly in certain cities in the United States among intravenous drug users [44] and prostitutes [45]. As a consequence of these observations, reactive HTLV-I EIA results may be reported as "repeatedly reactive for *HTLV-I/II* antibodies" meaning HTLV-I and/or HTLV-II, pending additional testing to distinguish between HTLV-I and HTLV-II.

Synthetic HTLV Peptides

To date, distinction of HTLV-I and HTLV-II infection has required viral culture or a modified polymerase chain reaction (PCR) [46], but these methods are costly, time-consuming, and limited to a very few research laboratories. As an alternative, synthetic peptides may be used to distinguish HTLV-I and HTLV-II antibodies. In one study, synthetic peptides correctly identified 91.7 percent of samples with anti-HTLV-I and 100.0 percent with anti-HTLV-II that had been confirmed by PCR [47]. Based on these findings, the American Red Cross's National Reference Laboratory for Infectious Diseases has begun to use HTLV-I and HTLV-II synthetic peptides as a part of confirmatory testing, reserving PCR for samples that cannot be characterized unequivocally by HTLV-I and -II peptide enzyme immunoassays.

CONCLUSION

The data summarized in this review document the significant progress that has been achieved in recent years to reduce the risk of transfusion-transmitted retroviral infections.

The number of blood donors who were subsequently identified by laboratory tests to be HIV-1 carriers decreased more than fourfold, from 35 per 100,000 donors in 1985 to eight per 100,000 donors in 1990. For HIV-2, surveillance studies, specific geographic exclusion criteria for potential donors, and laboratory testing with cross-reacting HIV-1 reagents are currently in place. Also, national blood collection agencies have indicated their intention to implement anti-HIV-2 testing, if ongoing surveillance studies indicate that such testing would be appropriate. For HTLV-I, the results of nationwide testing of all donated blood for HTLV-I antibodies has yielded two important observations. First, nearly 50 percent of blood donors with confirmed positive results by test reagents for HTLV-I antibodies are infected by HTLV-II. Second, nearly all of the HTLV-II-infected persons admit to intravenous drug abuse at some time, confirming the impression that past intravenous drug use is a major risk factor for transfusion-transmitted retroviral diseases.

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