

Seroincidence of Human T-Lymphotropic Virus Type I Infection and Characterization of Seroconverters in Jamaican Food Handlers

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Summary: In a prospective study of food handlers in Jamaica, we estimated the age- and sex-specific seroincidence of human T-lymphotropic virus type I (HTLV-I) infection. Of 682 sexually active adults (132 males and 550 females) who were initially seronegative, 12 (1 male and 11 females) seroconverted over 8 years of follow-up. The seroincidence was 1.2 per 1,000 person-years for males and 3.2 per 1,000 person-years for females. The age-standardized incidence was 1.8 times higher for females than for males ($P = 0.55$). Within a median of 4 years after seroconversion, the median HTLV-I provirus load was 500 copies/ 10^5 cells, and the median antibody titer was 1:3109. Four of 12 seroconverters developed antibody to the Tax regulatory protein. HTLV-I infection in this population occurred at a rate comparable with that described for a Japanese cohort. Provirus load, titer and appearance of antibody to the Tax regulatory protein were typical of chronic carriers within a few years of seroconversion.

Key Words: HTLV-I, seroincidence, provirus load, antibody titer, anti-Tax, Jamaica

Human T-lymphotropic virus type I (HTLV-I) is a retrovirus associated with adult T-cell leukemia/lymphoma^{1,2} and HTLV-I-associated myelopathy or tropical spastic paraparesis.^{3,4} More recently, HTLV-I has been implicated in other disease entities, including infective dermatitis in children⁵ and uveitis.⁶ HTLV-I carriers were

reported to have excess mortality attributed to liver cancer and heart disease, such that HTLV-I infection may also affect diseases not known to be related to this virus.⁷

HTLV-I infection has a peculiar geographic distribution: the virus is endemic in pockets of southern Japan, the Caribbean, parts of Africa, the Middle East, South America, and the Pacific Melanesian Islands.⁸ The seroprevalence varies widely by geographic areas, with a reported prevalence of 3%–5% in Jamaica. In all areas of endemicity, the prevalence of HTLV-I infection increases with age and is universally higher among females than males. The probability of infection by transfusion of contaminated blood products has been reported to be the highest,^{9,10} but sexual transmission is thought to be the most common vehicle of infection in adult life. Trans-

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mission of HTLV-I also occurs during infancy, primarily through breast-feeding. Although most cases of adult T-cell leukemia/lymphoma are thought to occur after decades of latency in persons who were infected perinatally, HTLV-I-associated myelopathy or tropical spastic paraparesis and other immunologic conditions may develop with a shorter latency in persons who become infected later in life.⁸

Virologic markers are important predictors of the outcome of HTLV-I infection. Both the amount of integrated HTLV-I genome in host cells, known as "provirus load," and antibody titers are higher in persons with HTLV-I-associated diseases than in asymptomatic carriers.¹¹⁻¹⁴ These measures were higher in carriers who subsequently developed disease than in those who did not.^{15,16} Many carriers also develop antibody to the Tax regulatory protein (anti-Tax), which is expressed when viral replication is active.¹⁷ Because Tax protein promotes not only transcription of HTLV-I but also that of other host genes, it has been thought to play a major role in HTLV-I pathogenesis.^{18,19}

Few studies have examined the changes of HTLV-I viral markers in persons who recently have become infected. In addition, directly observed seroincidence of HTLV-I infection among adults in the Caribbean has not been reported. In the present study, we estimated the overall and sex- and age-specific HTLV-I seroincidence among participants of the Food Handlers Study cohort in Jamaica. In addition, we characterized the initial viral markers of the seroincident cases and described early immune responses to HTLV-I infection.

METHODS

Study Population

The Food Handlers Study was a series of epidemiologic investigations of HTLV-I infection in Jamaica. Between March 1985 and May 1986, 13,260 food licensure applicants ranging in age from 11 to 83 years who were from all Jamaican parishes were enrolled in a cross-sectional study to estimate the seroprevalence of HTLV-I.^{20,21} Between January 1987 and April 1988, 201 HTLV-I-seropositive subjects together with 225 age- and sex-matched seronegative controls from the initial cohort enrollees who were from Kingston and Clarendon parishes were enrolled in a nested case-control study to investigate risk factors for HTLV-I transmission and clinical outcomes. Blood samples and questionnaire data containing information on sexual behaviors were collected from these subjects.^{22,23} Between 1992 and 1994, a total of 666 HTLV-I-seropositive and -seronegative subjects from the initial cohort, mostly from Kingston and Clarendon parishes, were recalled for evaluation and collection of blood samples. The institutional review boards of the National Cancer Institute and the University of the West Indies approved the study protocols. Informed consent was obtained from all participants at each study visit. The present prospective cohort included 682 subjects who were HTLV-I-seronegative at the initial

screening in 1985-1986 and had specimens available from at least one follow-up screening visit.

HTLV-I Serology

As previously reported, serum samples from study subjects were tested for HTLV-I by enzyme-linked immunosorbent assay (Biotech Research Laboratories, Rockville, MD; Dupont, Wilmington, DE; Genetic Systems HTLV, Bio-Rad Laboratories, Redmond, Washington). Subjects who were seropositive for HTLV-I by enzyme-linked immunosorbent assay had confirmation by reactivity to both *gag* and *env* proteins, using one of two Western blot assays (Cambridge Biotech, Rockville, MD; HTLV Blot 2.4, Genelabs Diagnostics, Singapore). The former Western blot assay required detection of p19, p24, and either p21e or gp46 for HTLV infection (type unknown). Reactivity to p19 greater than or equal to that to p24 defined HTLV-I positivity, a scheme that has been shown to accurately distinguish between HTLV-I and HTLV-II.²⁴ For the latter assay, HTLV-I infection was confirmed by detection of p19, p21e, and rgp-46I bands.

HTLV-I Viral Markers

For confirmed HTLV-I-seropositive subjects, antibody titers in serum were determined by enzyme-linked immunosorbent assay (Cambridge Biotech; Organon Teknika Corporation, Durham, NC) on serial 4-fold dilutions. Anti-Tax was detected by enzyme-linked immunosorbent assay.²⁵ The proviral DNA level in peripheral blood mononuclear cells was quantified by a real-time automated polymerase chain reaction method as previously described.²⁶ Briefly, DNA was extracted (Gentra Systems, Inc., Minneapolis, MN) and amplified for 45 cycles with the AmpliTaq Gold polymerase and TaqMan PCR Reagent (P/N N808-02391, PE Applied Biosystems, Foster City, CA). The provirus load was normalized for the DNA input by determining the number of human endogenous retrovirus (ERV-3) copies. The sensitivity of the assay allowed detection of ≥ 10 proviral copies/ 10^5 peripheral blood mononuclear cells.

Statistical Analysis

Person-years of observation for subjects who remained seronegative extended from the first known seronegative dates to the last known seronegative dates. For subjects who seroconverted, the date of seroconversion was assigned as the midpoint between the last known seronegative dates and the first known seropositive dates. We calculated the expected number of seroconversions by multiplying the person-years of observation in each 10-year age group accumulated by the prospectively followed up subjects by the change in seroprevalence from the corresponding 10-year age group to the next age group, based on the seroprevalence in the 1985-1986 study cohort.²⁰

Seroincidence is presented per 1,000 person-years, and exact 95% confidence intervals (CIs) were calculated assuming a Poisson distribution for the occurrence of seroconversion.²⁷ The female-to-male ratio of seroconversion rates was calculated using age-standardized rates, which were derived using the age distribution of the entire 1985-1986 cohort as the standard. Statistical tests for the rate ratios were based on exact binomial tests.²⁸ The Spearman rank correlation coefficient was used to estimate the association between HTLV-I proviral load and antibody titer.

RESULTS

The prospective cohort included 682 HTLV-I-seronegative participants (132 males and 550 females) who attended the baseline screening in 1985–1986 and had at least 1 additional visit (mean follow-up, 6.3 years). One hundred three (15.1%) of these 682 participants had 2 follow-up visits in 1987–1988 and 1992–1994. The other 579 participants had only 1 follow-up visit: 124 (18.2%) in 1987–1988 and 455 (66.7%) in 1992–1994. The mean age of these 682 study participants at the baseline visit was 32 years. All but 2 subjects were residents of the metropolitan area of Kingston and Clarendon.

A total of 12 subjects, including 1 (0.8%) of 132 males and 11 (2.0%) of 550 females, seroconverted (Table 1). The age distribution of those who seroconverted closely matched that of the entire prospective cohort of 682 subjects. All 4 seroconverters assessed in 1987–1988, a time at which risk factor data for HTLV-I infection were collected, were sexually active by their mid to late teenage years. None reported a history of injection drug use. One subject had received a blood transfusion shortly before the 1987–1988 screening visit.

Provirus loads in 6 seroconverters who had DNA samples available for testing were between 60 and 2750 copies/ 10^5 lymphocytes, with most measurements determined 4 to 5 years after seroconversion. One subject (subject 3 in Table 1) had an additional provirus load measurement 7 years later. Excluding this observation, the median provirus load for these 6 seroconverters was 500 copies/ 10^5 lymphocytes. Antibody titers in 12 seroconverters ranged from 1:548 to 1:26,478, with a median of 1:3109 based on the first antibody titer measurement

for each participant. Proviral DNA levels and antibody titers measured simultaneously in 6 subjects were strongly positively correlated (Spearman rank correlation coefficient = 0.89; $P = 0.019$). Anti-Tax was not detectable in 3 subjects followed up only through 1987–1988, but it was detected in 4 (44.4%) of 9 subjects followed up through 1992–1994 (Table 1). Subject 3 became positive for anti-Tax at the second of the two follow-up screening visits. The provirus load in this subject did not change appreciably over a 7-year period, but the antibody titer increased 2.8-fold.

The overall HTLV-I seroincidence among participants followed up through 1994 was 2.8 per 1,000 person-years (95% CI, 1.1–4.9). Although the rate was higher among females (3.2 per 1,000 person-years; 95% CI, 1.6–5.7) than among males (1.2 per 1,000 person-years; 95% CI, 0.04–6.7; Table 2), the age-standardized rates were not significantly different (rate ratio = 1.8; $P = 0.55$). The sex-combined seroincidence was similar (~4.5 per 1,000 person-years) among those subjects aged 30–39 and 40–49 years. The seroincidence among the 124 participants who were followed up through 1987–1988 was 12.3 per 1,000 person-years (3 per 244 person-years), whereas the rate was 2.2 per 1,000 person-years (9 per 4,052 person-years) for 558 participants who were followed up from 1985–1986 through 1992–1994 ($P = 0.06$).

Our calculation of the expected number of seroconversions in females and males based on age- and sex-specific seroprevalence of HTLV-I in the entire cohort indicated that 11.6 females would have seroconverted, most between the ages of 20 and 39 years (Table 2); we observed 11 seroconversions in females, with 9 occurring in the age group of 20–39 years. As would be ex-

TABLE 1. Characteristics of 12 seroconverters in the food handlers study (1985–1994)

Subject	Sex	Age at SC	Risk factor(s)	Year of follow-up	Year(s) since SC	Antibody titer	Proviral load ^a	Anti-Tax
1	F	34	Sexual activity starting at age 18	1987	1.0	1938	N/A	Negative
2	F	31	Sexual activity starting at age 17; blood transfusion at age 30	1987	1.0	641	96	Negative
3	F	30	Sexual activity starting at age 14	1987	1.1	4898	1714	Negative
				1993	7.6	13,528	2125	Positive
4	F	43	Sexual activity starting at age 18	1987	0.9	19,032	N/A	Negative
5	F	39	N/A	1994	4.5	18,141	2750	Negative
6	F	23	N/A	1994	4.5	3083	644	Positive
7	F	46	N/A	1994	4.5	1170	355	Negative
8	F	32	N/A	1994	4.4	8147	N/A	Positive
9	F	28	N/A	1992	3.6	26,478	N/A	Positive
10	F	32	N/A	1992	3.6	3134	N/A	Negative
11	F	29	N/A	1994	4.4	548	N/A	Negative
12	M	45	N/A	1993	4.1	1027	60	Negative

SC, seroconversion; N/A, not available.

^a Provirus loads are ERV-3 normalized and expressed in copy numbers per 10^5 peripheral blood mononuclear cells.

TABLE 2. Age- and sex-specific HTLV-I seroincidence in the food handlers study (1985-1994)

Age group (y)	Females (n = 550)					Males (n = 132)					Total (n = 682)				
	Prev (%)	Exp	Obs	PY	Rate ^a	Prev (%)	Exp	Obs	PY	Rate ^a	Prev (%)	Exp	Obs	PY	Rate ^a
10-19	1.9	0.2	0	88	0.0	1.7	0.0	0	10	0.0	1.8	0.2	0	98	0.0
20-29	4.0	6.0	3	1256	2.4	2.3	0.9	0	357	0.0	3.4	6.9	3	1613	1.9
30-39	8.8	2.6	6	1066	5.6	4.8	0.0	0	271	0.0	7.7	2.1	6	1336	4.5
40-49	11.2	2.2	2	567	3.5	4.3	0.1	1	93	10.8	9.3	1.8	3	660	4.6
50-59	15.1	0.2	0	271	0.0	5.7	0.1	0	43	0.0	12.1	0.1	0	314	0.0
60-69	15.7	0.3	0	177	0.0	7.8	0.1	0	51	0.0	12.5	0.1	0	227	0.0
70 or older	17.4	0.2	0	38	0.0	9.1	0.0	0	9	0.0	13.0	0.0	0	47	0.0
Total	7.3	11.6	11	3463	3.2	3.6	1.2	1	834	1.2	6.1	11.0	12	4296	2.8

Prev, prevalence from 1985-1986 cohort; Exp, expected number of seroconversions; Obs, observed number of seroconversions; PY, person-years. Expected number was calculated by multiplication of total person-years in each 10-year age category by the annual percentage change in prevalence between two adjacent 10-year age categories. The annual percentage change in prevalence among the 70 years or older age group was assumed to be the same as that among the 60- to 69-year age group. Changes were set to 0 when there was a decrease in seroprevalence from one age group to the next.

^a Seroincidence, per 1,000 person-years.

pected, 1 male seroconverted, although this occurred at an older age (about 45 years) than predicted (20-29 years).

DISCUSSION

This investigation estimated the seroincidence of HTLV-I infection among adults in Jamaica, where sexual transmission is likely the major route of viral transmission.²² Although the age of subjects at the baseline screening ranged from 15 to 74 years, all 12 seroconversions occurred in persons in their 20s to 40s, when sexual activity is at its peak.²⁹ In addition, 4 subjects with detailed information on HTLV-I risk factors were confirmed as sexually active, with only 1 person also having a history of blood transfusion (Table 1).

The overall seroincidence of HTLV-I infection among this Jamaican cohort, 2.8 per 1,000 person-years, was similar to that found in a population-based study in Japan.³⁰ In 600 adults 40 years of age or older who lived on 2 small islands in southwest Japan where HTLV-I infection is endemic, the seroincidence of HTLV-I infection based on 8 seroconversions (3 men and 5 women) was ~2.0 per 1,000 person-years. Two of the 8 seroconverters in the Japanese study had a history of blood transfusion. Similar HTLV-I seroincidence in the two geographic areas is of interest given substantial differences in overall seroprevalence of infection, age distribution, and risks of HTLV-I-associated diseases in the two populations. Notably, infection acquired in adulthood as compared with that in infancy has been associated with a higher risk of HTLV-I-associated myelopathy or tropical spastic paraparesis, which has a much higher incidence in Jamaica than in Japan.

We found that the risk of acquiring infection was 1.8 times higher in females than in males. Although the difference was not statistically significant, our finding parallels the observation of a higher prevalence of HTLV-I infection among women than among men in this cohort.²⁰ Because risks of mother-to-child and parenteral transmission of HTLV-I in Jamaica do not differ by gender,^{10,31} sexual transmission is likely to explain the higher HTLV-I seroprevalence among females than among males. Evidence supporting the differential risks of HTLV-I transmission in males and females via sexual contact is supported by findings of population-based studies in Japan. For married Japanese couples in whom spouses were HTLV-I-serodiscordant, it was estimated that over 10 years 60% of the wives but only 1% of the husbands would seroconvert.³² In another prospective cohort study of HTLV-I-serodiscordant couples in Japan, the wives were about four times more likely to seroconvert than were the husbands.³³

Studies from Japan have reported that seroprevalence increases with age, most notably in women older than 50 years.^{32,34,35} The absence of seroconversions in persons older than 50 years in our cohort may be, in part, due to the limited number of older participants. However, increases in seroprevalence in our cohort were more prominent among 20- to 49-year age groups, particularly females (Table 2), suggesting that the expected seroincidence would be higher among those younger than 50 years in this Jamaican population. The observed numbers of seroconversions in men and women were close to the expected numbers. Therefore, bias due to a birth cohort effect is unlikely to be substantial.

When seroincidence was calculated separately for subjects followed up through 1987-1988 and those followed up through 1992-1994, the rate in the former period was

higher than that in the latter period (12.3 versus 2.2 per 1,000 person-years; $P = 0.06$). Although this observation may reflect a secular trend of aging of the cohort with behavior change, it might also reflect a greater attrition of study participants with an increased risk of HTLV-I infection.

Levels of viral markers in the present study exhibited large variations from subject to subject. Broad ranges of HTLV-I proviral load and antibody titer were also noted for 15 seroconverters in a Japanese study,³⁶ with no significant changes over 2–10 years. In a prospective study of transfusion recipients in Jamaica, proviral DNA levels in 10 seroconverters ranged nearly 100-fold between individuals after an average of 14 months after transfusion.¹⁴ As the HTLV-I genome is highly conserved with no clearly defined differences in pathogenesis, these findings raise the possibility that host factors are important determinants of immune response and viral replication.

As previously shown for chronic carriers, we found a strong positive correlation between proviral DNA level and antibody titer ($r = 0.89$; $P = 0.019$) within a few years of seroconversion. Similarly high positive correlations ($r \geq 0.8$) between these two markers were reported for transfusion recipients 1 year after infection.¹⁴ For HTLV-I carriers who have been infected much longer, the reported correlation appears to be somewhat weaker ($r = 0.4$ – 0.6)³¹ (Maloney et al., unpublished data).

In the present study, the prevalence of anti-Tax was nil among 4 seroconverters during the first year after seroconversion and 44% among those followed up longer. Anti-Tax was present in 3 (60%) of 5 transfusion recipients within 1 year after infection.³⁷ The prevalence of anti-Tax also was ~60% among asymptomatic HTLV-I carriers in Japan.^{38,39} Subsequent appearance of anti-Tax in 1 person with multiple measurements is consistent with the previous observation in transfusion recipients that anti-Tax may appear several years after infection is established.³⁷

There were several limitations in the present study. First, recall at each follow-up screening was restricted to subjects from Kingston and Clarendon, thereby limiting the generalizability of the study results. Second, ~2% of HTLV-I-negative persons in the initial 1985–1986 screening were recruited in the 1987–1988 investigation, and only 17% of the original cohort members participated in the 1992–1994 investigation. However, we think that a large selection bias is unlikely because the HTLV-I seroprevalence was uniform across all parishes²⁰ and the expected number of seroconversions based on the seroprevalence for the entire cohort was virtually identical to the observed number of seroconversions in our study

(Table 2). Third, because data on partners' HTLV-I serostatus were lacking, we were unable to estimate risk of infection for persons who are truly exposed to HTLV-I. In a study of subjects known to be exposed to HTLV-I through their seropositive spouses, the reported male-to-female seroconversion was much higher: 49 per 1,000 person-years.³³ Fourth, knowledge of their HTLV-I infection status may have resulted in alteration of risk behaviors in some HTLV-I carriers during the study period. However, this is unlikely to have caused a substantial underestimation of the transmission risk, because although HTLV-I status results were made available upon request, few participants sought results or received counseling. Fifth, our ability to assess the route of infection was limited because detailed information on sexual activity and other behavioral risk factors for infection had not been collected for all subjects. Small numbers of seroconversions also may have limited the statistical power to detect sex-specific differences in seroconversion. Detailed evaluation of longitudinal changes in viral markers was not possible since only 1 seroconverter had multiple measurements.

In summary, HTLV-I seroconversion in Jamaica appears to be somewhat higher among females than among males, possibly reflecting differential sexual transmission. Provirus load and antibody titer become like those in chronic carriers within a couple of years after initial infection, but anti-Tax appears only later. Longer follow-up of these carriers for development of morbidity in relation to viral markers would be of interest. An international comparison of viral steady state in asymptomatic carriers may also help clarify the differential risks of HTLV-I-associated disease across geographic areas.

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REFERENCES

1. Poiesz BJ, Ruscetti FW, Gazdar AF, et al. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci U S A*. 1980;77:7415–7419.
2. Miyoshi I, Kubonishi I, Yoshimoto S, et al. Type C virus particles in a cord T-cell line derived by co-cultivating normal human cord leukocytes and human leukaemic T-cells. *Nature*. 1981;294:770–771.
3. Gessain A, Barin F, Vernant JC, et al. Antibodies to human T-

- lymphotropic virus type-I in patients with tropical spastic paraparesis. *Lancet*. 1985;2:407-410.
4. Osame M, Usuku K, Izumo S, et al. HTLV-I associated myelopathy, a new clinical entity. *Lancet*. 1986;1:1031-1032.
 5. LaGrenade L, Hanchard B, Fletcher V, et al. Infective dermatitis of Jamaican children: a marker for HTLV-I infection. *Lancet*. 1990;336:1345-1347.
 6. Mochizuki M, Watanabe T, Yamaguchi K, et al. HTLV-I uveitis: a distinct clinical entity caused by HTLV-I. *Jpn J Cancer Res*. 1992;83:236-239.
 7. Arisawa K, Soda M, Akahoshi M, et al. Human T-lymphotropic virus type-I infection, antibody titers and cause-specific mortality among atom bomb survivors. *Jpn J Cancer Res*. 1998;89:797-805.
 8. Manns A, Hisada M, La Grenade L. Human T-lymphotropic virus type I infection. *Lancet*. 1999;353:1951-1958.
 9. Okochi K, Sato H, Hinuma Y. A retrospective study on transmission of adult T cell leukemia virus by blood transfusion: seroconversion in recipients. *Vox Sang*. 1984;46:245-253.
 10. Manns A, Wilks RJ, Murphy EL, et al. A prospective study of transmission by transfusion of HTLV-I and risk factors associated with seroconversion. *Int J Cancer*. 1992;51:886-891.
 11. Yoshida M, Osame M, Kawai H, et al. Increased replication of HTLV-I in HTLV-I-associated myelopathy. *Ann Neurol*. 1989;26:331-335.
 12. Kira J, Koyanagi Y, Yamada T, et al. Increased HTLV-I proviral DNA in HTLV-I-associated myelopathy: a quantitative polymerase chain reaction study. *Ann Neurol*. 1991;29:194-201.
 13. Wattel E, Mariotti M, Agis F, et al. Quantification of HTLV-I proviral copy number in peripheral blood of symptomless carriers in the French West Indies. *J Acquir Immune Defic Syndr*. 1992;5:943-946.
 14. Manns A, Miley WJ, Wilks RJ, et al. Quantitative proviral DNA and antibody levels in the natural history of HTLV-I infection. *J Infect Dis*. 1999;180:1487-1493.
 15. Hisada M, Okayama A, Shioiro S, et al. Risk factors for adult T-cell leukemia among carriers of human T-lymphotropic virus type I. *Blood*. 1998;92:3557-3561.
 16. Taylor GP, Tosswill JH, Matutes E, et al. Prospective study of HTLV-I infection in an initially asymptomatic cohort. *J Acquir Immune Defic Syndr*. 1999;22:92-100.
 17. Ehrlich GD, Glaser JB, Abbott MA, et al. Detection of anti-HTLV-I Tax antibodies in HTLV-I enzyme-linked immunosorbent assay-negative individuals. *Blood*. 1989;74:1066-1072.
 18. Rosen CA, Park R, Sodroski JG, et al. Multiple sequence elements are required for regulation of human T-cell leukemia virus gene expression. *Proc Natl Acad Sci U S A*. 1987;84:4919-4923.
 19. Seiki M, Inoue J, Hidaka M, et al. Two cis-acting elements responsible for posttranscriptional trans-regulation of gene expression of human T-cell leukemia virus type I. *Proc Natl Acad Sci U S A*. 1988;85:7124-7128.
 20. Murphy EL, Figueroa JP, Gibbs WN, et al. Human T-lymphotropic virus type I (HTLV-I) seroprevalence in Jamaica. I. Demographic determinants. *Am J Epidemiol*. 1991;133:1114-1124.
 21. Maloney EM, Murphy EL, Figueroa JP, et al. Human T-lymphotropic virus type I (HTLV-I) seroprevalence in Jamaica. II. Geographical and ecologic determinants. *Am J Epidemiol*. 1991;133:1125-1134.
 22. Murphy EL, Wilks R, Hanchard B, et al. A case-control study of risk factors for seropositivity to human T-lymphotropic virus type I (HTLV-I) in Jamaica. *Int J Epidemiol*. 1996;25:1083-1089.
 23. Murphy EL, Wilks R, Morgan OS, et al. Health effects of human T-lymphotropic virus type-I (HTLV-I) in a Jamaican cohort. *Int J Epidemiol*. 1996;25:1090-1097.
 24. Wiktor SZ, Alexander SS, Shaw GM, et al. Distinguishing between HTLV-I and HTLV-II by western blot. *Lancet*. 1990;335:1533.
 25. Sawada T, Tohmatsu J, Obara T, et al. High risk of mother-to-child transmission of HTLV-I in p40^{tax} antibody-positive mothers. *Jpn J Cancer Res*. 1989;80:506-508.
 26. Miley WJ, Suryanarayana K, Manns A, et al. Real-time polymerase chain reaction assay for cell-associated HTLV type I DNA viral load. *AIDS Res Hum Retroviruses*. 2000;16:665-675.
 27. Breslow NW, Day NE. *Statistical Methods in Cancer Research. Vol II. The Design and Analysis of Cohort Studies*. Lyon: International Agency for Research on Cancer, 1997.
 28. Rothman KJ, Boice JD Jr. *Epidemiological Analysis with a Programmable Calculator*. Boston: Epidemiology Resources, Inc, 1982.
 29. Mueller N. The epidemiology of HTLV-I infection. *Cancer Causes Control*. 1991;2:37-52.
 30. Takezaki T, Tajima K, Komoda H, et al. Incidence of human T lymphotropic virus type I seroconversion after age 40 among Japanese residents in an area where the virus is endemic. *J Infect Dis*. 1995;171:559-565.
 31. Hisada M, Maloney EM, Sawada T, et al. Virus markers associated with vertical transmission of human T lymphotropic virus type I in Jamaica. *Clin Infect Dis*. 2002;34:1551-1557.
 32. Kajiyama W, Kashiwagi S, Ikematsu H, et al. Intrafamilial transmission of adult T-cell leukemia virus. *J Infect Dis*. 1986;154:851-857.
 33. Stuver SO, Mueller NE. Re: Sexual transmission of human T-lymphotropic virus type I among female prostitutes and among patients with sexually transmitted diseases in Fukuoka, Kyushu, Japan. *Am J Epidemiol*. 1995;142:1247-1248.
 34. Mueller N, Okayama A, Stuver S, et al. Findings from the Miyazaki cohort study. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996;13(suppl 1):S2-S7.
 35. Hinuma S, Komoda H, Chosa T, et al. Antibodies to adult T-cell leukemia-virus-associated antigen (ATLA) in sera from patients with ATL and controls in Japan: a nation-wide seroepidemiologic study. *Int J Cancer*. 1982;29:631-635.
 36. Okayama A, Stuver S, Iga M, et al. Sequential change of virus markers in seroconverters with community-acquired infection of human T lymphotropic virus type I. *J Infect Dis*. 2001;183:1031-1037.
 37. Manns A, Murphy EL, Wilks R, et al. Detection of human T-cell lymphotropic virus type I antibody patterns during seroconversion among transfusion recipients. *Blood*. 1991;77:896-905.
 38. Yokota T, Cho MJ, Tachibana N, et al. The prevalence of antibody to p42 of HTLV-I among ATLL patients in comparison with healthy carriers in Japan. *Int J Cancer*. 1989;43:970-974.
 39. Shioiri S, Tachibana N, Okayama A, et al. Analysis of anti-Tax antibody of HTLV-I carriers in an endemic area in Japan. *Int J Cancer*. 1993;53:1-4.