Evaluation of Risk Factors Associated with HIV in Chinese Donors

Understanding the risk factors associated with HIV infection in donors is essential for developing donor behavioral screening policies. Injection drug use, sexual transmissions, transfusion history, and medical injections are thought to be major routes of HIV transmission in China but their relative importance in blood donors is unknown.

We propose to conduct a large, multi blood center case-control study designed to address the following main questions of interest:

1. What are the primary risk factors for HIV infection in Chinese blood donors?
2. What is the relative importance of injection drug use, heterosexual transmission, family history, transfusion history, history of previous whole blood or plasma donation, male to male sex, medical injections, acupuncture, and tattoos as routes of transmission for HIV?

3. Are there other important routes of transmission for this virus such as sex with an injection drug user, snorting drugs, living with someone who has HIV, living with someone who injects drugs, sharing a toothbrush or a razor, having been in jail, occupational history, having surgery, etc.?

Study Population

Each of the five REDS-II blood centers, located in the cities of Kunming, Urumqi, Luoyang, Mianyang, and Liuzhou, will participate in this study. Cases will be donors with confirmed anti-HIV antibody reactivity. Controls will be randomly-selected HIV non reactive donors matched by month and location of donation.

Study Procedures

Questionnaire Design: We have developed a Risk Factor Questionnaire (RFQ) that will be used for assessing risk factors for HIV, HCV, and HBV infections (the same questionnaire will be used in a separate study to assess risk factors for HBV and HCV infections). The questionnaire will collect general demographic and risk factor information pertinent to all three viruses (HIV, HCV, and HBV). The questionnaire has been developed based on a thorough review of the current international and Chinese literature. Efforts have been made to ensure that our questionnaire is comprehensive and culturally appropriate. The questionnaire has been translated into Chinese and Uyghur languages. The Uyghur translation will be used for Uyghur donors in Urumqi, Xinjiang. We have conducted focus group discussions and cognitive testing to improve the potential reliability of responses.

Donor Enrollment and Questionnaire Administration: Blood donors who gave consent to be included in the REDS-II China Core Donation Database will be eligible for this study. At the time of donation, these donors have already given consent for their samples and information to be used for blood safety research. Each donor had also been assigned

a REDS-II Study ID under which donor and donation information can be identified in the REDS-II China Core Donation Database (this database does not include any personally identifying information).

Routinely, screening tests for HIV infection are done at blood centers while confirmatory testing is the responsibility of local Chinese CDC (C-CDC) laboratories. Local C-CDCs are also responsible for notifying, counseling and follow-up care to donors with confirmed anti-HIV results. REDS-II blood centers will collaborate with local C-CDCs in this study. This study will follow all policies and rules established by the Chinese government for protecting the confidentiality and other rights of HIV infected individuals.

1, All donors with anti-HIV results confirmed by local C-CDC laboratories will be eligible as Cases for this study. During C-CDC's routine notification/counseling meeting with a donor with confirmed anti-HIV results, a trained staff member from C-CDC (or the blood center) will explain the purpose and procedures of this study and administer an informed consent form. Consented donors will be interviewed by trained staff using the RFQ. The location for this activity can be either at the local C-CDC office or blood center.

2, Blood Centers will select a random group of donors with negative infectious disease test results as Controls for this study. Controls will be enrolled with a 2:1 ratio to Cases and will be matched to the Cases by blood center and donation month. Blood Centers will contact potential Controls by phone and/or mail, inviting them to come back to participate in this study. Controls will be consented and interviewed using the same RFQ by C-CDC or blood center staff, either at the local C-CDC or blood center.

3, Results of interviews will be entered into the REDS-II China database using a data entry system designed for this study.

4, All Cases will be defined by the local C-CDC's official anti-HIV confirmatory test results. During this study, blood centers will also send serum samples of all donors with preliminary (screening) reactive anti-HIV results to the REDS-II Central Laboratory at the Institute of Blood Transfusion (IBT). At IBT, a FDA approved anti-HIV1/2 EIA assay will be performed on all screening positive samples. Then samples with a positive result in the FDA approved EIA assay performed at IBT will undergo HIV-1 Western Blot testing using a FDA licensed kit. This sequential EIA testing approach has been shown to reduce cost and minimize the problem of indeterminate findings from Western Blot analysis. Discrepant results (comparing results from the C-CDC to those from IBT) will be provided to the C-CDC laboratory.

5, As a separate study, we plan to conduct "Detuned" testing for samples with confirmed anti-HIV results to gain information on the rate of recent infections and to calculate an incidence rate. Serum samples from confirmed anti-HIV positive samples will be stored in IBT's REDS-II sample repository.

Confidentiality Assurances:

This study will follow all policies and rules established by the Chinese government for protecting the confidentiality and rights of HIV infected individuals. All study personnel are aware that it is critically important to maintain confidentiality of all study participants. The followings are specific procedures that have been established for this study:

-All interviewers and other study personnel will be required to sign a code of confidentiality t which they must abide as a condition of their employment.

-All survey and test results will be kept confidential to the extent allowable by law. All study related computer files are kept in password protected computers. Forms with contain study numbers, not personal identifiers.

-The link between the study numbers and personal identifiers will be kept in a logbook in a secure location at the local blood center and local CDC, accessible only to key personnel from the blood centers and the CDC offices who already have access to such information according to government establish HIV testing and notification procedures. This linkage is not accessible to REDS-II study personnel from outside of blood centers and CDC. Test and interview results that will be entered into the REDS-II database will not include any personal identifying information, identified only by the study number.

-Potential study participants will be contacted by phone by local CDC offices according to CDC's standard procedure. Mail will not be used in communicating with potential study participants.

Data Compilation: HIV confirmatory results and results from the risk factor interviews will be entered into the REDS-II China database on a routine basis (weekly) using double key entry. Data will be checked for logical errors and consistency.

Variables to be Collected and Data Analysis: Case/Control status will be the main outcome variable (e.g., HIV-positive vs. control), whereas the various risk factors will be the independent variables of main interest. Other variables such as age, gender, ethnicity, first-time/repeat status could be potential confounders or effect modifiers and will be evaluated. Information from the HIV "detuned' testing regarding whether an individual has recent or long-established HIV infection will be incorporated as an additional variable in this analysis. We will first produce frequency tables and associated Chi-square tests (or Exact tests for small sample size), and review potential associations. We will calculate odds ratios (OR) with 95% CI using logistic regression analysis to compare the odds of seropositive donors having a risk factor compared to seronegative donors. Models will be constructed both unadjusted and adjusted for factors that may affect the association between the risk factor and the infection of interest. We will also determine what final set of independent risk factors appear to be associated with the infection of interest by building a multivariable model that includes as independent variables all risk factors that are independently

associated with each infection. We will probably use a stepwise selection procedure to build this multivariable model and will examine interactions between independent variables, as appropriate. JHU and Westat epidemiologists and statisticians are experienced at building such models.

Statistical Considerations (Sample Size and Power)

Table 1 shows the sample size that would provide 80% power to detect ORs of 1.5, 2.0 or 3.0 with an alpha of 0.05 for various risk factor prevalence values (from 1% to 10%). The OR compare the odds of having a risk factor between seropositive and seronegative donors.

Table 1. Sample size required to detect with 80% power for a given OR with alpha of 0.05

	Risk Factor Prevalence in Controls				
OR	0.01	0.02	0.03	0.05	0.1
1.5	8,075	4,100	2,800	1,725	930
2	2,400	1,225	**830**	**525**	290
3	810	420	285	180	103

For this study, using the estimate of identifying about 200 HIV confirmed seropositive donors per year at the five blood centers, enrolling cases and controls over a 30 month period (10/08 to 3/11) will allow us to identify about 500 HIV confirmed seropositive donors. Assuming a 70% response rate from donors, we anticipate that about 350 donors will be enrolled in this group which would permit detection of an OR of about 2.0 with a risk factor prevalence of about 6.5%. We are assuming a comparable response rate for controls, therefore we plan to approach approximately 1000 controls to enroll 700.

If the final sample size will allow for a stratified analysis, we will stratify results by blood centers, in order to identify potential risk factor information specific for a region.

Survey Considerations

The primary limitations of this study are those which are inherent with questionnaire surveys to ascertain specific risk factors. The data may be influenced by socially desirable responses, recall bias and sampling bias. We will attempt to maximize the reliability of the results by assuring the participants of the confidential nature of the study. A detailed explanation will be given to each participant about the research objectives and his or her individual rights as a research subject. Study results will be entered into the REDS-II China database using a REDS-II China study ID. Although a link between the REDS-II Study ID and a donor's personal identifying information (name, citizen ID, contact information etc.) is maintained at the blood center, this link is not available to and can not be accessed by the REDS-II China data center.

Note:

1, This study relies on the collaboration of Chinese blood centers and the local C-CDC offices. Standardized study procedures will be followed by all participating blood centers and local C-CDCs. Some blood center and local C-CDC pairs prefer the location of result notification/consultation and risk factor interview to be at the blood center, while other pairs prefer the local C-CDC sites. Some pairs will use trained staff from local-C-CDC, other local C-CDC will train blood center staff for result notification/consultation and risk factor interview.

2, Slight variations exist between the exact procedures used by different local C-CDC laboratories in confirmatory testing of screening reactive HIV samples. These procedures all follow the Chinese Ministry of Health (MOH) established guidelines in confirmatory testing of HIV screen reactive blood donors.

We propose to conduct independent confirmatory HIV testing at the REDS-II China Central Laboratory in IBT, Chengdu. We will compare our results with that of the local C-CDC and notify them of any discrepant findings (with the suggestion that the C-CDC repeat its testing). Only the C-CDC's official results will be used in donor notification and eligibility determination for this study.