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RISK FACTORS FOR HTLV-II INFECTION IN PERUVIAN MEN WHO HAVE SEX WITH MEN

JOSEPH R. ZUNT*, **ALBERTO M. LA ROSA**, **JESÚS PEINADO**, **JAVIER R. LAMA**, **LUIS SUAREZ**, **MONICA PUN**, **CESAR CABEZAS**, and **JORGE SANCHEZ**
Department of Neurology, Center for AIDS and STD, University of Washington School of Medicine, Seattle, Washington; Asociación Civil Impacta Salud y Educación (IMPACTA), Oficina General de Epidemiologia, Instituto Nacional De Salud, Lima, Peru

Abstract

Human T-cell lymphotropic virus type-II (HTLV-II) infection is endemic in indigenous groups in the Americas and injection drug users (IDUs) worldwide. In Peru, HTLV-II infection was previously identified in two indigenous Amazonians. We examined risk factors for HTLV-II infection in 2,703 Peruvian men who have sex with men (MSM): 35 (1.3%) were HTLV-II positive. HTLV-II infection was associated with syphilis, HSV-2 infection, unprotected receptive anal intercourse, and older age. This is the first report of HTLV-II in a non-indigenous non-IDU population in Peru. Additional studies are needed to determine if HTLV-II is a sexually transmitted infection in this and other sexually active populations.

INTRODUCTION

Human retroviruses are transmitted sexually, through blood transfusion, injection drug use, or from mother-to-child. Transmission efficiency varies by retrovirus, with HIV being transmitted more efficiently than human T-cell lymphotropic virus type I or II (HTLV-I, HTLV-II).[1,2] In the United States and Europe, HTLV-II infection is most common in injection drug users (IDUs), whereas in Latin American countries, HTLV-II has been reported in non-IDU indigenous populations in Argentina, Brazil, Colombia, Panama, Paraguay, and Venezuela.[2–4] In Peru, HTLV-II infection was previously detected in two individuals from Amazonian indigenous populations: the Boca Colorado and the Galilea.[5] Although HIV and HTLV-I infections are endemic in Peruvian groups at high risk for transmitting sexually transmitted infections (STIs), such as men who have sex with men (MSM) and female sex workers (FSW), HTLV-II infection has not been reported previously in these groups or in the general population.[6–8]

In cross-sectional studies, HTLV-I and-II infections were transmitted more efficiently from male-to-female than female-to-male, with higher transmission rates associated with longer duration of relationship and higher HTLV-II viral load in the seropositive male.[9] In a recent prospective study of HTLV-I and-II infection in IDUs, infection was transmitted equally

*Address correspondence to Joseph R. Zunt, MD, MPH Harborview Medical Center, Department of Neurology, Box 359775, 325 Ninth Avenue South, Seattle, WA 98104. E-mail: E-mail: jzunt@u.washington.edu.
Authors' addresses: Joseph R. Zunt, Harborview Medical Center, 325 Ninth Avenue, Box 359775, Seattle, WA 98105, E-mail: jzunt@u.washington.edu. Alberto M. La Rosa, Jesús Peinado, Javier R. Lama, and Jorge Sanchez, Asociación Civil Impacta Salud y Educación (IMPACTA), Grimaldo del Solar 805, Lima, Peru; Luis Suarez and Monica Pun, Oficina General de Epidemiologia, Jr. Camilo Carrillo 402, Lima, Peru. Cesar Cabezas, Instituto Nacional de Salud, Capac Yupanqui, 1400, Jesús Maria, Lima, Peru.

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efficiently from male-to-female as from female-to-male.[10] In IDU populations, higher rates of HTLV-II infection have been associated with non-white race, heroin use, older age, and history of herpes simplex virus type 2 (HSV-2), gonorrhea, or other STIs.[11–14] Injection drug use is uncommon in Peru; in a prior study of 400 FSW, none reported IDU.[15] In non-IDU indigenous populations, higher rates of infection were associated with earlier onset of sexual intercourse, greater number of sexual partners, and sexual intercourse with an FSW. Unlike in IDU populations, presence of HSV-2 antibody in serum and reported history or symptoms of STIs were not associated with higher risk of HTLV-II infection.[2] We recently reported the detection of HTLV-II infection in MSM living in three Peruvian cities.[16] This study examines the risk factors associated with HTLV-II infection in these men.

MATERIALS AND METHODS

Study population

Males older than 18 years of age who reported sexual intercourse with one or more men during the past year and living in one of six Peruvian cities, Arequipa (Highlands), Iquitos or Pucallpa (Amazon Jungle), Lima, Piura, or Sullana (Coast), were eligible to participate. Subjects were recruited by trained recruiters and/or peer educators using outreach work and "snowball" techniques, whereby recruited subjects were invited to receive training and recruit other subjects. The study protocol was approved by the Peruvian National AIDS and STD Control Program, and the Institutional Review Boards of the Asociación Civil Impacta Salud y Educación (Impacta, Lima, Peru), the US Navy Medical Research Center Detachment, and the University of Washington.

At each study site, a counselor obtained informed consent from each subject. A structured interview using computer-assisted self-interviewing (CASI) was used to collect information about demographics, sexual risk behavior, previous HIV-1 testing and diagnosis, sexual identity and sexual role, and number and sex of sexual partners in the past 3 months. Study physicians performed a medical history and targeted physical examination, including examination of the genitals, lymph nodes, skin, and oropharynx. Blood and genital samples were obtained for testing for HIV-1, HTLV, and STIs.

In exchange for participation, subjects received risk reduction counseling, condoms, and lubricants. Subjects diagnosed with HIV-1 and/or STIs received post-diagnosis counseling and education and treatment in accordance with Peruvian STI Treatment Guidelines. Subjects with HIV-1 infection were referred to HIV specialists for treatment and management of HIV infection.

Laboratory assessments

Blood samples were tested for antibodies to HIV-1 by enzyme-linked immunosorbent assay (ELISA) (Vironostika; Organon Tecnica, Durham, NC) with Western blot confirmation (Biorad Laboratories, Hercules, CA) and for early HIV infection with a less-sensitive HIV-1 enzyme immunoassay (EIA) (Dilviron; Organon Tecnica). Blood was also tested for *Treponema pallidum* by quantitative rapid plasma reagin (RPR; Organon Tecnica) with micro-hemagglutination assay (MHA-TPA) confirmation (Organon Tecnica); syphilis was defined as RPR titer $\geq$ 1:1 with reactive MHA-TPA. Herpes simplex virus type 2 (HSV-2) infection was detected by type-specific ELISA (Focus Technology, Cypress, CA); HSV-2 seropositivity was defined as reactive ELISA with an index ratio of $\geq$ 3.5. Testing for hepatitis B infection was performed with ELISA to detect Hepatitis B surface antigen (HbsAg) (Hepanostika HBsAg Uni-Form II; bioMériux, Marcy l'Etoile, France). For HIV-seropositive subjects, quantitative CD4+/CD8+ cell counts were measured using a FACScan Analytic Flow Cytometer (Becton, Dickinson and Co., Franklin Lakes, NJ).

HTLV testing

Serum samples were tested for HTLV-I/II antibody using ELISA (Vironostika) with Western blot confirmation of ELISA-positive samples (HTLV-I/II blot 2.4; Genelabs Diagnostics, Singapore). An individual was considered HTLV-I seropositive if the ELISA was positive, and confirmatory Western blot revealed bands representing gag (p24, p19), gp46, and two env proteins (GD21 and rgp 46-I). Individuals with p24, GD21, and rgp46-II bands were considered HTLV-II seropositive. If gag and env proteins were absent but other HTLV-specific bands were present, the individual was considered indeterminate. Subjects with indeterminate results were excluded from the analysis.

Statistical analysis

Univariate analyses of categorical variables were performed using χ^2 and Fisher exact tests. Continuous variables were evaluated using *t* test for independent samples and Mann-Whitney *U* tests. Multivariate analyses to assess independent factors associated with HTLV-II infection included those variables found to be significant in the univariate analyses; this was performed using a backward stepwise logistic regression with the likelihood ratio test. These analyses yielded odds ratios (ORs) and 95% confidence intervals (CIs). All reported *P* values represent two-sided tests. Analyses were performed using SPSS (v11.5.0; SPSS, Chicago, IL) and Stata (v7.0; Stata Corp., College Station, TX).

RESULTS

Of 2,703 MSM enrolled in the study, 35 (1.3%) had HTLV-II infection detected by ELISA with Western blot confirmation. HTLV-II was detected in 4 (0.4%) of 929 MSM enrolled in Lima, 24 (8.5%) of 283 MSM in Iquitos, and 7 (2.5%) of 277 MSM in Pucallpa. No HTLV-II infection was detected in Arequipa, Piura, or Sullana. Western blot was indeterminate in 12. Of 338 HIV-seropositive men identified, 9 (2.7%) were co-infected with HTLV-II; all lived in either Lima or Iquitos. In comparison, the HTLV-II seroprevalence rate among HIV-seronegative men was much lower (1.1%). Although not discussed further here, HTLV-I infection was detected in 56 (2.1%) MSM. Of the 2,703 men who received HTLV testing, 2,655 had complete questionnaire and STI testing available and were included in further analyses.

When divided into groups by HTLV serostatus, HTLV-II seropositive men were older, more likely to self-identify as homosexual, and more often the receptive male during anal sex (Table 1). Compared with HTLV-II–seronegative men, HTLV-II–seropositive men had significantly higher prevalences of HIV, HSV-2, and syphilis infections, were more likely to report symptoms of anal trauma (anal pain, fissure, condiloma, proctitis), and had more evidence of anorectal abnormalities on clinical examination. In multivariate analyses, HTLV-II infection was associated with syphilis (OR, 2.55; 95% CI, 1.22–5.31; $P = 0.01$), HSV-2 infection (OR, 5.88; 95% CI, 1.32–26.15; $P = 0.02$), unprotected receptive anal intercourse (OR, 2.73; 95% CI, 1.19–6.29; $P = 0.02$), and age > 40 years (OR, 3.05; 95% CI, 1.44–6.44; $P = 0.003$; Table 2).

There was no statistically significant difference in frequency of travel to other Peruvian cities or other countries between HTLV-II–seropositive and –seronegative groups. Information regarding racial identity of sexual partners was not obtained, nor was history of injectable medications, blood transfusion, tattooing, or circumcision. No subject reported IDU.

DISCUSSION

Prior studies of MSM living in the United States, Trinidad, and Jamaica have detected HTLV-II infection in 1 (0.07%) of 1,515 men.[17–19] We detected HTLV-II infection in 35 (1.3%) of 2,703 MSM in Peru. To our knowledge, this is the first report of HTLV-II infection in a non-indigenous Peruvian population—a population that denies IDU. Consistent with studies of HTLV-II infection in IDUs, we detected a significant association of HTLV-II infection with both syphilis and HSV-2 infection. In multivariate analyses, HTLV-II infection remained significantly associated with syphilis, HSV-2 infection, unprotected receptive anal intercourse, and age > 40 years. Although not significant in the multivariate model, HTLV-II infection was more common in HIV-infected MSM and in MSM with physical symptoms of rectal trauma. Our findings suggest that, in sexually active MSM, HTLV-II infection is likely transmitted sexually through receptive anal intercourse, with higher risk of transmission in men who are co-infected with other sexually transmitted infections.

Because no prior study of HTLV infection in Peruvian MSM has been performed, we cannot state whether HTLV-II infection is an old or newly emergent infection in the MSM population. In 1996, HTLV-II infection was detected in 2 of 64 (3.1%) indigenous Peruvians living in the Amazon Jungle.[5] The higher prevalence of HTLV-II in MSM living in Iquitos and Pucallpa, Amazonian cities in close geographic proximity to where HTLV-II infection was detected, suggests that HTLV-II could have been transmitted from an indigenous group to MSM. The lack of other risk factors traditionally associated with HTLV-II transmission, such as IDU, also supports this hypothesis. Subjects in our study did not self-identify as indigenous, but we did not ask if their sexual partners were from indigenous groups.

A recent study of 200 Peruvian FSWs living in Iquitos did not detect HTLV-II infection.[20] If HTLV-II recently bridged from indigenous groups into the MSM population through sexual transmission, we would expect HTLV-II infection to be present in other sexually active groups, such as FSWs—especially because FSWs are more numerous and more socially acceptable than MSM. Because HTLV-II was not present in FSWs, other factors may be responsible for HTLV-II infection detected in MSM; for example, MSM may be more likely than FSWs to have sexual contact with indigenous people with endemic HTLV-II infection.

In studies of HIV transmission, unprotected receptive anal intercourse has been associated with a higher risk of transmission than vaginal or oral sex.[21,22] In our study, clinical findings of disruption of normal rectal architecture, such as rectal secretion, fissures, and hemorrhoids, were more common in HTLV-II–infected MSM than in uninfected MSM; these findings were not significant in the multivariate model but suggest that, similar to HIV infection, receptive anal intercourse is associated with a higher rate of transmission, especially if disruption of the normal rectal architecture is present.

Our study was limited by lack of information regarding demographic characteristics of sexual partners, especially whether partners were from indigenous populations, and other potential routes for acquisition of HTLV-II infection, such as use of injectable medications, medical or dental procedures, tattoos, or participation in ethnic rituals that produce disruption of the skin or mucous membranes. Future studies will include questions addressing these factors and could provide additional insight regarding risk factors for HTLV-II transmission.

In conclusion, HTLV-II infection is present in Peruvian MSM and is likely transmitted through unprotected anal intercourse. Additional studies of MSM and other groups at high risk for acquiring sexually transmitted infections, such as FSWs and their clients, could assess if HTLV-II is spreading to these groups and determine the risk factors associated with such spread.

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TABLE 1

Characteristics of HTLV-II–seronegative and –seropositive men

	HTLV-II seronegative [No. (%)]	HTLV-II seropositive [No. (%)]	*P**
Characteristic			
Total	2622	33	
Median age, years (range)	24 (18–71)	34 (20–51)	< 0.001
Age by category			< 0.001
18–20	675 (25.7)	1 (3.0)	
21–25	851 (32.5)	2 (6.1)	
26–30	486 (18.5)	9 (27.2)	
31–40	445 (17.0)	15 (45.5)	
41+	165 (6.3)	6 (18.2)	
City of enrollment			< 0.001
Piura/Sullana	738 (28.2)	0	
Lima	904 (34.5)	4 (12.1)	
Iquitos	281 (10.7)	23 (69.7)	
Pucallpa	272 (10.4)	6 (18.2)	
Arequipa	427 (16.3)	0	
Self-reported sexual orientation			
Homosexual	1410 (53.9)	28 (84.8)	
Bisexual	932 (35.7)	4 (12.1)	
Heterosexual	272 (10.4)	1 (3.1)	
Self-described current sexual role			< 0.001
“Activo” (insertive)	1123 (42.9)	4 (12.1)	
“Pasivo” (receptive)	1070 (40.8)	25 (75.8)	
“Moderno” (both insertive and receptive)	428 (16.3)	4 (12.1)	
Sex of sexual partners (previous 90 days)			0.03
Male partners only	1555 (59.4)	28 (84.9)	
Female partners only	210 (8.0)	1 (3.0)	
Both male and female partners	714 (27.2)	4 (12.1)	
None	142 (5.4)	0	
Age of sexual partners			
Any partner > 5 years younger	892 (47.3)	6 (18.2)	< 0.001
Any partner < 5 years younger	995 (52.7)	30 (90.9)	0.44
Sexual role with sexual partner			< 0.001
Only receptive UAI with male partner	674 (25.7)	23 (69.7)	
Only insertive UAI with male partner	495 (18.9)	0 (0)	
Both insertive and receptive UAI with male partner	115 (4.4)	1 (3.0)	
Only insertive UAI with female partner	1335 (51.0)	9 (27.3)	
Physical signs and serologic evidence of STI in HTLV-II–seronegative and –seropositive men			
Characteristic			
Total	*N* = 2,446	*N* = 33	
Specific anorectal abnormality (% of males with sign)			

		HTLV-II seronegative [No. (%)]	HTLV-II seropositive [No. (%)]	*P**
Ulcer		23 (0.9)	0 (0)	0.73
Condyloma		75 (3.1)	2 (6.1)	0.27
Anal secretion		38 (1.6)	3 (9.1)	0.02
Anal fissures		19 (0.9)	3 (9.1)	0.003
Hemorrhoids		99 (4.1)	4 (12.1)	< 0.001
Abscess		19 (0.9)	3 (9.1)	0.99
Any anorectal abnormality				
Abnormal		230 (9.4)	12 (26.4)	< 0.001
Normal		2216 (90.6)	21 (63.6)	
HIV infection				
Yes		329 (12.4)	9 (25.7)	0.02
No		2334 (87.6)	26 (74.3)	
Early HIV infection				
Yes		44 (1.7)	1 (2.9)	0.056
No		284 (10.7)	8 (22.8)	
No HIV infection		2334 (87.6)	26 (74.3)	
Serlogic testing		*N* = 2,621	*N* = 33	
Syphilis	Reactive	334 (12.7)	16 (48.5)	< 0.001
Herpes simplex-type 2	Positive	1176 (44.9)	31 (93.9)	< 0.001
HIV	Positive	320 (12.2)	9 (27.3)	0.02

*P value based on t test for continuous variables and χ^2 for discrete variables.

UAI, unprotected anal intercourse.

TABLE 2

Risk factors for HTLV-II seropositivity after multivariate analysis

Risk factor	OR (95% CI)*	*P*
Syphilis reactivity (positive MHA-TP and RPR)	2.55 (1.22–5.31)	0.01
Receptive UAI	2.73 (1.19–6.29)	0.02
Herpes simplex type-2 infection	5.88 (1.32–26.15)	0.02
Age > 40 years	3.05 (1.44–6.44)	0.003

*Binomial logistic regression.

UAI, unprotected anal intercourse.