

TSS/NHLBI SUBJECT REPOSITORY

TITLE: **SUBJECT REPOSITORY (Transfusion Safety Study)**

CONTRACT

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OVERALL SUMMARY OF THE TRANSFUSION SAFETY STUDY SUBJECT 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.

The TSS/NHLBI Subject Repository was also included as a requirement in the RFP. This provided for the establishment of a repository of plasma and cell samples from the study cohort for use in future scientific studies.

Confirmation in May 1984, of infection with a specific virus as the underlying cause of AIDS 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 for AIDS because of human immunodeficiency virus type 1 (HIV-1) infection became specifically identifiable by serologic testing.

Objectives and Methods

The overall objective of the repository was to collect for long-term storage plasma and cells at the time of each observation from each person entered into the study. This would serve as a source of specimens in future years for evaluating agents to which persons in the target populations may have been exposed.

The study cohorts included: HIV-infected donors and controls; HIV-exposed transfusion recipients and controls; sexual contacts of HIV study recipients; HTLV-infected donors and controls; HTLV-exposed recipients and controls; household contacts of HTLV study donors and recipients; and, persons with congenital clotting disorders or congenital anemias and their respective household and sexual contacts.

At enrollment, a medical history and blood samples for serologic, hematologic, immunologic evaluation, and long-term storage were obtained. Follow-up visits at 6-month intervals included interval medical history and repeat laboratory testing.

Collection of the Subject Repository

Subject enrollment began August 1985. A total of 4,084 were enrolled and followed every six months. The number of visits per subject ranged from 1 to 23; the longest period of observation was 5 1/2 years. At each visit, blood specimens were collected and processed for storage in the repository as plasma and buffy coat. For HTLV-I/II subjects, lymphocyte samples were also stored.

The repository contains 50,041 buffy coat specimens, each containing 1-3 million cells stored in liquid nitrogen at -196° C, and 44,771 plasma specimens stored at -75° C. Approximately 3500 lymphocyte samples from 1701 follow-up visits of 726 subjects were also stored in liquid nitrogen at -196° C

Laboratory Testing of Subjects Represented in the Repository

All subjects have been screened for anti-HIV-1 by EIA. All reactive subjects were subsequently retested to confirm their status. Subjects with a negative result were tested at each succeeding visit. Subjects in the HTLV cohort were tested at each visit for anti-HTLV I/II. A combination of Western blot, RIPA, and PCR were used to confirm HIV and HTLV I/II positivity. HTLV subtyping was performed by a combination of PCR and peptide-based assay.

All subjects were tested at each visit for hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs) and antibody to hepatitis B core antigen (anti-HBc) by RIA, and for ALT. Starting in 1989, all subjects were tested for anti-HBc and ALT only. When a specific test for hepatitis C became available in 1989, all subjects still in follow-up were tested at each subsequent visit by the first generation HCV EIA1.0. For subjects not in follow-up, serum from the last available visit was tested and, if positive, samples from the entry visit and interval visits were tested to determine the probable period of infection. When the second generation HCV test became available, serum from the last available visit from all HCV EIA1.0 negative subjects was tested and, if positive, samples from the entry visit and interval visits were tested to determine the probable period of infection. Selected groups of HCV EIA reactive subjects were further characterized by HCV recombinant immunoassay (RIBA).

Selected groups of subjects have been tested for HAV, HEV, HDV, parvovirus B19, CMV, and EBV. Any seroconversions were further characterized by PCR and IgM antibody screening. When antibody levels to HAV and HBsAg were quantified, internationally-accepted reference standards were used.

Examples of Subsequent Use of the Subject Repository

Kaposi's sarcoma-associated herpesvirus (KSHV) in selected TSS cohorts:

Stored plasma were evaluated for KSHV infection by a recently-developed immunofluorescence assay for antibody to nuclear antigen in B cells latently KSHV-infected. The prevalence rate of 30% among HIV-infected homosexual donors was significantly higher than the 2 to 5% rate for HIV-infected hemophiliacs and transfusion recipients. This suggests that KSHV is a sexually-transmitted pathogen. [Kedes et al, Nature Medicine, 1996; 2:918-924.]

KSHV transmission from infected donors to their recipients was not observed. Three HIV-1 infected recipients (2 of washed red cells, 1 of platelets) had KSHV seropositive donors; none became seropositive. [Operskalski et al, Transfusion 1996;38:57S.]

Relative effect of host versus viral factors in determining HIV infection and progression among donors and recipients:

Viral sequencing of two HIV strain-specific groups, each with a recipient simultaneously exposed to two infected HIV-1 infected donors, gave differing results. In 1 recipient, dual infection by the two different HIV-1 strains was documented; the other showed detectable infection by only one strain. [Diaz et al, in press.]

Viral sequencing of donation sera and plasma samples from a 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 strain-specific groups showed that intragroup variation in HIV-1 RNA plasma levels and clinical and immunological progression were as marked as intergroup variation. No strain variation in virulence was observed. [Operskalski et al, in preparation.]

Parvovirus infection among congenital anemia (CA) patients:

Stored sera from 352 CA patients and 139 household contacts were tested for HPV IgG, IgM and DNA. At entry, anti-HPV seroprevalence was 28% among CA patients and 32% among household contacts. During follow-up, the incidence of anti-HPV seroconversion was higher among the 252 susceptible CA patients (13%) than their 94 susceptible contacts (3%). The higher frequency of seroconversion among CA patients is compatible with HPV transmission by blood components. [Nowicki et al, abstract submitted.]

Items of Significance to Other Investigators

The TSS database links subjects' demographic characteristics, medical history, and laboratory results with the TSS/NHLBI Subject Repository Inventory. Investigators can identify subjects with specific characteristics of interest. Specimens from these subjects that are most appropriate for answering the scientific questions can then be located using an interactive computer program known as Repository Management System (RMS) for TSS.