TITLE:	**SERUM REPOSITORY FOR HTLV-III TESTING (Transfusion Safety Study)**
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CONTRACT NO.:	**NO1-HB-4-7002**
TIME PERIOD OF CONTRACT:	**May 1984 through February 1985**
CONTRACTING AGENCY:	**Division of Blood Diseases and Resources** **National Heart, Lung, and Blood Institute** **National Institutes of Health** **Bethesda, Maryland 20205**

OVERALL SUMMARY OF THE TRANSFUSION SAFETY STUDY DONOR REPOSITORY

Background

The Transfusion Safety Study (TSS) was organized as a response to the RFP entitled "*Association of Blood Product Use with Immune Function Changes: Relation to Acquired Immunodeficiency Syndrome (AIDS) - A Prospective Study*", issued in September, 1983. The rationale was to determine the extent to which changes in immunologic indices among persons receiving blood and blood products were attributable to the unknown factor(s) responsible for AIDS. The method of approach was a comparison of non-specific parameters in transfused populations in areas with a high and low prevalence of AIDS.

Confirmation in May, 1984, of infection with a specific virus as the underlying cause of AIDS, however, changed the laboratory emphasis. Another factor modifying the emphasis of TSS was Gallo's description of a method of producing HIV-1 antigens in large amounts. His approach made feasible the rapid development of commercial assays for serologic screening of blood donors. Thus, the persons at risk of AIDS because of human immunodeficiency virus type 1 (HIV-1) became specifically identifiable by serologic testing.

With the anticipation of licensure and routine application of screening assays, in 1984, under emergency powers, the National Heart, Lung, and Blood Institute (NHLBI) issued a contract (NO1-HB-4-7002) for the collection of 200,000 serum samples from routine blood donors in high AIDS prevalence areas of the United States. These were to be collected and stored prior to the availability of screening tests for antibodies to HIV (anti-HIV). The immediate use for the TSS/NHLBI Donor Repository was to identify potentially infectious donors and evaluate transmission of HIV to recipients by the components of the donation. However, the potential use of this Donor Repository for the study of transmission of other transfusion-associated viruses was also recognized and permission for testing for other infectious agents was included in the informed consent signed at the time of donation.

Objectives and Methods

Study sites and target sizes for serum sample collections for the four geographic areas with the highest prevalence of AIDS were: Greater New York area, served by the New York Blood Center (80,000 samples); South Florida area, served by the South Florida Blood Service, now the American Red Cross Regional Blood Services (30,000 samples); San Francisco and Bay area counties to the north of that city, served by the Irwin Memorial Blood Bank (30,000 samples); and, Los Angeles County, served by the American Red Cross Regional Blood Services (60,000 samples).

From early September, 1984, until early February, 1985, donors at the participating blood services were asked to permit the collection of an additional 10 ml of clotted blood for HIV antibody testing when a licensed test became available and for testing for other infectious agents which might be transmitted by blood. They were also asked for permission to contact them later if the results of such tests indicated that further observations would yield useful scientific information.

Collection of the Donor Repository Itself

At the end of Repository collections in February 1985, the target total of 200,000 donor serum specimens had been stored. Their distribution was as follows: New York Blood Center, 77,760; American Red Cross Blood Services, South Florida Region, 31,104; Irwin Memorial Blood Bank, 27,500; and American Red Cross Blood Services, Los Angeles-Orange Counties Region, 67,418.

Screening Conducted on the Donor Repository

HIV-1: All donations (196,684) were screened using EIA. Confirmation of positives was by Western Blot and RIPA.
Results: Prevalence: 16 per 10,000 donations. Test seeking at blood collection agencies by persons at risk for HIV-1 was found to have contributed to HIV-1 prevalence.
Kleinman et al, *"Prevalence of Antibodies to Human Immunodeficiency Virus Type 1 Among Blood Donors Prior to Screening"*, Transfusion 1989; 29:572-580.

p24 antigen: A selected sample of 8,597 males, age 18-44, from high-risk zipcodes were screened using EIA.

Results: Prevalence: 1.54 %. No p24 antigen positive, anti-HIV-1 negative donors were identified.
Busch et al, "*Screening of Selected Male Blood donors for p24 Antigen of Human Immunodeficiency Virus Type 1"*, New England Journal of Medicine 1990; 323:1308-1312.

HTLV-I/II: All donations (196,684) were screened using EIA. Confirmation of positives was by Western Blot and RIPA.
Results: Prevalence: 0.7 to 0.9 per 1000 donations among the four blood services. Sex- and age-specific prevalences did not differ significantly; sources of infection were varied.
Parks et al, "*Human T-Cell Lymphotropic Virus Infection among Blood Donors in South Florida",* Journal of Acquired Immune Deficiency Syndromes, 1991; 4:89-96.
Tomasulo et al, *"Human T-Cell Lymphotropic Virus Infection among Blood donors: Epidemiologic Pattern Compared with That of Human Immunodeficiency Virus Type 1*". (Work In Process)

Subsequent Use of the Donor Repository

Repository screening identified subjects for enrollment in long-term follow-up by the TSS:

Beginning August, 1985, 4,063 donors and their recipients were followed at 3 to 6 months intervals. The number of visits ranged from 1 to 23 and the longest period of observation was 66 months. At each visit blood specimens were collected and processed for storage as plasma and buffy coat in the TSS/NHLBI Subject Repository.

Factors Influencing HIV-1 Transmission to recipients:

Duration of storage (shelf life) of red cells prior to administration is a determinant of transmission. Donegan et al, *"Transfusion Transmission of Retroviruses: Human T-Lymphotropic Virus Types I and II Compared with Human Immunodeficiency Virus Type 1*", Transfusion 1994; 34:478-483.

Repository specimens from Donors whose Recipients were enrolled were evaluated by quantitiative HIV-1 RNA PCR. Viral concentration at donation is significantly related to transmission to recipients. When viral load and shelf life of red cells are considered together, there was a statistically significant association for both. *"Factors Influencing Human Immunodeficiency Virus Type 1 Transmission by Blood Transfusion"*. Busch et al, Journal of Infectious Diseases; 1996, in press.

Differentiation of relative effect of host versus viral factors in determining HIV infection and progression:

Viral sequencing of donation sera and plasma samples from the blood donor, his two recipients, and a recipient's sexual partner showed that the variation in the HIV quasispecies that occurs over time does so in an individual-specific manner with resulting divergence from shared early genomes. Diaz et al, manuscript in preparation.

Serial evaluations of 43 other such strain-specific groups showed that intragroup variation in HIV-1 RNA levels and clinical and immunological progression were as marked as intergroup variation -- no strain variation in virulence was observed. Operskalski et al, in preparation.

Two clusters, each with a recipient simultaneously exposed to two infected HIV-1 infected donors, gave differing results. One documented the occurrence of a resulting dual infection in the recipient by the two different HIV-1 strains; the other resulted in detectable infection by only one strain. Diaz et al, in press.

Items of Significance to Other Investigators

This is the only large-scale, multi-center repository of donor blood specimens which immediately predates the introduction of screening for antibody to HIV. To assess the sensitivity of new HIV tests using present-day donors, up to 1 million samples may have to be collected and processed to provide an evaluation comparable with that of the Repository.

All specimens have been screened for anti-HIV-1 and anti-HTLV I/II. Donor anti-HIV-1 prevalence was 1.6/1000 while donor anti-HTLV I/II prevalence was 0.8/1000.

Specimens from high-risk donors have been screened for HIV-1 p24 antigen, showing no p24 antigen positive, anti-HIV-1 negative donors.

The demographic characteristics, lab results, and repository information for the TSS/NHLBI Donor Repository are linked with follow-up data for the donors and their recipients in TSS/NHLBI Subject Repository. These data can be accessed with an interactive computer program available from NHLBI known as RMS for TSS. This program provides an easy-to-use methodology for selecting subjects and specimens which meet the investigator's criteria of examination, and for using the resulting dataset in further analyses and statistical models.