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RESEARCH ARTICLE

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High risk of heterosexual transmission of human T-cell lymphotropic virus type 1 infection in Brazil

Arthur Paiva[1,2] | Jerusa Smid[3] | Michel E.J. Haziot[3] | Tatiane Assone[1,2] | Samara Pinheiro[2] | Luiz A.M. Fonseca[4] | Augusto C.Penalva de Oliveira[3] | Jorge Casseb[1,2]

[1] Institute of Tropical Medicine of São Paulo, São Paulo, São Paulo, Brazil

[2] Department of Dermatology, Laboratory of Dermatology and Immunodeficiencies, University of São Paulo Medical School, Butantã, São Paulo, Brazil

[3] Institute of Infectious Diseases "Emilio Ribas" (IIER), São Paulo, São Paulo, Brazil

[4] Department of Preventive Medicine, University of São Paulo Medical School, Butantã, São Paulo, Brazil

Correspondence
Jorge Casseb, Laboratory of Investigation in Dermatology and Immunodeficiencies – LIM56, Av. Dr. Eneas de Carvalho Aguiar 500, 3rd Floor, Building II, São Paulo, São Paulo, Brazil.
E-mail: jcasseb10@gmail.com

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Human T-cell lymphotropic virus type 1 is transmitted primarily either through sexual intercourse or from mother to child. The current study investigated sexual transmission and compared the HTLV-1 proviral load between seroconcordant and serodiscordant couples by examining both men and women among the index partners without using subjective criteria to establish the direction of sexual transmission. Between January 2013 and May 2015, 178 HTLV-1-positive patients had spouses, 107 of which had tested partners, thus increasing the initial sample size (46 men and 61 women). Individuals co-infected with HTLV-2 or human immunodeficiency virus were not included in the analysis. From among the included participants, 26 men and 26 women were paired with each other, resulting in 26 seroconcordant couples; 12 seroconcordant couples were formed from another four men and eight women. Forty-three serodiscordant couples were formed from 16 men and 27 women. The rate of seroconcordance was 46.9%. The HTLV-1 proviral load was compared between 19 and 37 seroconcordant and serodiscondant couples, respectively, and the concordant couples showed higher proviral loads ($P = 0.03$). There were no differences between the groups according to age, relationship length, having a mother or sibling with HTLV-1, race, ethnicity, nationality, education, history of blood transfusion, HAM/TSP, ALT, or hepatitis C virus status. In multivariate analysis, relationship time was shown associated with ocurrence of seroconcordance status. The apparent association between high circulating levels of provirus and seroconcordance rate among couples suggests that proviral loads contribute markedly to the risk of sexual transmission, regardless of gender index.

KEYWORDS
Brazil, HTLV-1, proviral load, sexual transmission

1 | INTRODUCTION

Human T-cell lymphotropic virus type 1 (HTLV-1) infection is an endemic infection in several parts of the world, including Africa, Japan, the Caribbean Basin, and South America, with more than 10 million individuals infected worldwide.[1] The major routes of transmission are vertical and sexual[2] There is no consensus regarding the specific risk factors for transmission, but they may be linked to both the virus and host, such as proviral load (PVL) and human leukocyte antigen (HLA) type.[3–6]

Until now, only one long-term large study has investigated heterosexual transmission in an endemic area; the study was performed in Kagoshima city, Japan, in the mid-1980's.[7] The study showed a predominantly male-to-female higher risk for transmission.[7] The probability of transmission from husband to wife over a 10-year period was 61%, compared to only 0.4% from wife to husband.[7] Direct cell-to-cell contact is necessary for efficient transmission of HTLV-1[8] and lymphocytes infected with HTLV-1 are considered the primary vectors of sexual transmission[9–11]; lymphocytes are more numerous in semen than in vaginal secretions, which likely explains the more efficient male-to-female transmission.[7]

Brazil is endemic for HTLV-1, with the highest prevalence in the Northeast (Maranhão and Bahia) and North (Para) regions, where close to 1 in 100 persons is infected.[12] These data obtained by serological

screening using enzyme-linked immunoassay (EIA) test performed in 27 large urban areas in the 27 States of Brazil were confirmed in a recent study involving three regional Brazilian Blood Banks located in São Paulo, Minas Gerais, and Pernambuco during 2007-2009, in which serological results were confirmed by Western blot.[13] Although not typically considered a highly endemic area, São Paulo city has the highest absolute number of infected persons in the country due to migration from endemic regions, with more than 38 000 persons harbouring the virus.[12,14]

Therefore, studies on the transmission of HTLV-1 between couples are increasingly relevant; except for some studies in Japan,[7,15–17] there have been few investigations involving couples.[3,5,18,19] In addition,additional and more recent data, particularly from endemic areas, are necessary to establish national guidelines in Brazil. Only two studies have been performed in Brazil; in the first, 36% of the sexual partners of 117 seropositive donors in Belo Horizonte were also positive for HTLV-1. In that study, 24 male partners of 55 seropositive women were positive, compared with 18 female partners of 62 HTLV-1-seropositive men.[19] In another study in Belém, the prevalence of HTLV-1 in 39 wives of seropositive individuals was 51%, compared to 14% among 21 husbands of seropositive women.[20] These conflicting results as to the more likely direction of sexual transmission further emphasize the need for more studies, especially in endemic countries other than Japan and Brazil.

Previous studies have evaluated the factors involved in the sexual transmission of HTLV-1,[21] including proviral load (PVL) in peripheral blood mononuclear cells (PBMC). Indeed, a high proviral load is considered a possible risk factor for sexual transmission.[3,5,15–17] A high PVL in PBMC, especially T CD4+ and monocytes cells, may be associated with increased genital excretion of HTLV-1 and consequently higher risk for sexual transmission.[9] However, most studies on sexual transmission have focused on high-risk populations, such as sex workers and individuals in clinics that provide care for sexually transmitted diseases; fewer studies have involved couples[3,5,7,15–17]; or the quantification of PVL.[3,5] Moreover, these previous studies have limitations such as the inclusion of HTLV-2-infected persons,[3,5] a sole gender (males),[3] or a small sample size.[5] The current study aimed to identify laboratory markers associated with the risk of HTLV-1 transmission, especially through sexual intercourse, in a cohort followed up in São Paulo city.

2 | MATERIALS AND METHODS

2.1 | Patient population

The HTLV outpatient clinic of the Institute of Infectious Diseases "Emilio Ribas" (IIER) has been following up HTLV-infected patients since 1997. These patients generally come from blood banks or are referred from other health services. The patients were initially tested for the presence of HTLV-1/2 antibodies by HTLV-1/2 enzyme-linked immunosorbent assay (ELISA); positive enzyme immunoassay (EIA) was followed by testing by Western blot assay. All individuals with positive ELISA or Western blot results were also tested by a qualitative HTLV-1/2 DNA polymerase chain reaction (PCR) test. The present study included only patients more than 18 years old, positive for HTLV-1 by Western blot and PCR, who were actively followed-up from January 2013 to May 2015, and were married or were living as married with a permanent sexual partner for more than one year, as well as their spouses. This stable partnership was established based on self-reporting.

During the study period, 323 individuals were diagnosed as HTLV-1-positive, of which 82 (25.4%) had HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), two had adult T-cell leukaemia (ATL), and one patient had both complications. There were 178 HTLV-1-positive individuals (60%) with spouses; the partners of 107 of these individuals also tested for HTLV-1, increasing the study sample size (46 men, 61 women). Subsequently, the selected individuals with their respective pairs were classified into seroconcordant couples or serodiscordant couples according to serological findings. The HTLV-1 proviral loads were compared between groups. Only seroconcordant couples with PVL results for both spouses were included in this analysis.

Patients who presented with co-infections with other retroviruses, including HIV or HTLV-2, were not included in this report; however, patients positive for hepatitis C virus (HCV) were not excluded.

2.2 | Database collection

Data were collected and managed using Research Electronic Data Capture (REDCap).[22] We transferred data from the medical records of patients with HTLV-1 to RedCap, ensuring that all procedures were performed to exclude discarded cases and checking for inconsistencies, thus consolidating a database for conducting epidemiological and statistical analyses.

2.3 | Ethics issues

The Ethical Board of the IIER/FMUSP approved the protocol (Number 407/12), and a signed informed consent form was obtained from all participants prior to their study inclusion.

2.4 | Sample analyses

Blood samples were collected in an acid-citrate-dextrose solution, and the PBMC were separated by Ficoll density gradient centrifugation (Pharmacia, Uppsala, Sweden). Cells were washed with saline solution; the cell number was adjusted to 2×10^6 cells and the samples were stored at −80°C. DNA was extracted using a commercial kit (Illustra Tissue and Cells GenomicPrep Mini Spin kit, Easton Turnpike, Fairfield, CA) according to manufacturer's instructions. The DNA was stored at −80°C until later analysis.

2.5 | Quantification of HTLV-1 DNA PVL

HTLV-1 PVL was quantified by real-time PCR, using primers and probes targeting the pol gene: forward primer SK110, reverse primer SK111, and HTLV-1 TaqMan probe, as described previously.[23,24] The

results were expressed as the number of copies of HTLV-1 per 10^4 PBMC.

2.6 | Statistical analysis

Mann-Whitney's U tests were used to compare age, relationship time, and PVL between the seroconcordant and serodiscordant couple groups, as well as to compare PVL between individuals with and without HAM/TSP and between individuals with and without HCV. The average PVL of seroconcordant couples was used for comparison with the PVL of infected individuals who formed discordant pairs. The categorical variables "having mother or brother with HTLV-1," HAM/TSP, ATL, race/ethnicity (based on self-determination), birthplace, HCV, history of blood transfusion, and education level were compared between groups by likelihood-ratio tests. P values < 0.05 were considered statistically significant. The above variables were obtained from the REDCap database (see "Database collection"). Variables with $P < 0.2$ in bivariate analysis were included in multivariate analysis, as well as the study group (seroconcordant and serodiscordante).

3 | RESULTS

3.1 | Study subject characteristics

The study group contained 107 individuals with stable sexual partners whose spouses were also serologically tested, resulting in a total of 46 men and 61 women with their respective partners. Among the 46 men, 30 (65.2%) of their wives were positive for HTLV-1; among the 61 women 34 (55.7%) of their husbands were positive. Taken together, they indicated a 46.9% rate of seroconcordance between the evaluated couples.

Thirty-eight concordant pairs were recorded from 30 men and 34 women and their respective partners. Among these 64 HTLV-1-positive participants, 26 men and 26 women were paired with each other. Additionally, four positive wives and eight positive husbands who were not included in the initial sample were added to the study population, resulting in a total of 38 concordant couples (Fig. 1). Forty-three discordant pairs were established formed from 16 men and 27 women with negative spouses.

The median ages of the seroconcordant and discordant couples were 51 and 48 years, respectively ($P = 0.55$), and 48 years overall. There was no statistically significant difference in the median age among men in the seroconcordant group (55 years, range 41-65), compared to 54 (46-57) years among men in the serodiscordant group ($P = 0.98$) as well as between women in the seroconcordant and serodiscordant groups, at 46 (40-57) and 45 (38-55) years, respectively ($P = 0.54$).

The relationship lengths ranged from 8 to 45 years, with a median of 25 (12-32) years for seroconcordant couples and from 5 to 56 years with a median of 16 (12-25) years for serodiscordant couples ($P = 0.15$). The relationship time for men in the seroconcordant and serodiscordant groups were 25 (12-32) and 20 (11-32) years ($P = 0.54$), respectively, and women, 25 (12-32) versus 16 (12-23) years for women ($P = 0.13$). Although previous studies have reported an association between relationship time and risk of HTLV, we did not observe an association between the relationship time and belonging to either the seroconcordant or discordant group; this lack of association persisted even after gender-based analysis. However, in multivariate analysis (which included the variables proviral load, relationship length, and mother or brother HTLV-1-positive), the relationship time was shown independently associated with seroconcordant status ($P = 0.046$).

Only 5.4% of the participants reported using condoms for sexually transmitted disease protection or prevention of pregnancy. All couples had a steady relationship for periods of several years to decades and the result does not appear to have been influenced by the use of condoms, reported by only six percent of couples. For example, only one serodiscordant wife who had been married for 56 years, and who was the mother of three seronegative sons, with low HTLV-1 PVL (6 copies), reported regular use of condoms for contraception; another serodiscordant wife, married for 31 years, with high PVL (132 copies) started using condoms after a 20-year relationship after her diagnosis, and one seroconcordant husband had started using condoms after 5 years of relationship. Drug addiction history did not influence the results because it was reported by only one individual who did not transmit the virus to his wife (data not shown).

There was no statistically significant difference between the seroconcordant and serodiscordant groups regarding the distribution of HAM/TSP, ATL, having an HTLV-1 positive mother or sibling, race, birthplace, history of blood transfusion, educational level, or hepatitis C-positive status.

4 | HTLV-1 DNA PVL

PVL is an important factor during the HTLV-1 infection; it has been associated with HAM/TSP progression, and may also be associated with transmission, regardless of the transmission path.[21] In this report, we analyzed the PVL in 56 couples, including 19 seroconcordant couples and 37 serodiscordant couples, the latter including 25 women and 12 men. Table 1 shows the comparison of the two groups regarding the analyzed variables. Nineteen seroconcordant couples were excluded from this analysis due missing data on PVL for one spouse, as well as six serodiscordant couples whose PVL results were missing from the database.

PVL quantification values ranged from undetectable to 3 020 copies/10^4 PBMC (global mean: 218 copies), with higher dispersion among seroconcordant couples, as shown in Fig. 2. PVL was higher among couples in which both partners were infected (19 couples) than among discordant pairs (37 couples); the mean and median among seroconcordant couples were 363 (SD 433) and 179 (5-597) copies/10^4 PBMC, respectively, and 145 (SD 145) and 8 (0-143) copies/10^4 PBMC, respectively, among serodiscordant couples ($P = 0.03$). Among serodiscordant couples, there was no statistically significant difference in the distribution of PVL between 12 HTLV-positive men with seronegative wives, with a mean of 142 (DP 294) and median of 17 (0-173) copies/10^4 PBMC. Among 25 HTLV-1-positive women with non-infected

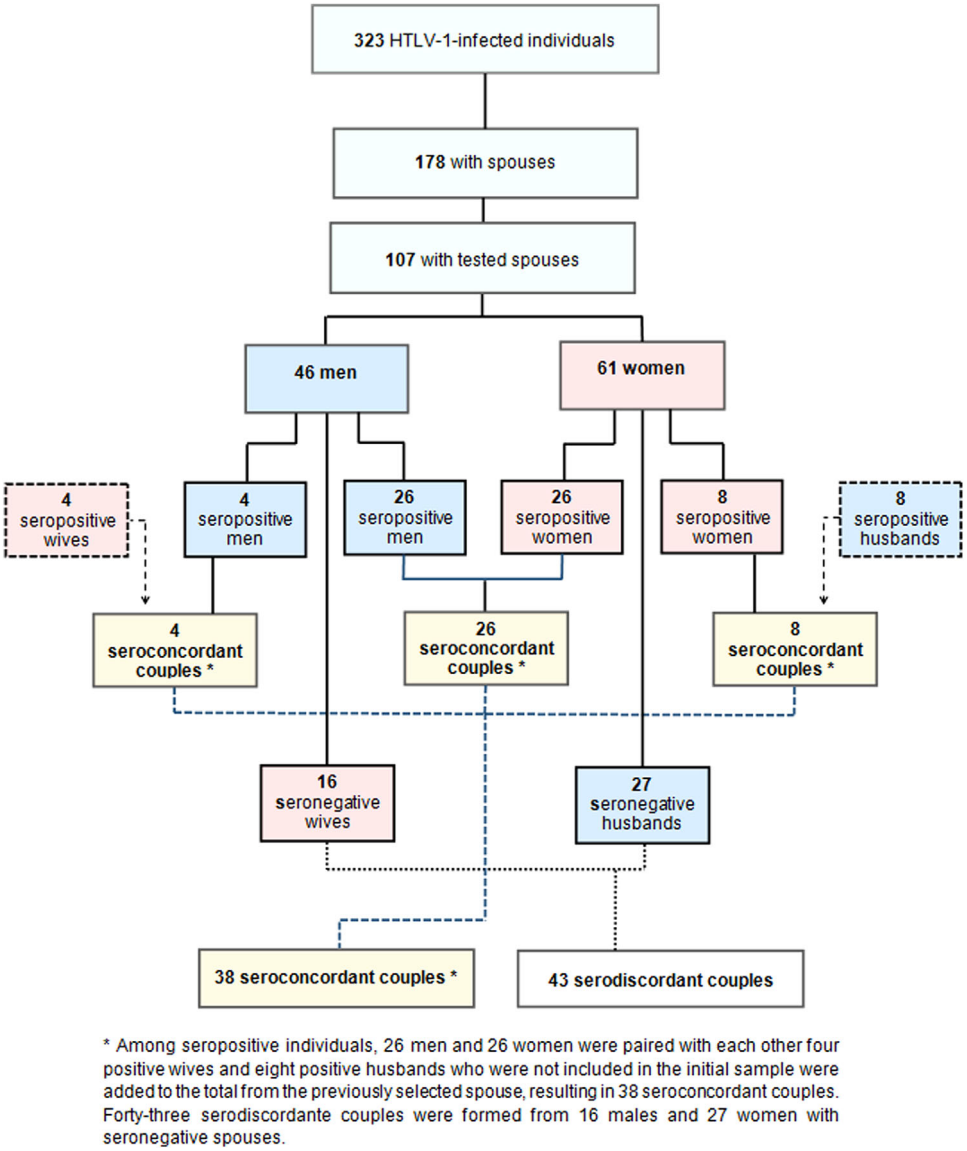

FIGURE 1 HTLV-1 Seroconcordant or serodiscordant couples established from their tested partner during follow-up from January 2013 to May 2015

husbands, the mean was 151 (DP 246), while the median was 8 (1-101) copies/10^4 PBMC ($P = 0.95$) (data not shown).

Interestingly, several seroconcordant couples showed PVL several times higher in one spouse (Fig. 3). This was observed among both husbands and wives.

5 | DISCUSSION

The results demonstrate that higher PVLs among HTLV-1-positive patients were significantly associated with couples where the viral sexual transmission was established based on seroconcordance, compared to serodiscordant couples.

Patients with either HIV ($n = 15$) or HTLV-2 ($n = 2$) co-infections were not included in this report because HIV-1 can activate HTLV-1 viral expression in co-infected patients, resulting in higher HTLV-1 PVL in these patients[25]; similarly, changes in CD4 T lymphocyte counts in co-infected patients may be associated with fluctuations in PVL,[26,27] which could lead to confounding factors. In turn, HTLV-2 usually results in lower PVL than HTLV-1 and some studies have reported no differences in transmission between genders among those with HTLV-2 infections.[5,28]

The seroconcordant rate of 46.9% among seroconcordant couples suggests the high potential for HTLV-1 transmission in this population, indicating the important role of sexual transmission. There was no significant difference in the proportion of positive partners among men and women positive for HTLV-1 (66.7% vs. 56.9%). These results are surprising since a previous study in Japan reported a lower rate of transmission from women to men, less than 0.5%.[7]

Only two previous studies in Brazil and a few others elsewhere have studied sexual transmission. The reported rates of 36% and 38% in Belem and Belo Horizonte, respectively,[19,20] were lower than that in the present study (46.9%). Those differences may be due to older age and longer relationship times among couples the São Paulo cohort. In

TABLE 1 Proviral load and demographic and epidemiological risk factors for serostatus for HTLV-1 infection in seroconcordant and serodiscordant groups

	Group		
Variables	**Seroconcordant couples (*n* = 38)***	**Serodiscordant couples (*n* = 37)***	***P* value**
Age median (years)	51 (41-60)	48 (41-56)	0.55
Male	55 (41-65)	54 (46-57)	0.98
Female	46 (40-57)	45 (38-54)	0.54
Relationship time (median, years)	25 (12-32)	16 (12-25)	0.15
Male	25 (12-32)	20 (11-32)	0.54
Female	25 (12-32)	16 (12-23)	0.13
Proviral load (copies/10^4 PBMC)	179 (5-597)	8 (0-143)	0.03
Mother or brother HTLV-1-infected person	1 (2.6%)	4 (10.8%)	0.15
HAM/TSP	13 (34.2%)	10 (27%)	0.50
ATL	1 (2.6%)	0	0.32
Race/ethnicity			0.62
White	17 (44.7%)	19 (51.4%)	
Brown	15 (39.5%)	12 (32.4%)	
Black	2 (5.3%)	4 (10.8%)	
Asian	4 (10.5%)	2 (5.4%)	
Birthplace (Region in Brazil)			0.85
Northeast	11 (28.9%)	12 (32.4%)	
Southeast	22 (57.9%)	21 (58.8%)	
South	3 (7.9%)	3 (8.1%)	
Midwest	2 (5.3%)	1 (2.7%)	
HCV positive	4 (10.5%)	2 (5.4%)	0.41
Blood transfusion (before 1993)**	3 (7.9%)	5 (13.5%)	0.43
Education time (years)			0.80
0 to 8	14 (36.9%)	15 (40.5%)	
9 to 11	18 (47.4%)	19 (51.3%)	
12 or more	6 (15.8%)	3 (8.1%)	

Data are expressed as median and interquartile ranger or absolute number and percentage.
HAM/TSP = HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis; ATL = adult T-cell leucemia; HCV = hepatitis C vírus.
*The average proviral load of 19 seroconcordant couples (38 individuals) and the proviral load of infected individuals who formed 37 discordant pairs were used for comparison between groups.
**In Brazil testing in blood donors has been mandatory since 1993.

fact, older men were more likely to transmit infections to their sexual partners,[3] probably due to an increased PVL in the index case. Age was also not relevant to the outcome of the transmission, even after adjusting for gender.

The factors associated with the risk of sexual infection included the relationship duration, indicating a possible cohort factor. Indeed, extended relationship length has been associated with the risk of infection through sexual intercourse, probably as a result of repeated exposure to an infected partner.[3,16,18] This fact could have contributed to the higher rates of sexual transmission observed in our cohort as well as in another cohort from Brazil.[19,20] In fact, in multivariate analysis the relationship time (over 20 years) was shown independently associated with seroconcordant status. This result reinforces the importance of the repeated long-term sexual exposure to an infected partner associated with the high serconcordance rate among couples in the study population.

In addition to epidemiological factors, it is also necessary to assess the possible laboratory markers for risk of transmission. Thus, the present study assessed whether PVL in peripheral blood differed significantly between HTLV-1 seroconcordant and serodiscordant couples. The seroconcordant couples had higher mean PVL compared to that of the HTLV-1-serodiscordant couples, suggesting that higher PVL were probably associated with increased genital shedding of the virus, resulting in increased risk of sexual transmission; however, this hypothesis was not tested in the current study.

The initial studies of couples showed an association between the risk of sexual transmission and the presence of high antibody titres and/or anti-Tax antibodies, probably related to higher circulating PVLs. This association was observed between HTLV-positive men in concordant pairs or those whose wives seroconverted during the study follow-up[15–17]; semi-quantitative analysis of the proviral DNA levels of HTLV-1 showed that high proviral DNA levels were more

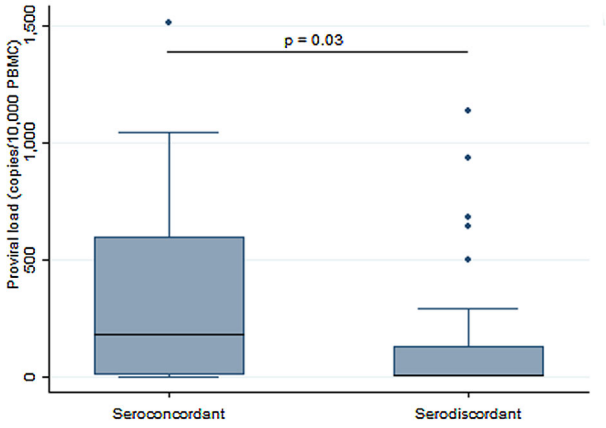

FIGURE 2 Box plot representing 38 seroconcordant and 43 serodiscordant couples and the DNA-HTLV-1 proviral load distributions for each group. The average proviral load of the concordant couples was compared to that of the infected individuals who formed discordant pairs

common among husbands positive for anti-Tax antibodies.[17] Furthermore, an average male age over 60 years was a strong predictor for infection transmission,[16] likely due to increased viremia with increasing age or the increased relationship time with the infected partner and consequently increased HTLV-1 exposure.

The roles of PVL and sexual transmission have been shown in other cohorts, despite the small sample size of HTLV-1-infected persons. A previous study using risk factors to determine the direction of transmission between concordant couples reported higher PVL to be a possible risk factor for sexual transmission from men with HTLV-1 or HTLV-2.[3] The only prospective study of couples to examine PVL found no statistically significant association between higher PVL in positive index partners and the risk of sexual transmission of HTLV, probably because of the small number of seroconversions detected.[5] Instead, they found a significant 2-$\log_{10}$ difference in the PVL of those who seroconverted, which could have been the result of the shorter duration of infection in the newly infected partner or due to the small inoculum required for sexual transmission.[5] In that same study, the data on directional transmission did not reveal a difference between genders.

Nineteen seroconcordant couples were excluded from the analysis due to a lack of information on PVL for their spouse, who were asymptomatic and did not return to perform the PVL measurement, including four patients living in other regions of the country. However, the exclusion of these data does not seem to influence the findings because even after considering only the average PVL of seroconcordant couples, the difference remained statistically significant compared to the levels in the serodiscordant group. Several seroconcordant couples showed differences in PVL several times higher in one spouse for both husbands and wives (Fig. 3). Additionally, among the seroconcordant couples, only one spouse respectively had a history of blood transfusion and HCV or only blood transfusion (the wife in couple 16 and husband in the couple 14), but none husband had a history of HCV. We have an ongoing unfinished study which shows 14% of vertical transmission rate, similar to other studies[19,29] and the rate of HTLV-1 infection in the general population in the State of São Paulo is 0.32%. Consequently, other transmission routes do not appear to have a significant influence on transmission between the studied couples. Nevertheless, the study was cross-sectional; thus, we could not determine the direction of viral transmission among couples and cannot say with certainty that the women in these couples did not acquire HTLV-1 from her partner.

Higher PVL tend to be associated with complications related to HTLV-1, including HAM/TSP, adult T-cell leukaemia-lymphoma, HTLV-1-associated infective dermatitis, and HTLV-1 uveitis.[21] Thus, differences in PVL between couples might be due to differences in the distribution of patients with these complications between the seroconcordant and serodiscordant groups. However, there was no difference in the distribution of HAM/TSP between groups (Table 1),

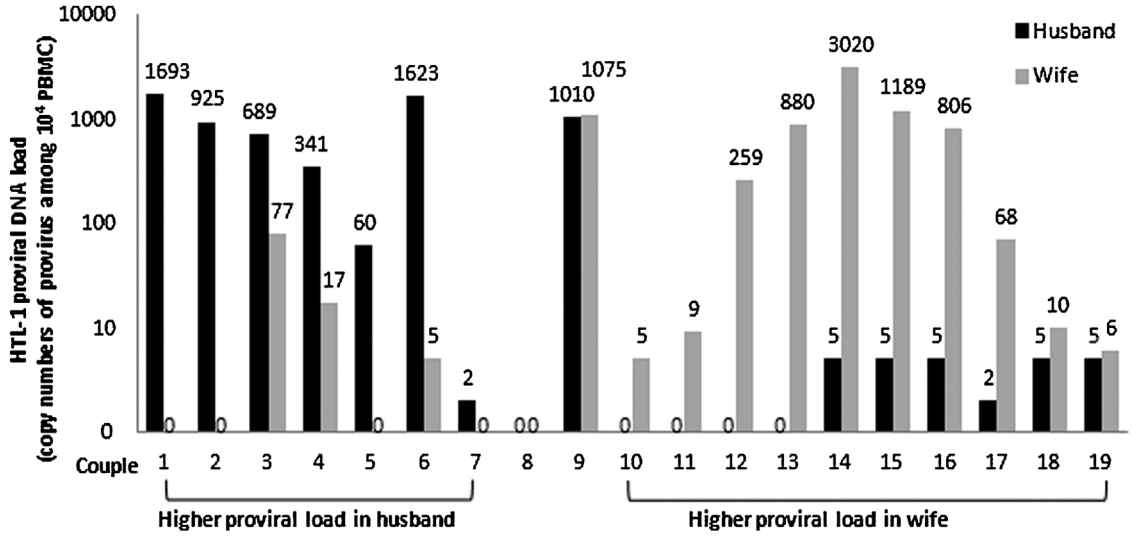

FIGURE 3 Proviral load among 19 seroconcordant couples according to gender. Undetectable proviral loads are represented by an asterisk (*)

and the higher PVL among patients with HAM/ TSP was not statistically different when compared to individuals without HAM/ TSP ($P = 0.09$) (data not shown). Similarly, the incidence of ATL, another complication associated with HTLV-1 among seroconcordant couples, did not differ statistically significantly between groups. A history to suggestive of other routes of transmission, such as blood transfusion, having a mother or siblings HTLV-1 positive, or hepatitis C positivity did not influence the results (Table 1).

HTLV-1 differs in prevalence according to the region of Brazil, probably due to the ethnic origin of the underlying population, with a higher prevalence in individuals with black skin colour or African descent.[12,13] However, there were no significant differences between both groups regarding the sociodemographic characteristics, including education level.

Our study expands existing knowledge by examining stable sexual partners with HTLV-1 infection but without HTLV-2, and including both men and women as index partners, without using subjective criteria to establish the direction in which sexual transmission may have occurred. The large number of couples with HTLV-1 of in this study, conducted in a population diverse from those in previous studies also allowed additional insights.

However, a major limitation of our study was its cross-sectional design, which prevented determination of the direction of viral transmission among couples. A prospective epidemiological study, including determination of HTLV-1 PVL with follow-up of serodiscordant couples, would provide more solid and robust data in this population. Furthermore, comparison of such data to those from similar groups in other populations could be also important to answer questions regarding differences in sexual transmission rates and the direction in which the virus is mainly transmitted. Although it appeared that most of the couples in the current study did not acquire HTLV-1 infections through other means than sexual transmission, genetic evidence of transmission between spouses by determining the molecular strain could also offer support for this conclusion.[30]

Although HTLV-1 transmission is reportedly more efficient from men to women than from women to men [7] and lower inoculum is usually required for sexual transmission,[5] there were no significant differences in the distribution of PVL among discordant couples with HTLV-positive husbands and those discordant couples with HTLV-positive wives. However, the number of couples studied does not allow us to draw firm conclusions on this lack of difference. In conclusion, the most important finding of this study was the apparent association between high circulating levels of PVL and seroconcordance between couples regardless of gender index, reinforcing that DNA HTLV-1 load could contribute to increased sexual transmission, likely associated with increased genital shedding of the virus. Furthermore, the long-term sexual exposure to an infected partner was shown independently associated with ocurrence of seroconcordant status.

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REFERENCES

1. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. *Front Microbiol* 2012;3:388.
2. Catalan-Soares BC, Proietti FA, Carneiro-Proietti ABF. Os vírus linfotrópicos de células T humanos (HTLV) na última década. *Rev Bras Epidemiol* 2001;4:81–95.
3. Kaplan JE, Khabbaz RF, Murphy EL, Hermansen S, Roberts C, Lal R, Heneine W, Wright D, Matijas L, Thomson R, Rudolph D, Switzer WM, Kleinman S, Busch M, Schreiber GB. Male-to-female transmission of human T-cell lymphotropic virus types I and II: association with viral load. The Retrovirus Epidemiology Donor Study Group. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996;12:193–201.
4. Hisada M, Maloney EM, Sawada T, Miley WJ, Palmer P, Hanchard B, Goedert JJ, Manns Al. Virus markers associated with vertical transmission of human T lymphotropic virus type 1 in Jamaica. *Clin Infect Dis* 2002;34:1551–1557.
5. Roucoux DF, Wang B, Smith D, Nass CC, Smith J, Hutching ST, Newman B, Lee TH, Chafets DM, Murphy EL, Investigators HOS. A prospective study of sexual transmission of human T lymphotropic virus (HTLV)-I and HTLV-II. *J Infect Dis* 2005;191:1490–1497.
6. Biggar RJ, Ng J, Kim N, Hisada M, Li HC, Cranston B, Maloney EM. Human leukocyte antigen concordance and the transmission risk via breast-feeding of human T cell lymphotropic virus type I. *J Infect Diseases* 2006;193:277–282.
7. Kajiyama W, Kashiwagi S, Ikematsu H, Hayashi J, Nomura H, Okochi K. Intrafamilial transmission of adult T cell leukemia virus. *J Infect Dis* 1986;154:851–857.
8. Igakura T, Stinchcombe JC, Goon PK, Taylor GP, Weber JN, Griffiths GM, Tanaka Y, Osame M, Bangham CR. Spread of HTLV-I between lymphocytes by virus-induced polarization of the cytoskeleton. *Science* 2003;299:1713–1716.
9. Iwahara Y, Takehara N, Kataoka R, Sawada T, Ohtsuki Y, Nakachi H, Maehama T, Okayama T, Miyoshi I. Transmission of HTLV-I to rabbits via semen and breast milk from seropositive healthy persons. *Int J Cancer* 1990;45:980–983.
10. Lairmore MD, Anupam R, Bowden N, Haines R, Haynes RAH, II, Ratner L, Green PL. Molecular determinants of human T-lymphotropic virus type 1 transmission and spread. *Viruses* 2011;3:1131–1165.
11. Pique C, Jones KS. Pathways of cell-cell transmission of HTLV-1. *Front Microbiol* 2012;3:378.
12. Catalan-Soares B, Carneiro-Proietti AB, Proietti FA. Heterogeneous geographic distribution of human T-cell lymphotropic viruses I and II (HTLV-I/II): serological screening prevalence rates in blood donors from large urban areas in Brazil. *Cadernos de Saude Publica* 2005;21:926–931.
13. Carneiro-Proietti AB, Sabino EC, Leao S, Salles NA, Loureiro P, Sarr M, Wright D, Busch M, Proietti FA, Murphy EL. Human T lymphotropic vírus type 1 and type 2 seroprevalence, incidence, and residual transfusion risk among blood donors in Brazil during 2007–2009. *AIDS Res Hum Retroviruses* 2012;28:1265–1272.
14. Brasil, Departamento de Estatística IBGE, *IBGE: Censo demográfico 2010*. Brasilia, Brasil 2015.
15. Chen YM, Okayama A, Lee TH, Tachibana N, Mueller N, Essex M. Sexual transmission of human T-cell leukemia virus type I associated with the presence of anti-Tax antibody. *Proc Natl Acad Sci USA* 1991;88:1182–1186.
16. Stuver SO, Tachibana N, Okayama A, Shioiri S, Tsunetoshi Y, Tsuda K, Mueller NE. Heterosexual transmission of human T cell leukemia/ lymphoma virus type I among married couples in southwestern Japan: an initial report from the Miyazaki Cohort Study. *J Infect Dis* 1993; 167:57–65.

17. Shioiri S, Stuver SO, Okayama A, Murai K, Shima T, Tachibana N, Tsubouchi H, Essex M, Mueller N. Intrafamilial transmission of HTLV-I and its association with anti-Tax antibody in an endemic population in Japan. *Int J Cancer* 1998;75:15–18.
18. Sullivan MT, Williams AE, Fang CT, Notari EP, Poiesz BJ, Ehrlich GD. Human T-lymphotropic virus (HTLV) types I and II infection in sexual contacts and family members of blood donors who are seropositive for HTLV type I or II. American Red Cross HTLV-I/II Collaborative Study Group. *Transfusion* 1993;33:585–590.
19. Catalan-Soares B, Carneiro-Proietti AB, Proietti FA. Human T-cell lymphotropic virus in family members of seropositive blood donors: silent dissemination. *Rev Panam Salud Publica* 2004;16:387–394.
20. da Costa CA, Furtado KC, Ferreira LS, Almeida DS, Linhares AC, Ishak R, Vallinoto AC, de Lemos JA, Martins LC, Ishikawa EA, de Sousa RC, de Sousa MS. Familial transmission of human T-cell lymphotrophic virus: silent dissemination of an emerging but neglected infection. *PLoS Negl Trop Dis* 2013;7:e2272.
21. Paiva A, Casseb J. Sexual transmission of human T-cell lymphotropic virus type 1. *Rev Soc Bras Med Trop* 2014;47:265–274.
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–381.
23. Dehee A, Cesaire R, Desire N, Lezin A, Bourdonne O, Bera O, Plumelle Y, Smadja D, Nicolas JC. Quantitation of HTLV-I proviral load by a TaqMan real-time PCR assay.. *J Virol Methods* 2002;102:37–51.
24. Montanheiro PA, Oliveira AC, Posada-Vergara MP, Milagres AC, Tauil C, Marchiori PE, Duarte AJ, Casseb J. Human T-cell lymphotropic virus type I (HTLV-I) proviral DNA viral load among asymptomatic patients and patients with HTLV-I-associated myelopathy/tropical spastic paraparesis. *Braz J Med Biol Res* 2005;38:1643–1647.
25. Casseb J, Penalva De Oliveira AC, Posada Vergara MP, Montanheiro P, Bonasser F, Ferreira CM, Smid J, Duarte AJ. Presence of tropical spastic paraparesis/human T-cell lymphotropic virus type 1-associated myelopathy (TSP/HAM)-like among HIV-1-infected patients. *J Med Virol* 2008;80:392–398.
26. Machuca A, Soriano V. In vivo fluctuation of HTLV-I and HTLV-II proviral load in patients receiving antiretroviral drugs. *J Acquir Immune Defic Syndr* 2000;24:189–193.
27. Machuca A, Rodés B, Soriano V. The effect of antiretroviral therapy on HTLV infection. *Virus Res* 2001;78:93–100.
28. Ishak R, Harrington WJ, Jr, Azevedo VN, Eiraku N, Ishak MO, Guerreiro JF, Santos SB, Kubo T, Monken C, Alexander S, Hall WH. Identification of human T cell lymphotropic virus type IIa infection in the Kayapo, an indigenous population of Brazil. *AIDS Res Hum Retroviruses* 1995;11:813–821.
29. Percher F, Jeannin P, Martin-Latil S, Gessain A, Afonso PV, Vidy-Roche A, Ceccaldi PE. Mother-to-Child transmission of HTLV-1 epidemiological aspects, mechanisms and determinants of mother-to-Child transmission. *Viruses* 2016;8:40.
30. Iga M, Okayama A, Stuver S, Matsuoka M, Mueller N, Aoki M, Mitsuya H, Tachibana N, Tsubouchi H. Genetic evidence of transmission of human T cell lymphotropic virus type 1 between spouses. *J Infect Dis* 2002;185:691–695.

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