Increased Incidence of Infectious Diseases During Prospective Follow-up of Human T-Lymphotrophic Virus Type II– and I–Infected Blood Donors

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Background: To determine whether human T-lymphotropic virus type II (HTLV-II) infection is associated with an increased incidence of bacterial infections, we prospectively observed cohorts of HTLV-I– and HTLV-II–infected and seronegative subjects in 5 US cities.

Methods: Of 1340 present and former blood donors examined at enrollment, 1213 (90.5%) were re-examined after approximately 2 years, including 136 HTLV-I– and 337 HTLV-II–seropositive subjects and 740 demographically stratified HTLV-seronegative subjects. All subjects were seronegative for human immunodeficiency virus. Odds ratios (ORs) for incident disease outcomes were adjusted for covariates, including age, sex, race or ethnicity, education, and, if significantly associated with the outcome, blood center, donation type, income, smoking, alcohol intake, and injected drug use.

Results: Compared with seronegative status, HTLV-II infection was associated with an increased incidence of bronchitis (OR, 1.81; 95% confidence interval [CI], 1.20-2.75), bladder and/or kidney infection (OR, 1.94; 95% CI, 1.26-2.98), oral herpes infection (OR, 9.54; 95% CI, 3.33-27.32), and a borderline increased incidence of pneumonia (OR, 2.09; 95% CI, 0.92-4.76); HTLV-I infection was associated with an increased incidence of bladder and/or kidney infection (OR, 2.79; 95% CI, 1.63-4.79). One incident case of HTLV-I–positive adult T-cell leukemia was observed (incidence, 348 per 100,000 HTLV-I person-years), and 1 case of HTLV-II–positive tropical spastic paraparesis–HTLV-associated myelopathy was diagnosed (incidence, 140 per 100,000 HTLV-II person-years).

Conclusions: These data support an increased incidence of infectious diseases among otherwise healthy HTLV-II– and HTLV-I–infected subjects. They are also consistent with the lymphoproliferative effects of HTLV-I, and with neuropathic effects of HTLV-I and HTLV-II.

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SUBJECTS AND METHODS

SUBJECTS AND STUDY DESIGN

The REDS cohort has been described in detail elsewhere. In brief, HTLV-I– and HTLV-II–seropositive blood donors were recruited from 5 major US blood donation centers (Baltimore, Md; and Washington DC; Detroit, Mich; Oklahoma City, Okla; San Francisco, Calif; and Los Angeles, Calif) participating in the REDS and 6 smaller blood banks in the San Francisco and Los Angeles areas. To allow for attrition during the course of the study, approximately twice as many HTLV-seronegative blood donors were selected within strata defined by age, sex, race or ethnicity, type of donation (homologous, autologous, or directed), and center of the seropositive subjects.

From November 1990 to February 1993, 154 HTLV-I– and 387 HTLV-II–infected and 790 HTLV-seronegative subjects enrolled in the study. Demographic characteristics of enrolled vs nonenrolled donors were similar in all 3 groups. At enrollment and first follow-up visit, all subjects underwent a structured interview (copies available from the authors on request) to ascertain symptoms and diagnoses and a screening physical examination, both by trained study nurses. A proportion of subjects with interview responses fitting predetermined criteria for possible HTLV-related conditions also underwent examinations by study physicians. Interviews and examinations were not performed blinded to HTLV status, because the subjects were aware of their HTLV status, and counseling in the prevention of secondary transmission was also performed according to guidelines for seropositive subjects from the Centers for Disease Control and Prevention. However, interviews and examinations were standardized across all sites, and a central panel of physicians performed blinded reviews of the data to ensure that all the subjects fitting predetermined criteria were referred for physician examination. The study protocol was approved by the human subjects committees of the American Red Cross, the Oklahoma Blood Institute, Oklahoma City, and the University of California, San Francisco.

MEDICAL HISTORY AND PHYSICAL EXAMINATION OUTCOMES

For medical history outcomes, we considered only diagnoses that the subject reported as having been made by a health care professional and that were reported by at least 15 subjects without regard to HTLV status, except for accidents, injuries, and surgical procedures. For chronic diseases, only new diagnoses reported by subjects without that disease at enrollment into the cohort were considered. For acute conditions such as infections, all episodes of the diagnosis occurring in the interval between enrollment and the first follow-up visit were analyzed, regardless of whether the subject had previously reported the diagnosis. We also evaluated whether neurologic and urologic symptoms present at enrollment had worsened.

STATISTICAL ANALYSIS

We performed logistic regression modeling using commercially available software (Statistical Analysis System PROC LOGISTIC; SAS Institute, Cary, NC) to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Logistic regression was chosen as the primary analysis strategy, because self-reported dates of onset of the medical conditions were judged to be potentially unreliable. Additional analyses using Poisson regression (PROC GENMOD) and survival time regression (PROC LIFEREG) were performed for the bronchitis and bladder or kidney infection variables for which sufficient events were available.

Unadjusted ORs were calculated using separate logistic models for each health outcome, with HTLV status as the only independent variable. Adjusted ORs were then calculated for each outcome using logistic models, all of which contained HTLV status, age, sex, race or ethnicity, and education. Blood center, donation type, income, time from enrollment to follow-up visit, smoking, alcohol consumption, and IDU history were then added to every model using a forward selection process, but each was retained in the model only if it significantly (P<.05) changed the likelihood ratio. Body mass index, determined by dividing weight in kilograms by the square of height in meters, was considered as a potential confounding variable in the models for the following conditions or symptoms: arthritis, muscle spasms, and urinary frequency or urgency. Models for muscle spasms and urinary frequency or urgency were run including and excluding the 6 donors with a diagnosis of TSP-HAM.

RESULTS

STUDY POPULATION

Of the 1340 subjects enrolled in the study, 1213 subjects (90.5%) completed the interview at the second visit, including 136 (88.3%) of 154 subjects seropositive for HTLV-I, 337 (87.1%) of 387 subjects seropositive for HTLV-II, and 740 (92.6%) of 799 subjects seronegative for HTLV. Physical examinations were completed for 134 HTLV-I– and 336 HTLV-II–infected and 719 HTLV-seronegative subjects. All subjects were seronegative for
HIV. A total of 127 subjects did not return for the second visit. Reasons for nonreturn included death (3.1%; 1 seronegative subject due to renal carcinoma, 1 HTLV-I–infected subject due to stroke, 1 HTLV-II–infected subject due to a drug overdose, and 1 HTLV-I–infected subject of unknown cause), illness (2%; all seronegative subjects), mental incompetency (1%), inability to locate (29%), other commitments (14%), and refusal (51%). Subjects who did not return for the second visit were more likely to be seropositive for HTLV-I or HTLV-II, to be black or Hispanic, to be less educated, to be previous IDUs, and to have smoking and alcohol use (all Ps < .05) than subjects who returned.

The median and interquartile range of days elapsed between enrollment and second visit were slightly shorter (P < .05) for seronegative subjects (median, 700 days; range, 652-738 days) than for HTLV-I– (median, 724 days; range, 686-749 days) and HTLV-II–infected subjects (median, 714 days; range, 674-750 days). Demographic and other characteristics of subjects returning for the second visit are shown in Table 1. Because of the stratified design of the study, the HTLV-I– and HTLV-II–infected groups were comparable to the HTLV-seronegative group for age, sex, race or ethnicity, blood center, and donation type at enrollment. Subjects infected with HTLV-I or HTLV-II were more likely to have a lower level of education and to smoke more than HTLV-seronegative subjects (P < .05). Subjects seropositive for HTLV-II were more likely to be heavy drinkers, to have ever been IDUs, and to have lower income than seronegative subjects (P < .05). However, most IDU history was remote, with only 3 HTLV-II–infected subjects reporting being present IDUs among the 76 with lifetime histories. Self-report of IDU status was corroborated by physical examination for signs of recent injection.

### ACUTE INFECTIONS

Table 2 shows the frequency of new, self-reported infectious disease diagnoses in subjects with or without a history of the diagnosis at enrollment. Compared with HTLV-seronegative subjects, HTLV-I–infected subjects were more likely to report bladder or kidney infection (adjusted OR, 2.79; 95% CI, 1.63-4.79). Infection with HTLV-II was associated with an interval diagnosis of bronchitis (adjusted OR, 1.81; 95% CI, 1.20-2.75), bladder or kidney infection (adjusted OR, 1.94; 95% CI, 1.26-2.98), and oral herpes infection (adjusted OR, 9.54; 95% CI, 3.33-27.32). A Kaplan-Meier plot of the incidence of bronchitis and bladder or kidney infection for the 3 subject groups is presented in the Figure. In addition, HTLV-II–infected subjects had an increased odds of pneumonia that was almost significant (adjusted OR, 2.09; 95% CI, 0.92-4.76; P = .08).

Multivariable analysis of the bronchitis and bladder or kidney infection end points using Poisson regression or survival analysis gave similar results to the logistic regression analysis. We also examined whether the observed excesses of these diagnoses were due to new (not mentioned at enrollment) or recurrent (mentioned at enrollment) infections, but no consistent pattern emerged. After exclusion of the 4 present IDUs, we again performed the analysis, but found no change in the adjusted ORs. A lifetime history of being an IDU was associated with bronchitis, but not bladder or kidney infection or oral herpes incidence, in models without HTLV status, leaving open the possibility of co-
founding by IDU history. We therefore attempted to force the lifetime IDU variable as well as an HTLV-IDU interaction term into the models with HTLV status, but neither maneuver changed the association with HTLV status.

INCIDENCE OF CANCER AND CHRONIC DISEASES

For chronic conditions, we only considered the new onset of symptoms or diagnoses in subjects previously free of the complaint or condition. One case of ATL in an HTLV-I–infected subject was diagnosed in 287 HTLV-I–infected person-years (incidence, 348 per 100 000 HTLV-I–positive person-years; 95% CI, 9 × 10−5 to 780 × 10−5) and 1 case of TSP-HAM in an HTLV-II–infected subject was diagnosed in 714 HTLV-II–infected person-years of observation (incidence, 140 per 100 000 person-years; 95% CI, 4 × 10−3 to 780 × 10−3).

The frequencies for other symptoms and diagnoses of HTLV-II infection, all subjects were seronegative about HTLV-related leukemia and neurologic disease, no specific infectious diseases. We did not observe an increased incidence of autoimmune, malignant, or other chronic diseases in the HTLV-I– and HTLV-II–infected subjects. The higher infection rate therefore appears to be a specific finding, and not the result of a generalized reporting bias among subjects aware of their chronic HTLV infection. Although subjects had been counseled about HTLV-related leukemia and neurologic disease, no information on infectious disease risk was given. Stratified enrollment ensured that HTLV-seronegative subjects were generally similar to HTLV-I– and HTLV-II–seropositive subjects with regard to age, sex, race or ethnicity, blood center, and type of blood donation. Small remaining differences in demographics between HTLV-seropositive and -seronegative subjects as well as larger differences in socioeconomic status, IDU history, cigarette smoking, and alcohol consumption were controlled for in the multivariable analyses. Although we cannot completely rule out the possibility that the bronchitis association was confounded by IDU history, the results were consistent whether logistic regression, Poisson regression, or survival analysis was used, and they persisted after various attempts to control for present and lifetime IDU. Finally, and in contrast to several other studies of HTLV-II infection, all subjects were seronegative

We report an increased incidence of common infectious diseases among prospectively observed blood donors who were seropositive for HTLV-I and HTLV-II, supporting our prior hypothesis of a link between HTLV seropositivity and increased susceptibility to infectious disease. This finding is supported by appropriate control for potential confounding variables within the study, consistency with other studies, and the strength of the associations observed.

The finding of increased susceptibility to infection was manifested by an increased frequency of several common infectious diseases. We did not observe an increased incidence of autoimmune, malignant, or other chronic diseases in the HTLV-I– and HTLV-II–infected subjects. The higher infection rate therefore appears to be a specific finding, and not the result of a generalized reporting bias among subjects aware of their chronic HTLV infection. Although subjects had been counseled about HTLV-related leukemia and neurologic disease, no information on infectious disease risk was given. Stratified enrollment ensured that HTLV-seronegative subjects were generally similar to HTLV-I– and HTLV-II–seropositive subjects with regard to age, sex, race or ethnicity, blood center, and type of blood donation. Small remaining differences in demographics between HTLV-seropositive and -seronegative subjects as well as larger differences in socioeconomic status, IDU history, cigarette smoking, and alcohol consumption were controlled for in the multivariable analyses. Although we cannot completely rule out the possibility that the bronchitis association was confounded by IDU history, the results were consistent whether logistic regression, Poisson regression, or survival analysis was used, and they persisted after various attempts to control for present and lifetime IDU. Finally, and in contrast to several other studies of HTLV-II infection, all subjects were seronegative

**Table 2. Incidence of Infectious Disease Diagnoses and Chronic Conditions and Symptoms in Subjects Without the Condition at Enrollment**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HTLV-I–Seropositive Subjects (n = 136)</th>
<th>HTLV-II–Seropositive Subjects (n = 337)</th>
<th>HTLV-Seronegative Subjects, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of Cases</td>
<td>Unadjusted OR (95% CI)</td>
<td>Adjusted OR† (95% CI)</td>
</tr>
<tr>
<td><strong>Infectious Diseases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus infection</td>
<td>2 (1.5)</td>
<td>0.49 (0.11-2.10)</td>
<td>0.55 (0.12-2.46)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12 (8.8)</td>
<td>1.00 (0.53-1.92)</td>
<td>1.16 (0.60-2.25)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (2.9)</td>
<td>1.57 (0.51-4.85)</td>
<td>1.38 (0.44-4.37)</td>
</tr>
<tr>
<td>Bladder or kidney infection</td>
<td>24 (17.6)</td>
<td>2.32 (1.50-4.22)</td>
<td>2.79 (1.63-4.79)</td>
</tr>
<tr>
<td>Yeast infection (women)§</td>
<td>11 (11.3)</td>
<td>0.74 (0.38-1.45)</td>
<td>0.84 (0.41-1.71)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>2 (1.5)</td>
<td>2.19 (0.42-11.43)</td>
<td>2.72 (0.51-14.37)</td>
</tr>
<tr>
<td><strong>Chronic Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed cancer</td>
<td>3 (2.2)</td>
<td>1.48 (0.41-5.36)</td>
<td>1.57 (0.39-6.26)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (4.9)</td>
<td>1.89 (0.68-5.27)</td>
<td>1.66 (0.59-4.80)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>5 (5.0)</td>
<td>1.47 (0.54-4.00)</td>
<td>1.34 (0.46-3.88)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>4 (3.2)</td>
<td>1.63 (0.53-5.03)</td>
<td>1.34 (0.42-4.28)</td>
</tr>
<tr>
<td>Urinary frequency or urgency</td>
<td>8 (8.1)</td>
<td>1.15 (0.52-2.50)</td>
<td>0.97 (0.42-2.23)</td>
</tr>
</tbody>
</table>

*HTLV indicates human T-lymphotropic virus; OR, odds ratio; CI, confidence interval.
†Adjusted models contained the following variables: for sinus infection and bronchitis: age, sex, race, education, and center; for pneumonia, bladder or kidney infection, and herpes: age, sex, race, and education; for yeast infection: age, race, education, center, and smoking (pack-years); for cancer: age, sex, race, education, and center (injected drug use could not be tested due to low numbers); for hypertension and muscle spasms: age, sex, race, and education; for arthritis: age, sex, race, education, donation type, and body mass index; and for urinary frequency or urgency: age, sex, race, education, and smoking (pack-years).
‡P < .05 compared with HTLV-seronegative subjects.
§Applicable to women only. For HTLV-I–seropositive women, n = 97; for HTLV-II–seropositive women, n = 255; and for HTLV-seronegative women, n = 501.
||The n for each of these diagnoses differs because subjects with the diagnosis at baseline were excluded.
for HIV and few were present IDUs at enrollment due to blood donor deferral criteria.

These results are consistent with other reports of HTLV-I and increased susceptibility to infectious diseases.28 Although HTLV-I infection does not appear to be associated with a higher prevalence of Strongyloides stercoralis infection as detected by results of stool examination or serologic testing.29,30 HTLV-I–infected persons, and particularly those with ATL, are more susceptible to disseminated Strongyloides infection.15,16 In Jamaica, a syndrome of infectious dermatitis, characterized by eczematous lesions superinfected with Staphylococcus and Streptococcus bacteria, has been associated with HTLV-I infection in children.31 However, the condition has not been observed in Japanese HTLV-I–endemic areas, suggesting that lower socioeconomic status may be a cofactor. Infection with HTLV-I has also been linked with diminished, delayed hypersensitivity reactions to purified protein derivative testing for tuberculosis infection among middle-aged to older Japanese,32,33 and there is inconclusive evidence of an increased susceptibility to leprosy.28

There has been less research into the immunologic effects of HTLV-II infection, but a few studies have also suggested a predisposition to bacterial infection. An early study found higher HTLV-II seroprevalence among IDUs with previous skin abscess compared with those without abscess,20 and 2 cases of severe dermatitis with dermatopathic lymphadenopathy among HIV- and HTLV-II–coinfected IDUs have been reported.32 A study among Navajo Indians in New Mexico reported cases of pneumonia and tuberculosis among subjects who were seropositive for HTLV-II, although the prevalence of these conditions among all subjects was not known.8 A cross-sectional study of the medical records of HTLV-II–seropositive and –seronegative control outpatients in San Francisco found that HTLV-II–seropositive IDUs were significantly more likely to have previous diagnoses of pneumonia, abscess, and lymphadenopathy, whereas HTLV-II–seronegative IDUs had only slightly increased odds of these conditions, both compared with HTLV-II–seronegative non-IDUs.21 Finally, cross-sectional data from the enrollment visit of our cohort study indicated that HTLV-II infection was significantly associated with a history of pneumonia (OR, 2.6), minor fungal infection (OR, 2.9), and bladder or kidney infection (OR, 1.6) within the past 5 years, and with a lifetime history of tuberculosis (OR, 3.9).22 Thus, our findings are consistent with previous reports of increased susceptibility to infectious disease among HTLV-II–seropositive subjects.

There are little data on possible biological mechanisms for an increased susceptibility to infections among HTLV-II– and HTLV-I–seropositive subjects. Whereas HTLV-I predominantly infects CD4+ lymphocytes in vivo, HTLV-II has broader tropism for CD8+ and CD4+ lymphocytes as well as macrophages, as determined using semi-quantitative polymerase chain reaction performed on limiting dilutions of sorted cells from infected individuals.33 Humans infected with HTLV-I and HTLV-II also have elevated levels of immunoglobulin compared with seronegative subjects, due to nonspecific activation of B lymphocytes.34 On the other hand, specific B-lymphocyte proliferation in response to pokeweed mitogen is decreased in HTLV-seropositive subjects,35,36 perhaps due to factors secreted by HTLV-infected cells.7 Additional in vitro and in vivo studies of HTLV-I and HTLV-II effect on B-lymphocyte and macrophage function will be needed to define the immunopathogenic mechanisms underlying the infections we observed. The contribution of subclinical neurologic disease to the increased incidence of urinary tract infections must also be considered. Since the HTLV-II–infected group manifested a higher incidence of urinary frequency and urgency (Table 2) as well as a few cases of overt TSP-HAM at baseline22 and the first follow-up visit, it is conceivable that neurogenic changes in bladder function contributed to the higher incidence of urinary tract infection.

We observed 1 case of ATL in an HTLV-I–seropositive subject, for an incidence of 348 per 100 000 HTLV-I–positive person-years, with a wide 95% CI that was not inconsistent with other published estimates of 205 and 577,28 63 and 56,39 and 55 and 14540 for females and males, respectively, and of 60 for both sexes41 (all per 100 000 person-years). We did not replicate the excess incidence of nonhematological malignant neoplasms in HTLV-I–seropositive subjects reported by Muel ler et al.42 However, in the relatively brief follow-up of our cohort, we have accumulated only 20 cases of can-
cancer, with few cases of the potentially virus-related malignant neoplasms for which we found the strongest association. Finally, 1 new case of TSP-HAM was diagnosed in an HTLV-II–infected subject, for an incidence of 140 per 100,000 HTLV-II–positive person-years, much higher than the incidence of 3.1 per 100,000 HTLV-I–positive person-years for HTLV-I–associated TSP-HAM reported by the 1 other study of TSP-HAM incidence in endemic Japan. However, the 95% CIs on our estimate are wide, and the methods were different from the passive nationwide surveillance used by the Japanese study.

Our study has some potential shortcomings. First, the results may not be applicable to all HTLV-I– and HTLV-II–seropositive subjects, because blood donors are not characteristic of the general population. Furthermore, the use of seronegative blood donors as a comparison group may also have introduced a bias due to a healthy donor effect. However, since HTLV-seropositive subjects were enrolled when trying to give blood, we saw no alternative but to enroll HTLV-seronegative subjects from the same sampling frame. Because we enrolled only about half of all eligible HTLV-seropositive blood donors, and because there was a slight difference in return rates between HTLV-I– or HTLV-II–seropositive and –seronegative subjects, bias could have been introduced by the preferential enrollment oficker or healthier subjects or by a higher nonreturn rate in sicker subjects. We cannot estimate the magnitude of any initial self-selection beyond noting that the demographic characteristics of enrolled vs nonenrolled subjects were comparable. The magnitude of bias due to dropout from the study is likely to be small, since return rates were excellent in both seropositive subjects and controls, and general health status at enrollment did not differ between the 127 subjects subsequently unavailable for follow-up and those remaining in the cohort. Finally, neither the subjects themselves nor the nurse-interviewers were blinded to the HTLV status of the subjects, which could have led to a greater recall of health problems among seropositive subjects concerned about their HTLV infection. We cannot discount the possibility that recall bias may have influenced our findings, but the fact that we analyzed only diagnoses reported as having been made by health care providers, and the concentration of findings among infectious disease vs immunologic or chronic diseases, are evidence against generalized overreporting.

We reported prospective data consistent with a higher incidence of common infections among HTLV-I– and especially HTLV-II–seropositive blood donors. We have also observed lymphadenopathy and a single case of ATL among HTLV-I–infected subjects, and symptoms and signs consistent with subclinical or incipient neurologic disease among HTLV-I– and HTLV-II–seropositive subjects. Although the infectious disease findings are supported by previous cross-sectional studies, additional epidemiological studies, as well as in vitro investigations of HTLV-I and HTLV-II immunologic effects, are needed. If confirmed, these immunologic findings would be of importance in populations with high HTLV-II prevalence such as Amerindians and IDUs and in HTLV-I endemic areas such as the Caribbean basin, Japan, and Africa.

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REFERENCES