Human T-lymphotropic virus types I and II (HTLV-I and -II) cause myelopathy; HTLV-I, but not HTLV-II, causes adult T-cell leukemia. Whether HTLV-II is associated with other diseases is unknown. Using survival analysis, we studied medical history data from a prospective cohort of HTLV-I– and HTLV-II–infected and –uninfected blood donors, all HIV seronegative. A total of 152 HTLV-I, 387 HTLV-II, and 799 uninfected donors were enrolled and followed for a median of 4.4, 4.3, and 4.4 years, respectively. HTLV-II participants had significantly increased incidences of acute bronchitis (incidence ratio [IR] = 1.68), bladder or kidney infection (IR = 1.55), arthritis (IR = 2.66), and asthma (IR = 3.28), and a borderline increase in pneumonia (IR = 1.82, 95% confidence interval [CI] 0.98 to 3.38). HTLV-I participants had significantly increased incidences of bladder or kidney infection (IR = 1.82), and arthritis (IR = 2.84). We conclude that HTLV-II infection may inhibit immunologic responses to respiratory infections and that both HTLV-I and -II may induce inflammatory or autoimmune reactions.

Human T-lymphotropic virus types I and II (HTLV-I and -II) are presumed to have derived from primate T-lymphotropic viruses with which they share significant nucleotide sequence homology (1). They are transmitted by sexual intercourse; by parenteral modes such as unscreened blood or shared injection equipment; and from mother to child, predominantly by breast feeding (2–4). HTLV-I has been causally associated with adult T-cell leukemia and HTLV-associated myelopathy. HTLV-II has also been associated with HTLV-associated myelopathy, but not with leukemia (5).

Other possible health outcomes of chronic HTLV-I and -II infection have not yet been adequately investigated. Patients with adult T-cell leukemia may develop opportunistic infections such as Pneumocystis carinii pneumonia (6) or Strongyloides superinfection (7), but clinical immunodeficiency does not appear to develop in most persons with chronic HTLV-I or -II infection. On the contrary, syndromes suggestive of increased immunologic response such as uveitis (8), pneumonitis (9,10), and rarely, cases of lymphocytic arthritis (11,12) have been reported, although only uveitis has been epidemiologically associated with HTLV-I (8). Investigators in Japan have linked HTLV-I to a higher occurrence of various medical conditions (13) and virus-associated malignancies (14). Other investigators have reported an association between HTLV-II and pneumonia among injection drug users (15).

Case series and cross-sectional studies of HTLV-I and -II disease outcomes are vulnerable to potential bias and confounding. We have prospectively followed a large cohort of former blood donors with well-documented HTLV-I and -II infection at enrollment, and a similar group of uninfected donors, all of whom are HIV seronegative. We report on the occurrence of various disease outcomes in this cohort after a median follow-up of 4.3 years.

Methods

Study Design and Participants

This study is a prospective, multicenter cohort of persons with HTLV-I and -II infections, which were detected at the time of attempted blood donation at five U.S. blood centers and comparable HTLV–seronegative donors.
Details of the cohort enrollment and follow-up procedures have been published previously (16,17). The study protocol was approved by the UCSF Committee on Human Research and by IRB at other participating institutions.

We determined HTLV serostatus by obtaining enzyme immunoassay test results followed by confirmatory Western blot. A central laboratory performed HTLV-I versus -II typing with a type-specific serologic assay, polymerase chain reaction (PCR), or both, as previously described (18). Unequivocal results from the type-specific serologic assay correlated well with those from the polymerase chain reaction assay. All participants were seronegative for HIV when baseline test were performed. For most participants, hepatitis C virus antibody status was not available at the time of enrollment.

Disease Endpoints

Each visit with a study nurse consisted of an interviewer-administered health history questionnaire and phlebotomy of blood for complete blood count and other studies. Selected diagnoses (cancer, neurologic and autoimmune conditions) reported on the questionnaire triggered requests for confirmatory medical records. We included nine conditions or diseases (pneumonia, acute bronchitis, bladder or kidney infection, arthritis, hypertension, asthma, cancer, diabetes, and thyroid disease) and eight symptoms (trouble walking, climbing, or rising from chair; incontinence; pre- or post-void urgency; lymphadenopathy; night sweats; weight loss; foot paresthesias; and impotence [males]) in the data analysis.

Statistical Analysis

We used the Kaplan-Meier product limit method to calculate the unadjusted probability of disease-free survival during the study period for each disease outcome by HTLV status. Survival time was defined as the number of days from the baseline visit until the date that an adverse health outcome was first diagnosed or the end of observation. We performed the log-rank test to assess the differences in disease-free survival time (days) between HTLV-seronegative participants and HTLV-I– or HTLV-II–infected participants, respectively.

To adjust for possible confounding factors, we performed multivariable analysis with HTLV status as an independent variable, survival time as a dependent variable, and possible confounding factors as covariates. In constructing the survival analysis models, we considered a number of covariates, which are described as follows: demographic variables (forced into all models), education, smoking history (pack-years, forced into the models for bronchitis and pneumonia), alcohol consumption, blood center, community versus autologous donation type, injection drug use (except in models for arthritis, hypertension, cancer, neurologic and urologic symptoms), parity (in models for urinary symptoms, bladder and kidney infections, and in females only), and number of sex partners (in model for bladder and kidney infections only). Using a backward selection process, all these covariates were added to the initial model, but only covariates with significant independent associations themselves (p < 0.05), or which substantively modified HTLV incidence ratio, were retained in the final model. We did not include interaction terms because similar analyses of data from prior cohort visits had indicated the absence of significant interaction.

To examine the differences in the cumulative number of episodes of pneumonia, bronchitis, and bladder or kidney infection by HTLV status, we used the negative binomial model, a generalization of the Poisson model, to compute incidence rate ratios (RR) with 95% confidence interval (CI) for each of these outcomes. This model took into account that the recurrence of the disease in a participant may be associated with both the overall disease incidence and its previous occurrence in that participant. We also adjusted for possible confounding factors using the same modeling strategy as for the survival analyses.

For the analysis of symptoms, we calculated unadjusted and adjusted odds ratio (OR) with 95% CI for any occurrence of each symptom by HTLV status by using logistic regression models. To adjust for possible confounding, we added other possible confounding factors as covariates to the models by using the same approach as in the survival analyses. All analyses were performed using Statistical Analysis System (SAS) software (19).

Results

Study Population and Follow-up

During the initial visits in 1990 through 1992, we enrolled 154 HTLV-I, 387 HTLV-II, and 799 HTLV seronegative persons. Two HTLV-I participants were excluded from this analysis because they did not complete the screening physical examination at the initial visit. The baseline characteristics of the study population are given in Table 1. The HTLV groups and seronegative participants were comparable with respect to age, sex, race or ethnicity, blood center visited, and type of blood donation (autologous versus allogeneic), except for slightly higher proportions of blacks among the HTLV-I group and Hispanics among the HTLV-II group. The HTLV-II group had the lowest socioeconomic status, as indicated by educational attainment and income, and the HTLV-I group had intermediate status. Pack-years of cigarette smoking and amount of alcohol intake were higher in the HTLV-II group. Consistent with the recognized epidemiologic risk factors for HTLV-I and -II infection (3,4), the HTLV-I and -II groups had more lifetime sexual partners than seroneg-
Median follow-up did not differ by HTLV status and was through 1996. Median follow-up time was 4.3 years for all participants, and almost 24% of the HTLV-II participants had a lifetime history of injection drug use, although only 4.4% of the HTLV-II group admitted to current injection drug use.

We present data through the third study visit in 1995 (n = 152) and 1996 (n = 387) for HTLV-I and HTLV-II participants (Table 4). Compared to seronegative persons, HTLV-I–infected persons were more likely to have a new diagnosis of bladder or kidney infection (p = 0.009) and arthritis (p = 0.0002) (Figure). Among the HTLV-I–infected persons, two had asthma; an insufficient number to test the difference relative to seronegative persons. The HTLV-I participants showed no statistically significant differences in the incidence of pneumonia, acute bronchitis, and hypertension, cancer, diabetes, and thyroid disease (data not shown).

The number of incident cases diagnosed (limited to one case per person) and the unadjusted and adjusted incidence ratios (IR) for several diagnoses are given in Table 2. Compared with results for seronegative persons, and after multivariable adjustment for relevant confounding variables, HTLV-I infection was associated with bladder or kidney infection (IR 1.82, 95% CI 1.19 to 2.77) and arthritis (IR 2.84, 95% CI 1.51 to 5.33). The risks of developing pneumonia, acute bronchitis, hypertension, and cancer were not significantly increased. Too few cases of asthma (n = 2), thyroid disease (n = 1), and diabetes mellitus (n = 5) existed among the HTLV-I participants to perform survival analysis.

To further investigate the occurrence of infectious diseases, we also analyzed the incidence density of three infectious diseases by HTLV status, whether or not each diagnosis was a first or recurrent case (Table 3). In the incidence density analysis (Table 3), an average of 1.75 cases of bladder or kidney infection occurred per HTLV-I participant over the 4.4-year median follow-up time, compared with 0.63 per seronegative participant over the same period. The unadjusted and adjusted RRs for the HTLV-I group were significantly greater than unity for bladder or kidney infection. HTLV-I participants had increased prevalence rates of neurologic symptoms, self-reported lymphadenopathy, and night sweats, but they reported weight loss no more frequently than did HTLV-seronegative persons (Table 4).

### Table 1. Characteristics of the multicenter, prospective human T-lymphotropic virus (HTLV) cohort study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HTLV-I (n = 152)</th>
<th>HTLV-II (n = 387)</th>
<th>HTLV negative (n = 799)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–29</td>
<td>5 (3)</td>
<td>11 (3)</td>
<td>34 (4)</td>
</tr>
<tr>
<td>30–39</td>
<td>28 (18)</td>
<td>104 (27)</td>
<td>171 (21)</td>
</tr>
<tr>
<td>40–49</td>
<td>55 (36)</td>
<td>168 (43)</td>
<td>288 (36)</td>
</tr>
<tr>
<td>50–59</td>
<td>32 (21)</td>
<td>73 (19)</td>
<td>175 (22)</td>
</tr>
<tr>
<td>≥60</td>
<td>32 (21)</td>
<td>31 (8)</td>
<td>131 (16)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (28)</td>
<td>102 (26)</td>
<td>257 (32)</td>
</tr>
<tr>
<td>Female</td>
<td>109 (72)</td>
<td>285 (74)</td>
<td>542 (68)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>20 (13)</td>
<td>8 (2)</td>
<td>60 (8)</td>
</tr>
<tr>
<td>Black</td>
<td>61 (40)</td>
<td>125 (32)</td>
<td>248 (31)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (6)</td>
<td>104 (27)</td>
<td>150 (19)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>7 (2)</td>
<td>30 (4)</td>
</tr>
<tr>
<td>White</td>
<td>59 (39)</td>
<td>140 (36)</td>
<td>309 (39)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1)</td>
<td>3 (1)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>45 (30)</td>
<td>135 (35)</td>
<td>129 (16)</td>
</tr>
<tr>
<td>Some college</td>
<td>66 (43)</td>
<td>195 (51)</td>
<td>363 (46)</td>
</tr>
<tr>
<td>College</td>
<td>30 (20)</td>
<td>45 (12)</td>
<td>181 (23)</td>
</tr>
<tr>
<td>College (&gt;4 years)</td>
<td>11 (7)</td>
<td>11 (3)</td>
<td>123 (15)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$30,000</td>
<td>46 (30)</td>
<td>144 (38)</td>
<td>167 (21)</td>
</tr>
<tr>
<td>$30,000–$49,999</td>
<td>51 (34)</td>
<td>120 (32)</td>
<td>221 (28)</td>
</tr>
<tr>
<td>≥$50,000</td>
<td>55 (36)</td>
<td>113 (30)</td>
<td>401 (51)</td>
</tr>
<tr>
<td>Center</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>32 (21)</td>
<td>51 (13)</td>
<td>122 (15)</td>
</tr>
<tr>
<td>2</td>
<td>29 (19)</td>
<td>39 (10)</td>
<td>102 (13)</td>
</tr>
<tr>
<td>3</td>
<td>44 (29)</td>
<td>206 (53)</td>
<td>345 (43)</td>
</tr>
<tr>
<td>4</td>
<td>31 (20)</td>
<td>68 (18)</td>
<td>156 (20)</td>
</tr>
<tr>
<td>5</td>
<td>16 (11)</td>
<td>23 (6)</td>
<td>74 (9)</td>
</tr>
<tr>
<td>Blood donor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous</td>
<td>28 (18)</td>
<td>39 (10)</td>
<td>111 (14)</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>124 (82)</td>
<td>348 (90)</td>
<td>688 (86)</td>
</tr>
<tr>
<td>Smoking history (pack/y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>74 (52)</td>
<td>125 (36)</td>
<td>413 (54)</td>
</tr>
<tr>
<td>0–13</td>
<td>24 (17)</td>
<td>117 (33)</td>
<td>184 (24)</td>
</tr>
<tr>
<td>&gt;13</td>
<td>43 (31)</td>
<td>109 (31)</td>
<td>174 (23)</td>
</tr>
<tr>
<td>Alcohol intake (average drinks per wk)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondrinker</td>
<td>19 (13)</td>
<td>20 (6)</td>
<td>70 (9)</td>
</tr>
<tr>
<td>0–1</td>
<td>58 (41)</td>
<td>134 (38)</td>
<td>352 (46)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>64 (45)</td>
<td>200 (57)</td>
<td>339 (45)</td>
</tr>
<tr>
<td>Lifetime sex partners</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>56 (38)</td>
<td>87 (23)</td>
<td>381 (49)</td>
</tr>
<tr>
<td>≥6</td>
<td>92 (62)</td>
<td>292 (77)</td>
<td>403 (51)</td>
</tr>
<tr>
<td>Injection drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>148 (98)</td>
<td>294 (76)</td>
<td>787 (99)</td>
</tr>
<tr>
<td>Ex-injection drug user</td>
<td>2 (1)</td>
<td>75 (19)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Current injection drug user</td>
<td>1 (1)</td>
<td>17 (4)</td>
<td>1 (0)</td>
</tr>
</tbody>
</table>

(a)Missing data (up to 6%, depending upon the variable) were excluded from the calculation of percentages.

### HTLV-I Findings

Compared to seronegative persons, HTLV-I–infected persons were more likely to experience acute bronchitis (p < 0.0001), bladder or kidney infection (p = 0.0008), arthritis (p = 0.0003), and asthma (p = 0.0007); the likelihood of acquiring pneumonia was increased but not significantly (p = 0.08). Differences between the HTLV-II and HTLV-seronegative participants in the incidence of cancer, hyper-
tension, diabetes, or thyroid disease were not statistically significant.

The number of incident cases diagnosed (limited to one case per participant), and the unadjusted and adjusted IRs, for several diagnoses are given in Table 2. Compared with results for seronegative participants, and after adjusting for confounding variables, HTLV-II was associated with acute bronchitis (OR 1.68, 95% CI 1.24 to 2.29), bladder or kidney infection (OR 1.55, 95% CI 1.14 to 2.11), arthritis (OR 2.66, 95% CI 1.58 to 4.45), and asthma (OR 3.28, 95% CI 1.57 to 6.84). The association between HTLV-II infection and pneumonia was of borderline statistical significance (IR 1.82, 95% CI 0.98 to 3.38). IRs for hypertension and cancer were not increased for HTLV-II participants. Too few cases of thyroid disease (n = 7) and diabetes mellitus (n = 7) were found among the HTLV-II participants to perform survival analysis.

In the incidence density analysis of recurrent infections, an average of 0.21 cases of pneumonia, 1.10 cases of acute bronchitis, and 1.25 cases of bladder or kidney infection occurred among HTLV-II participants during their 4.3-year median follow-up time (Table 3). The corresponding incidence densities for the seronegative group were 0.08, 0.59, and 0.63, respectively, over their 4.4 year median follow-up time. Both unadjusted and adjusted RRs, calculated by using negative binomial modeling, were significantly greater than unity for all three diseases (Table 3). Compared with seronegative participants, HTLV-II participants had increased prevalence rates of several neurologic, lymphatic, and constitutional symptoms, but the prevalence of impotence (males) was not significantly increased (Table 4).

Figure. Kaplan-Meier survival curves showing disease-free survival for one noninfectious and three infectious diseases, by human T-lymphotropic virus (HTLV) status, through visits 2 and 3 of prospective observation. HTLV-I–infected (red triangles) and HTLV-II–infected (green squares) participants are compared to HTLV-seronegative participants (blue diamonds), respectively. Panels are as follows: A) pneumonia; B) acute bronchitis; C) bladder or kidney infection; and D) hypertension. The vertical axis scale has been compressed in panel A because of the lower overall incidence of pneumonia.
Study did not find that either HTLV-II or HIV are risk factors for skin and soft tissue abscess among injection drug users (21). LaGrenade et al. have documented an association between HTLV-I infection and *Staphylococcus*- and *Streptococcus*-related infective dermatitis among Jamaican children (22). An independent nested case-control study of pneumonia, abscess, and endocarditis among Baltimore injection drug users found no association between these infections and HTLV-II seropositivity (23). A number of opportunistic co-infections have been reported in conjunction with HTLV-I infection, including Strongyloides hyperinfection (7), *P. carinii* pneumonia (in patients with HTLV-I-related adult T-cell leukemia) (6), and leprosy (24).

The biologic basis for a putative increased susceptibility to certain infections in humans with chronic HTLV-II infection is not well described. In contrast to the predominant CD4+ lymphotropism of HTLV-I, HTLV-II provirus in vivo is integrated at highest levels into CD8+ lymphocytes but may also be demonstrated in CD4+, both CD45RO+ and CD45RO-, and even non-T (CD14, CD16, and CD19) lymphocytes (25). Delayed hypersensitivity response to mumps virus and *Candida* antigens is normal among HTLV-II participants, suggesting intact cell-mediated or T-helper 1-type immunity (26). Although subtle differences may exist, the overall distribution of lymphocyte subsets is not perturbed in persons with HTLV-II (27,28). However, total immunoglobulin G levels are high-

### Table 2. Incidence of medically diagnosed conditions and selected unadjusted and adjusted incidence ratios among human T-lymphotropic virus (HTLV)-I– and HTLV-II–infected participants and HTLV-seronegative participants, visits 2 and 3a

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HTLV-I (N = 152)</th>
<th>HTLV-II (N = 387)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (%)</td>
<td>IRb</td>
</tr>
<tr>
<td></td>
<td>Cases (%)</td>
<td>Adj. RR (95% CI)c</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25 (3)</td>
<td>0.80</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>103 (14)</td>
<td>5.74</td>
</tr>
<tr>
<td>Bladder or kidney infection</td>
<td>105 (14)</td>
<td>1.06</td>
</tr>
<tr>
<td>Arthritis</td>
<td>23 (3)</td>
<td>4.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (3)</td>
<td>1.25</td>
</tr>
<tr>
<td>Asthma</td>
<td>21 (3)</td>
<td>0.64</td>
</tr>
<tr>
<td>Cancer</td>
<td>21 (3)</td>
<td>2.29</td>
</tr>
</tbody>
</table>

aAdjusted for age, gender, race/ethnicity, and history of smoking.

### Table 3. Incidence density (ID) and standard deviation (SD) of medically diagnosed infectious diseases, and selected crude and adjusted rate ratios (RR), among human T-lymphotropic virus (HTLV)-I– and HTLV-II–infected participants and HTLV-seronegative participants, visits 2 and 3a

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HTLV-I (N = 152)</th>
<th>HTLV-II (N = 387)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ID (SD)</td>
<td>RRb</td>
</tr>
<tr>
<td></td>
<td>ID (SD)</td>
<td>Adj. RR (95% CI)c</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.07 (0.37)</td>
<td>1.49</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>0.13 (0.47)</td>
<td>1.38</td>
</tr>
<tr>
<td>Bladder or kidney infection</td>
<td>0.63 (2.04)</td>
<td>3.23</td>
</tr>
</tbody>
</table>

aEnumerated as the mean of the total number of infectious disease diagnoses divided by the number of participants (with or without the infection) in each group at baseline. The period of observation was 4.4 years (HTLV-I), 4.3 years (HTLV-II), and 4.4 years (HTLV-seronegative), and each participant may have multiple diagnoses of each condition.

bAdjusted. Adjusted models included age, gender, race/ethnicity and duration of follow-up for all infections, and injection drug use (for pneumonia), smoking (for acute bronchitis), and community versus autologous blood donation (for bladder/kidney infection).
er in HTLV-II-infected persons (29), in vitro cell proliferation in response to pokeweed mitogen is suppressed in HTLV-II infection (28), and HTLV-II may induce expression of interferon-γ, granulocyte macrophage-colony-stimulating factor, and other cytokines (30,31). Although HTLV-II provirus has also been demonstrated in macrophages (32), whether such infection influences macrophage regulation or function to a clinically notable degree is not known. Finally, lymphocytic pneumonitis has been reported in association with HTLV-I infection (9,10), and clinically diagnosed cases of pneumonia and acute bronchitis in HTLV-II-infected persons could conceivably represent autoimmune rather than infectious disease.

Our finding of an association of both HTLV-II and HTLV-I with bladder or kidney infection is consistent with a previous report of unspecified renal disease in a prospective cohort study of HTLV-I-infected persons in Japan (33). However, such associations must be interpreted cautiously in light of the known association of both retroviruses with HTLV-associated myelopathy (5,34,35). Since urinary frequency and urgency are among the first symptoms of bladder hyperreactivity due to the underlying myelopathy, HTLV-I- or -II-infected persons might seek medical care for these symptoms. Urinary tract infection or kidney disease secondary to unrecognized neurogenic bladder dysfunction might be diagnosed, or they may be treated presumptively for urinary tract infection on the basis of their bladder symptoms. In either case, an increased incidence of diagnosed bladder or kidney infection may not necessarily indicate that HTLV-I or -II infection is the cause of these urinary infections. Finally, although we controlled for the number of sexual partners, residual confounding by sexual activity could have influenced our bladder or kidney infection finding (36).

The increased incidence of arthritis observed for both persons infected with HTLV-I and HTLV-II supports reports of possible autoimmune syndromes with HTLV infection. HTLV-I has been epidemiologically associated with uveitis (8). Several previous reports of HTLV-I in case series of arthritis have been limited by the lack of appropriate controls (11,12). Nonetheless, high numbers of HTLV-I-infected lymphocytes have been demonstrated in synovial fluid from some of these case-patients. Although we obtained medical records to verify arthritis and other diagnoses, the records did not give sufficient information to classify the type of arthritis and diagnostic evaluations were limited in most cases. Although an association between HTLV-I infection and asthma has been reported among Japanese men (13), we are unaware of previous reports of an increased incidence of asthma in association with HTLV-II infection. Also, a few cases of lymphocytic pneumonitis have been reported in patients with HTLV-I infection, particularly those with myelopathy (9,10). We plan a more intensive diagnostic evaluation of the HTLV-II participants in this study with recurrent pneumonia or asthma to explore the possible contribution of undiagnosed lymphocytic pneumonitis to the observed clinical signs and symptoms.

We have previously reported a single case of adult T-cell leukemia which was diagnosed between the first and second visits of the patient in this cohort study (17); no additional cases have been diagnosed to date. That neither HTLV-I nor -II participants had an increased incidence of nonhematologic cancer in our current analysis is potentially reassuring to persons infected with these retroviruses. However, an increased incidence of some cancers, especially those thought to be induced by viruses, has been reported in a Japanese HTLV-I cohort (37). We might not have detected a small increase in IR because of the relatively small number of cases detected during our 4.3-year follow-up period. Alternatively, we might not have had enough HTLV-I or -II participants who were co-infected.
with other oncogenic viruses such as hepatitis C virus to
detect a synergistic effect between HTLV-I or -II and these
viruses (38).

The two- to three-fold higher prevalence of self-report-
ed neurologic symptoms, including trouble walking,
climbing stairs, or rising from a chair, and bladder symp-
toms may represent early spinal cord injury due to HTLV-
I or -II. As follow-up of the cohort continues, we shall be
able to determine whether those reporting such symptoms
in earlier visits have a higher incidence of overt myelopa-
thy than asymptomatic HTLV-infected participants. On the
other hand, the frequency of self-reported lymphadenopa-
thy and night sweats is unlikely to be caused by preclinical
hematologic malignancy, given the rarity of that disorder
in HTLV-I–infected persons and its lack of association
with HTLV-II. These symptoms might be related to known
effects of HTLV-I and -II on lymphocytic proliferation and
cytokine expression, or they might simply reflect reporting
bias.

Strengths of the current study include its controlled,
prospective, cohort design, stringent confirmation of
HTLV-I– and -II–infection status at baseline, and system-
atic ascertainment of disease outcomes. One potential
weakness is that differences in socioeconomic status and
risk behaviors could have confounded disease associations
between HTLV–infected and uninfected previous blood
donors, even though we selected the uninfected partici-
pants in strata defined by the age, sex, race or ethnicity,
center, and blood donation type of the HTLV groups. We
controlled for the socioeconomic and behavioral factors
using multivariate analyses, but residual confounding
could affect the magnitude of the associations we
observed. Second, recall bias may exist in that participants
with HTLV infection might differentially report more diag-
oses because of heightened concern about their own
health. Our questionnaire requested only medically con-
firmed diagnoses, and the absence of associations with
noninfectious disease, such as hypertension, diabetes, and
thyroid disease, suggests that generalized overreporting of
illness was not a problem. Additionally, infectious disease
associations with HTLV have not been widely reported, so
we do not think that recall bias specific to these diagnoses
was a serious concern. Finally, follow-up time to date is
modest for a chronic infection such as HTLV and our find-
ings may change with longer observation.

In conclusion, HTLV-II infection is associated with an
increased incidence of respiratory and urinary tract infec-
tions and asthma, and both HTLV-I and -II are associated
with increased incidence rates of arthritis, compared with
results for seronegative persons. These findings suggest
that chronic infection with HTLV-II may inhibit host
immunologic responses to infection, or more specifically,
to respiratory infections. The arthritis and asthma results,
and possibly the respiratory tract diagnoses, suggest that
other inflammatory or autoimmune reactions may be
induced by HTLV-I or HTLV-II infection. Additional in
vitro and in vivo research on the immunologic conse-
quences of HTLV infection is needed.

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