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High Endemicity of Human T-cell Lymphotropic Virus Type 1 Among Pregnant Women in Peru

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Summary

Human T-cell lymphotropic virus type 1 (HTLV-1) is associated with adult T-cell leukemia, tropical spastic paraparesis, and other immune-mediated diseases. There are reports of groups with high prevalences of HTLV-1 infection in Peru, but there is limited knowledge of the epidemiology of infection or which routes of infection are most important. We studied 2492 women presenting to a large maternity hospital in Lima for prenatal, delivery, or abortion services. HTLV-1 seropositivity was confirmed in 42 women (1.7%; 95% confidence interval, 1.2–2.2). Seroprevalence increased with age but did not vary by region of birth or recency of migration to Lima. Age greater than 30 years and sexual intercourse before 20 years of age were strongly and independently associated with infection. History of abortion and history of transfusion were of borderline significance. Women whose male partner had a characteristic that might be a marker for risk of sexually transmitted infections were also more likely to be infected. HTLV-1 is common among Peruvians throughout the country and is maintained by a low level of neonatally acquired infection that is amplified by sexual transmission. In addition to screening of the blood supply, instituted in 1997, programs designed to reduce neonatal and sexual transmission should be effective.

Keywords

HTLV-1; Peru; pregnant women

Human T-cell lymphotropic virus type 1 (HTLV-1) is associated with adult T-cell leukemia, tropic spastic paraparesis, and other immune-mediated diseases. Although the virus is distributed worldwide, it is highly endemic in areas of southern Japan.¹ Endemic foci also have been documented in Jamaica and other countries of the Caribbean basin, as well as in some South and Central American countries.^{1,2} The primary modes of transmission of HTLV-1 (i.e., breast-feeding, sexual activity, and parenteral exposure to contaminated blood) are well established. However, the relative importance of these routes varies across populations. Therefore, public health measures to reduce transmission of HTLV-1 must be based upon the local epidemiology of this infection.

Peru has been identified as an epicenter of high prevalence of HTLV-1 infection, and there are numerous reports of HTLV-1-associated disease occurrence.^{3–5} Prevalence is particularly high among Japanese immigrants (16%) and their first-generation offspring (4%).⁶ Also, high infection prevalences (4%–25%) have been observed among female sex workers and other groups at known risk for sexually transmitted infections.^{7–9} Some studies have suggested the infection is particularly prevalent among populations in the Peruvian Andes.^{5,9} A recent cross-sectional study demonstrated HTLV-1 endemicity in 3 regions of Peru.¹⁰ However, the study did not address the relative importance of the various routes by which HTLV-1 may be transmitted. Thus, there is limited knowledge of the epidemiology of HTLV-1 in the broader Peruvian population.

We have conducted a large cross-sectional study of HTLV-1 infection in Lima, the capital and major urban center of Peru. Our objectives were to determine the prevalence of and risk factors associated with HTLV-1 infection in a more representative population than those previously studied. Participants were pregnant women, a group that provides insight into the potential for the maintenance of HTLV-1 in the community. Because half of the study participants had moved to Lima from other parts of the country, we also were able to examine prevalence by region of birth and recency of immigration. In addition, our sample size is sufficiently large to assess the independent contributions of birthplace (i.e., Andean vs other) and risk factors for adult acquisition of infection.

METHODS

The present study involves a random sample of 2492 (20%) of 12,436 women who participated in a cross-sectional study examining risk factors for HIV infection and syphilis.¹¹ The study recruited consecutive women presenting to the Instituto Especializado Materno Perinatal (IMP) for prenatal, delivery, or abortion services between August 1996 and April 1997. As the primary maternity hospital in Lima, the IMP handles over 23,000 births each year or 15% of all deliveries in the region. Women attending the IMP are of low socioeconomic status; most of them live in the pueblos jóvenes or shanty towns that surround Lima. None of the women refused to participate, but some left before the interview. The study enrolled approximately 90% of women making a first prenatal visit, 70% with uncomplicated delivery, and 40% of women with complications of abortion. Additional details can be found in Alarcón et al.¹¹

Both the original and present study were reviewed and approved by the appropriate ethical committees in the United States and Peru. Following written informed consent, women completed an interviewer-administered questionnaire assessing demographic and behavioral risk factors and had blood drawn. Women also were asked their perceptions of their current male partner's behavioral risk factors.

Laboratory Methods

Pools of 4 or 5 sera each were screened for HTLV-1 by enzyme-linked immunosorbent assay (ELISA) (Cambridge Bioscience Corp, Worcester, MA). Seven of the randomly selected samples were tested individually because they were found after the time of testing of the serum pools. Specimens belonging to positive pools were then individually screened, and those that were repeat reactive were confirmed by an rp21e-enhanced Western blot assay (Cambridge Bioscience Corp). ELISA-positive specimens were considered to be HTLV-1 seropositive if the Western blot revealed bands at p24, and gp46 or rp21env. If only other viral-specific bands were present, such as p53 or p19, the specimen was considered indeterminant.

Antibodies to HIV-I were detected by ELISA (Ortho Diagnostic Systems, Raritan, NJ) and confirmed by Western blot (Organon Teknika, Durham, NC). Syphilis was diagnosed on the

basis of rapid plasma reagin test and *Treponema pallidum* hemagglutination assay (TPHA-Nosticon; Organon Teknika).

Statistical Analysis

The sample size of 2492 women was chosen to give a 95% confidence interval (CI) of plus or minus 1% around the estimate of HTLV-1 prevalence. HTLV-1 prevalence was calculated for the whole study sample and within strata formed by characteristics suspected to be risk factors or markers for infection. We used relatively sensitive statistical criteria, crude odds ratio (OR) estimate greater than 2.0 or 90% profile likelihood ratio CI around the OR estimate did not include 1.0, to select risk factors to include in a logistic regression model. A final model was constructed by backward elimination using the Wald test ($P < 0.05$) to identify independently associated factors.¹² Table 1 includes 95% CIs for variables remaining in this reduced model. We considered age as a continuous and as a categorical variable. The results were similar, and we show only the latter for ease of presentation.

RESULTS

The 2492 women selected for the present study were representative of the total IMP study population as summarized in Table 1. In general, participants were young (mean $\pm$ SD, 25.5 $\pm$ 6.6 years), and most were either married (23%) or living with a partner (62%). Only half of the women had graduated from secondary school, and most of them (79%) did not work outside their home. Half of the participants had immigrated to Lima from other departments within Peru, 17% within the previous 5 years. Most of the women presented for prenatal (46.9%) or delivery and postpartum (47.4%) care.

HTLV-1 infection was confirmed in 42 (1.7%; 95% CI, 1.2–2.2) of the 2492 women. Ten who were ELISA repeat reactive but indeterminant on Western blot are excluded from subsequent analyses. As expected, seroprevalence increased with age in general, and within region of birth (Fig. 1). Prevalence was greatest among women born in Lima and did not vary by recency of immigration; 1.4% of the 415 women who had lived in Lima for less than 5 years were seropositive as compared with 1.2% of the 770 who had lived in Lima for greater than 5 years (data not shown).

Potential Risk Factors Associated With HTLV-1 Infection: Crude 90% CI

In addition to age, a number of demographic and behavioral characteristics were univariately associated with HTLV-1 seropositivity (Table 1). Infection was more common among women presenting for abortion than for prenatal or postnatal care. Infection also was associated with potential markers of greater sexual exposure (i.e., age at first intercourse, marital status, previous sexual partner, previous pregnancy, or ever had abortion).

Exposure to contaminated blood products may also play a role in HTLV-1 transmission in this population. Women who reported a history of blood transfusion were nearly 4 times (90% CI, 1.7–7.6) as likely to be seropositive. However, only 4% of women reported this exposure. History of jaundice, reported by even fewer women, was also associated with HTLV-1 infection, but the association was not statistically significant (OR, 2.3; 90% CI, 0.7–5.6).

The association of HTLV-1 infection with other STIs was examined by history and serologic results (data not shown). None of the 57 participants who reported having had a sexually transmitted disease were HTLV-1 seropositive. Similarly, only one (2.1%) of the 48 women with syphilis was HTLV-1 seropositive as compared with 1.7% of the women without syphilis (OR, 1.2; 90% CI, 0.2–6.7). In contrast, although HIV infection was found in only 10 (0.4%) of the participants, one (10%) of these 10 also had HTLV-1 infection. The comparable

prevalence among HIV seronegative women was 1.6% (OR, 6.6; 90% CI, 0.7–28.7). The small number of HIV seropositive women makes this and other observations about their risk for HTLV-1 infection unreliable. We, therefore, excluded them from multivariable analyses.

Multivariate Analyses of Risk Factors

In a full model adjusting for all factors selected by our inclusion criteria age, age at first intercourse, and marital status were strongly associated with HTLV-1 seropositivity (Table 1: adjusted, full model, 90% CI). Lima birthplace, having a previous sexual partner, ever having had an abortion, and history of transfusion were of borderline significance. Factors were removed by backward elimination (Wald $P < 0.05$) to produce a final reduced model (Table 1: adjusted, reduced model, 95% CI). In that model, age and age at first intercourse remained strongly associated with HTLV-1 infection, and history of abortion and history of transfusion were of borderline significance.

Association of HTLV-1 Infection With Perceived Characteristics of Sex Partners

The role of partners' characteristics in HTLV-1 infection was explored for the 2359 women who indicated they had a current stable relationship (Table 2). In general, women who reported that their partner had a characteristic that might be a marker for risk of STI (ie, being a womanizer, frequenting prostitutes, frequently getting drunk away from home) were more likely to have HTLV-1 infection. However, none of the observed associations reached statistical significance.

DISCUSSION

We found HTLV-1 infection in nearly 2% (95% CI, 1.2–2.2) of women seeking prenatal, delivery, or abortion services in a large public hospital in Lima, Peru. Similar levels of HTLV-1 have been reported among pregnant women and other obstetric and gynecologic patients in Jamaica (3.5%), Martinique (1.9%), and Brazil (0.8%).^{13–15} Our findings are also consistent with the 3.1% (95% CI, 1.6–4.6) prevalence observed among women attending a public prenatal clinic in Lima during the 1980s.⁷ More recently, Sanchez-Palacios et al¹⁰ reported prevalence ranging from 1.3% to 3.8% among women in 3 different regions of Peru. Neither of these previous studies, however, evaluated the relative importance of the different routes by which HTLV-1 is transmitted. This large, cross-sectional study enabled the comparison of HTLV-1 prevalence across age and regional birth cohorts, while taking into account risk factors for adult acquisition of infection.

We found increasing age and earlier age at first sexual intercourse to be the strongest and independent risk factors for HTLV-1 infection. These risk factors are likely surrogates for numbers of exposures to an infected partner. Early onset of sex by females might also hypothetically be associated with greater susceptibility to acquisition of HTLV-1. Age-related increases in HTLV-1 prevalence have been observed consistently in endemic populations.^{16, 17} The increase is typically more pronounced in women, suggesting more efficient sexual transmission from man to woman than the reverse. A prospective study of 97 heterosexual couples serodiscordant for HTLV-1 infection found a 4-fold greater incidence among initially seronegative wives than among husbands.¹⁸ A more recent study reported a smaller and nonstatistically significant excess for man-to-woman transmission, but it included only 30 couples and had a high loss to follow-up (45%).¹⁹

It is of interest that women who indicated a history of abortion were more likely to be HTLV-1 seropositive. Because induced abortion is illegal in Peru, it was not considered possible to elicit an accurate history of this procedure. Indeed, the relationship was of borderline statistical significance and attenuated by adjustment for other risk factors. Abortion also was associated

with HIV in the cohort from which this study sample was derived.¹¹ Information regarding the circumstances leading to abortion will be required to interpret the nature of this association. It has been estimated that each year, 5.2% of Peruvian women aged 15 to 49 years are likely to have an abortion.²⁰

Transfusion with contaminated blood appears to have been a relatively uncommon route of transmission in our population but may have played a more important role in other regions. We detected infection in 5.5% of the 4% of participants with a history of blood transfusion. In a comparable study by Sanchez-Palacios et al,¹⁰ predominantly involving women in the Andean city of Huanta, HTLV-1 was detected in 13.6% of the 10% of women with this history. Interestingly, dental and other surgery, but not transfusion, were strongly associated with HTLV-1 infection among 211 pregnant women surveyed by Zurita et al⁹ in the Andean city of Quillabamba. These differences in risk may reflect regional differences in blood donation and screening practices. In a national survey conducted in 1997, 1.3% of blood donors were HTLV-1 seropositive by ELISA.²¹

Women born in the Andes were no more likely to be HTLV-1 seropositive than were those born in other regions of the country. This is consistent with the findings from the only population-based study conducted in Peru.¹⁰ The association between Andean birth and HTLV-1 infection observed in other studies may best be explained by selection bias and known behavioral risk factors.^{9,22} Similarly, although we found some evidence that women born in Lima may be at particularly high risk of infection, this relationship was of borderline statistical significance and did not remain in our final model which adjusted for risk factors operating during adulthood.

Conclusions about risk factors for incident infection are limited by the cross-sectional design of this study. Neonatal exposure to infection may have decreased over the represented birth cohorts, either due to changes in breast-feeding practices or prevalence in the maternal generation. Conclusions about prevalence by birth region must consider the possibility that our study participants differ from individuals who did not migrate to Lima. In addition, caution must be used in extrapolating our findings to the general population of Peru or even subsets such as all pregnant women in the same geographic region. As has been observed for HIV, selection bias may arise from factors associated with fertility (e.g., age, sexual behavior, contraceptive use) or clinic attendance (e.g., education level, geographic mobility).^{23,24} However, in a pair of studies from Salvador, Brazil prevalence of HTLV-1 infection among women presenting for prenatal care was quite comparable to that among similar aged women in a citywide population sample.^{15,25} Prevalence among pregnant women in Europe was consistently greater than that among blood donors, but the latter group might be expected to underestimate prevalence relative to the general population.²⁶ Finally, it is possible that our strategy of testing pooled specimens may have reduced the sensitivity for detecting HTLV-1 infection.²⁷ However, it is unlikely that any inaccuracy would be related to the risk factors under investigation.

Nearly 2% of the women in this study had HTLV-1 infection. This is an important indicator of the potential for sustained and endemic transmission in the general population. Our observations suggest HTLV-1 is maintained in Peru by a low level of neonatally acquired infection that is amplified by sexual transmission. The lack of geographic associations indicates prevention efforts must be broad based. Peru instituted universal screening of blood donors in 1997.²⁸ Counseling of HTLV-1 seropositive blood donors should include education regarding how to avoid transmitting the virus and might incorporate identification and testing of family members and sexual contacts. Safer sex messages directed at limiting transmission of HIV and other STIs should include HTLV-1 as a target. Finally, programs should be developed to reduce neonatal transmission. Peru's 2000 national health survey found over 90% of infants younger

than 9 months were breast-fed, and the median duration of breast-feeding was greater than 22 months.²⁹ Epidemiological data indicate that the risk of infection is greatest for children breast-feeding after 12 months of age, and transmission might be greatly reduced if HTLV-1 infected mothers avoid or limit duration of breast-feeding.³⁰

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FIGURE 1.
HTLV-1 seroprevalence by age within birth region.

TABLE 1
Association of HTLV-1 With Demographic and Behavioral Characteristics

Characteristic	HTLV-1 Seropositive				Adjusted	
	Total	n	(%)	Crude OR (90% CI)	Full Model* OR (90% CI)	Reduced Model† OR (95% CI)
Presentation at enrollment						
Abortion/miscarriage	143	5	3.5	2.3 (0.9–4.7) [‡]	1.4 (0.5–3.1)	
Prenatal	1169	17	1.4			
Postpartum	1180	20	1.7			
Region of birth						
Lima	1255	26	2.1	1.6 (1.0–2.8) [§]	1.7 (1.0–3.0)	
Andes	768	10	1.3			
Coast	361	5	1.4			
Jungle	103	1	1.0			
Age (years)						
<20	659	4	0.6	1.0	1.0	1.0
20–30	1303	21	1.6	2.7 (1.2–7.4)	2.7 (1.0–8.0)	2.8 (1.0–9.9)
>30	530	17	3.2	5.4 (2.3–15.1)	5.1 (1.7–17.0)	5.2 (1.8–19.3)
Age at first intercourse (years)						
≥20	690	5	0.7	1.0	1.0	1.0
<20	1797	37	2.1	2.9 (1.4–6.9)	3.6 (1.7–8.8)	3.9 (1.6–11.4)
Marital status [¶]						
Single	355	1	0.3	1.0	1.0	
Married or living together	2121	41	1.9	7.0 (1.8–66.8)	5.5 (1.4–54.3)	
Previous sexual partners [#] (other than current partner)						
No	1694	20	1.2	1.0	1.0	
Yes	797	22	2.8	2.4 (1.4–4.0)	1.7 (1.0–2.9)	
Previous pregnancy						
None	972	8	0.8	1.0	1.0	
One or more	1520	34	2.2	2.8 (1.5–5.5)	0.7 (0.3–1.6)	
Ever had abortion						
No	1763	19	1.1	1.0	1.0	1.0

Characteristic	HTLV-1 Seropositive			Adjusted		
	Total	n	(%)	Crude OR (90% CI)	Full Model [*] OR (90% CI)	Reduced Model [†] OR (95% CI)
Yes	729	23	3.2	3.0 (1.8–5.0)	1.9 (1.0–3.6)	2.0 (1.0–3.8)
Ever had transfusion						
No	2383	36	1.5	1.0	1.0	1.0
Yes	109	6	5.5	3.8 (1.7–7.6)	2.6 (1.1–5.6)	2.6 (0.9–6.1)
Ever had jaundice						
No	2409	39	1.6	1.0	1.0	
Yes	83	3	3.6	2.3 (0.7–5.6)	2.3 (0.7–5.9)	

* ORs are adjusted for all other variables in the table.

[†] ORs are adjusted only for those variables retained in the reduced model (Wald test, $P > 0.05$).

[‡] OR compares women presenting for abortion/miscarriage with all others.

[§] OR compares women born in Lima with all others.

[¶] The category “single” includes women who were identified as widowed ($n = 3$) or divorced/separated ($n = 13$). None of these women were HTLV-1 seropositive.

[#] Among 797 women with a previous partner, 698 had 1, 86 had 2, and 12 had 3 or more. HTLV-1 seroprevalence among these groups was 2.9%, 2.3%, and 0%, respectively.

TABLE 2
Association of HTLV-1 With Perception of Partner's Characteristics

Characteristic	HTLV-1 Seropositive			Crude OR (90% CI)
	Total	n	%	
Womanizer				
No	1617	28	1.7	1.0
Yes	320	8	2.5	1.5 (0.7–2.7)
Don't know	422	4	0.9	0.5 (0.2–1.2)
Frequents prostitutes				
No	1883	32	1.7	1.0
Yes	106	3	2.8	1.7 (0.5–4.1)
Don't know	370	5	1.3	0.8 (0.3–1.6)
Has another female partner				
No	2009	34	1.7	1.0
Yes	211	4	1.9	1.1 (0.4–2.5)
Don't know	139	2	1.4	0.8 (0.2–2.4)
Enjoys anal sex				
No	1705	31	1.8	1.0
Yes	611	9	1.5	0.8 (0.4–1.5)
Don't know	43	0	0	—
Frequently gets drunk away from home				
No	1702	24	1.4	1.0
Yes	651	16	2.5	1.8 (1.0–3.0)
Don't know	6	0	0	—
Uses drugs				
No	2296	38	1.7	1.0
Yes	35	1	2.9	1.7 (0.2–6.8)
Don't know	28	1	3.6	2.2 (0.2–8.7)
Uses IV drugs				
No	2329	39	1.7	1.0
Yes	1	0	0	—
Don't know	29	1	3.4	2.1 (0.2–8.3)
Has sex with other men				
No	2113	39	1.8	1.0
Yes	17	0	0	—
Don't know	229	1	0.4	0.2 (0.0–0.9)
Has been in jail				
No	2286	40	1.7	1.0
Yes	50	0	0	—
Don't know	23	0	0	—
Has received a transfusion				
No	2117	37	1.7	1.0
Yes	55	1	1.8	1.0 (0.1–4.0)

Characteristic	HTLV-1 Seropositive			Crude OR (90% CI)
	Total	n	%	
Don't know	187	2	1.1	0.6 (0.1–1.7)
Has been diagnosed with AIDS				
No	2248	39	1.7	1.0
Yes	5	0	0	—
Don't know	106	1	0.9	0.5 (0.1–2.1)
Has had tuberculosis				
No	2226	36	1.6	1.0
Yes	65	3	4.6	2.9 (0.9–7.2)
Don't know	68	1	1.5	0.9 (0.1–3.5)