

Supporting Statement B for

Transfusion-transmitted retrovirus and hepatitis virus rates and risk factors:  
Improving the safety of the US blood supply through hemovigilance  
(NHLBI)

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Dr. Simone Glynn,  
Two Rockledge Center  
Room 9142  
6701 Rockledge Drive  
Bethesda, MD 20892  
Phone: 301-435-0065  
Fax: 301-480-0867  
Email: [glynnsa@nhlbi.nih.gov](mailto:glynnsa@nhlbi.nih.gov)

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## **B. Collection of Information Employing Statistical Methods**

### **B.1. Respondent Universe and Sampling Methods**

The study sample will consist of Cases and Controls:

1. Cases: Blood Donors tested true positive for HIV, HCV, HBV and/or HTLV
2. Controls: Blood Donors tested false positive for HIV, HBV, HCV and/or HTLV

**Table 1: Overall expected participation in risk factor interview assuming both prospective and retrospective interviews for HIV positive and false positive donors.**

<b>Subject Type</b>	<b>HIV</b>	<b>HCV</b>	<b>HBV</b>	<b>HTLV</b>
Case (True positive)	350	500	500	300
Control (False positive)	2500			

#### **Sample Size Calculations:**

The estimation of optimal sample size is difficult because of limited information available on the prevalence of risk behaviors in accepted blood donors. For this reason we have focused on a power analysis to help guide our understanding of what risk estimate results are achievable given the number of each type of true positive donors we believe we will be able to interview. A survey study of undisclosed risk factors in accepted donors conducted by the Retroviral Epidemiology Donor Study in the 1990s found a prevalence of undisclosed risks of 186 per 10,000 donors or 1.86%. We assume this is the prevalence of undisclosed risks in the control group for our study. The sample size (as described below) will include 350 HIV confirmed positive donors, 500 HCV confirmed positive donors, 500 HBV confirmed positive donors, 300 HTLV confirmed positive donors. The table below shows the power (of an  $\alpha=0.05$  level test) to detect significant associations between risk factors with a prevalence of 1.86, 1.0 and 0.5% in

controls donors assuming 2, 3, 5, and 10-fold higher prevalence of the same risk factors in confirmed positive donors, by the four infectious markers (Table 4). The higher the prevalence of the risk behaviors is in the donor population and the larger the excess risk in confirmed positive donors the higher the power will be to detect a significant difference.

**Table 2: Power for various risk factor prevalence combinations in controls and cases**

Infectious Marker case/control sample sizes	Prevalence of risk factor in controls	Odds ratio to detect in cases			
		10	5	3	2
HIV 350/2500	1.86%	<99.9	<99.9	91.3	51.3
	1.0%	<99.9	97.6	72.1	32.2
	0.5%	99.5	83.9	46.7	18.3
HCV and HBV 500/2500	1.86%	<99.9	<99.9	96.7	62.3
	1.0%	<99.9	99.4	82.3	39.8
	0.5%	<99.9	91.4	56.1	22.4
HTLV 300/2500	1.86%	<99.9	99.8	88.0	46.7
	1.0%	<99.9	96.1	67.3	29.2
	0.5%	99.1	80.0	42.9	16.7

For HIV risk factors, a study of 350 confirmed positive donors and 2500 false positive donors will have more than 80% power to be able to detect a 5-fold increased prevalence of risk factors in true positive cases if the risk factor prevalence is 0.5% or higher in false positive donors. The results of the study will be informative for scientific, regulatory and policy reasons. For each infection specific viral infection power calculations were performed to determine what the power would be for the expected sample size. Given that we are inquiring about the possible behaviors or exposures that are associated with infection acquisition, we expect that for many risk factors the true

positive donors will have notably higher prevalence of the risk factors than the control donors. For that reason the power calculations allow us to say that even if the difference in the prevalence of specific risk factors is as low as only 5-fold higher for HIV or HTLV and 3-fold higher for HBV and HCV in cases compared to controls we will have sufficient ability to detect statistically significant differences. In fact the difference in the prevalence of risk factors may be much higher in cases than 3 or 5-fold when compared to controls.

A balance must be struck in donor eligibility that meets the simultaneous goals of achieving the safest blood supply possible while still ensuring that an adequate quantity of blood in the supply is available to meet transfusion needs. A difference of 3 to 5-fold in relative risk of infected donations among subsets of donors (differentiated based on donation type, demographic or behavioral risk factors) is generally accepted as the level of relative risk that drives policy decisions regarding blood donor eligibility criteria and content of the donor history questionnaire. For example there is a >20-fold difference in prevalence and an approximately 3-fold difference in incidence for major transfusion transmitted viral infections (TTVIs) among first time donors (which represent ~20% of donations but nearly 50% of donors each year) relative to repeat donors. There are also approximately 3 to 5-fold differences in prevalence and incidence of TTVIs when donors are sorted by demographic characteristics such as gender, race/ethnicity, country of birth or region of residence in the US. Consequently this level of relative risk is deemed acceptable, whereas higher relative risks for groups such as persons with histories of injection drug users or high risk sexual exposures have led to explicit questions and FDA-sanctioned deferral criteria. One goal of our study is to establish if there are additional

behavioral risk factors that exceed this tolerable level that should result in consideration of new deferral criteria (e.g., # of recent heterosexual partners).

If the risk factor prevalence in false positive donors is the same as reported in the previous REDS study (1.86%) we will have more than sufficient power to detect a 5-fold higher risk factor prevalence in true positive cases. For HTLV risk factors the power estimates are similar, but slightly lower at any given combination of risk factor prevalence in false positive donors and excess risk in true positive donors because of the lower number of HTLV true positive cases (300) we are planning to interview.

For HCV and HBV risk factors a study of 500 confirmed positive donors and 2500 false positive donors will have sufficient power to be able to detect a 3-fold increase in prevalence of risk factors in cases if the risk factor prevalence is 1.0% or higher in false positive donors.

These power analyses underpin our decision to seek to interview as many confirmed HIV and HTLV positive donors as possible, whereas we will sample of HCV and HBV confirmed positive donors. Assuming 75% participation of HIV and HTLV confirmed positive donors and the pre-specified maximum number of confirmed positive HCV and HBV participants, the overall number of interviews to be conducted by each organization are shown in Tables 1 and 3. We assumed this participation proportion because previous *retrospective* studies of risk factors for confirmed positive blood donors had participation rates of 56% (See Orton and colleagues HCV NAT risk factor study.) In that study donors who donated up to 4 years before were contacted, in our study we will be contacting donors in essentially real time leading us to believe we will be able to obtain higher participation rates. Plus we are leveraging the communication skills of

trained donor counselors and physicians to enroll donors in the study. Donor counselors and blood bank physicians have expertise and training in empathetic communication which should help in to obtain the expected participation proportion. We acknowledge the participation proportion we plan to achieve is relatively high for interview studies.

**Table 3. Expected confirmed positive donor participation in risk factor interview study by blood center based on 2007 data assuming both prospective and retrospective interviews for HIV positive and false positive donors.**

<b>Viral Infection</b>	<b>BSI</b>	<b>NYBC</b>	<b>ARC**</b>	<b>Total</b>
HIV-1	40	30	280	350
HCV	100	100	300	500
HBV	100	100	300	500
HTLV I/II	80*	31	189	300
Total Cases	320	261	1069	1650
Total Controls	486	396	1618	2500

\*Approximately half of HTLV infections at BSI are expected to be confirmed.

\*\* Includes interviews of Community Blood Centers of South Florida donors.

## **B.2. Procedures for the Collection of Information**

In-person interviews will be conducted with all of HIV positive donors and a few other true positives for other viruses of interest, depending on the preference of each participant. Telephone interviews will be conducted to administer risk factor questionnaire for false positive donors (controls). Case recruitment procedures and study sample numbers for the interviews to be conducted will be dependent on the type of infection.

### ***HIV and HTLV Cases***

HIV and HTLV cases will be contacted in accord with one of the three routes of subject contact for the study. HIV cases will come from the three participating organizations. In order to enhance the number of study subjects we will include HIV

confirmed positive donors from the Community Blood Centers of South Florida. For HTLV confirmed positive donors we will include donors from the 3 main participating organizations only (ARC, BSI, and NYBC).

### ***HCV and HBV Cases***

HCV and HBV cases will be contacted in accord with one of the three routes of subject contact for the study. Because of the number of confirmed HCV and HBV positives donors each year, we will sample cases for these infections. We will conduct 500 case interviews for each type of infection. ARC will conduct 300 HCV and 300 HBV interviews; BSI will conduct 100 HCV and 100 HBV interviews, and NYBC will conduct 100 HCV and 100 HBV interviews. We will preferentially contact all NAT-only cases and recent seroconversion cases. We expect that 75% of cases who are contacted will agree to participate in the study. These study numbers will be sufficient to provide up-to-date information on risk factors for confirmed HCV and HBV in persons who have recently donated. To achieve a sample that will be temporally representative of the year-long study interview period we will sample donors on a monthly basis. For ARC this means that 25 HCV and 25 HBV confirmed positive interviews will need to be conducted every month. For BSI and NYBC, 8 to 9 interviews for each infection will be conducted each month. HCV and HBV case interviews will be tallied starting at the beginning of every month and for each organization when the targeted number of interviews are reached HCV and HBV case interviews will end until the beginning of the next month.

## **Controls**

Controls for this study are intended to reflect the population of eligible blood donors who have successfully donated blood. In other words, the controls will represent all persons who have been determined eligible to donate and who have donated blood that has been tested for infectious disease markers. The study will define an eligible donor as one who has been determined eligible to donate **and** who has given blood. Controls will not be matched to cases so that we may include demographic characteristics in addition to risk factors in our multivariable logistic regression analysis of the predictors of infections in blood donors. Controls will be interviewed contemporaneously as cases. All interviewed controls will be included in each analysis comparing risk factors in confirmed positive for each infection to the entire control group. Therefore, the ratio of controls to cases will vary depending on the infection being examined. For HIV the ratio will be approximately 7 controls per case, for HCV and HBV the ratio will be 5 controls per case, and for HTLV the ratio will be approximately 8 controls per case. Each participating organization will have to ensure that the controls in the study are similar to population of eligible donors according to age, gender, race, and first time donor status. To accomplish this each organization will monitor the demographic characteristics of control donors so that study participants resemble the eligible donor population for that blood collection organization while the study is being conducted. For example we will select controls in bins or groups that largely resemble the eligible donor population with respect to gender, age group, race/ethnicity, and first time or repeat donor status. Procedures to be used at each blood center for the ongoing monitoring will be developed during the ramp-up phase of the study. It should be noted that, as a result of the low positive predictive value of these tests when used for blood donors, many false positive donors are found for each true positive identified.

### **Prospective and Retrospective Interviews**

The majority of risk factor interviews will be conducted soon after confirmatory testing is completed from donors who have been newly classified as true or false positive for each infection based on blood donation testing (prospective interviews). Depending on the length of study and the possibility that reduced numbers of infections possibly could be observed for unknown reasons during the planned study period and to account for the expected 75% participation of confirmed positive cases, we will also obtain human subjects approval to conduct risk factor interviews of donors from the beginning of 2010 in order to achieve the projected sample size for each infection. This issue is likely to only be relevant for HIV infections and this strategy will only be used for HIV because of the importance of achieving sufficient participation of subjects for HIV.

### **Data Analysis**

#### **Analysis of Infectious Disease Marker Prevalence and Incidence Rates**

Prevalence rates among first time donors and incidence rates among repeat donors for each infectious disease marker will be reported. Prevalence rate will be defined as the number of infected donations from first time donors divided by total number of first-time donations. Incidence rate will be defined as the number of infected donations from repeat donors divided by the person-years of time accrued (i.e. sum of inter-donation intervals for repeat donations).

Recent seroconversion can be distinguished from prevalent infection based on the combination of NAT results and antibody titer for HIV and HCV. Hence, for HIV and

HCV, incidence rates will additionally be reported for new infections among all donors. This incidence rate will be defined as the number of new infections divided by the estimated person-years (i.e. number of donations times average window period for identification of recent seroconversions).

Unadjusted logistic regression will be used to assess the association of various factors (e.g. age, gender, donation type, center) on prevalence rates. Unadjusted logistic regression will be followed by adjusted (i.e. multivariable) logistic regressions. Multivariable logistic regressions will include year as a covariate to assess any temporal change in prevalence rates.

Unadjusted poisson regression will be used to assess the association of various factors (e.g. age, gender, donation type, center) on incidence rates. Unadjusted poisson regression will be followed by adjusted (i.e. multivariable) poisson regressions. Multivariable poisson regressions will include year as a covariate to assess any temporal change in prevalence rates.

### **Analysis of Infectious Disease Marker Risk Factors**

Potential risk factors include (but are not limited) to the following: parenteral (examples: blood or blood product transfusion, transplantation, injection drug use, tattooing, body piercing, needlestick injury), sexual, perinatal (examples: during pregnancy, labor, delivery or breastfeeding), and household contact (examples: sharing toothbrushes or razor blades with an infected individual). The study is not designed to assess very rare or newly hypothesized risk factors.

Interviews on 2500 controls and an expected 1650 cases (350 HIV positive donors, 500 HCV positive donors, 500 HBV positive donors, and 350 HTLV positive donors). We will compute descriptive statistics, such as frequencies, in order to characterize the infected population and catalog donor-reported risk factors likely to be the route of virus acquisition. We will compare the risk factors reported by donors according to demographics and in different regions of the country to determine if patterns of infection acquisition vary using the Chi-square or t-test depending on the structure of the predictor variable included in the analysis.

Multinomial logistic regression analysis will be used to determine the association between risk behaviors and infectious disease markers. The multivariable analysis will be important so that we may account for potential differences between cases and controls with regard to factors such as socio-economic status. In addition, analyses restricted to confirmed positive donors will also be conducted. For example, risk factors for recent and remote infections will be compared for each virus to determine if incident infections are associated with specific risk behaviors.

### **B.3. Methods to Maximize Response Rates and Deal with Non-response**

To improve the response rates, all HIV cases will be interviewed in-person at the time of their counseling visit to the blood center. We will also try and conduct in-person interviews with as many true positives in HBV, HCV and HTLV categories as possible. To make the response better for the control group, these individuals will be requested to complete the questionnaire over the phone when the blood center staff calls them for result notification and counseling.

#### **B.4. Test of Procedures**

In order to assess the average time per response, four randomly selected individuals were asked to complete the risk factor questionnaire in-person. Based on this testing, it was concluded that average time spent to understand and complete the questionnaire was 35 mins (used for burden hour calculations in Supporting Statement A).

#### **B.5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data**

Individuals consulted include biostatisticians on statistical aspects of the study design; the blood centers researchers responsible for enrollment, administering questionnaires, and collection of samples; and the CC staff for protocol development, developing the study timeline and OMB submissions. Data analysis will be performed by the analytic staff that includes experts in qualitative data analysis along with epidemiologists and biostatisticians, with assistance and oversight provided by the REDS-II sub-committee.