MAJOR ARTICLE

A Prospective Study of Sexual Transmission of Human T Lymphotropic Virus (HTLV)–I and HTLV-II

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Background. Cross-sectional studies support sexual transmission of human T lymphotropic virus (HTLV)–I/II; however, prospective incidence data, particularly for HTLV-II, are limited.

Methods. A cohort of 85 HTLV-positive (30 with HTLV-I and 55 with HTLV-II) blood donors and their stable (⩾6 months) heterosexual sex partners were followed biannually over the course of a 10-year period.

Results. Four of 85 initially seronegative sex partners of HTLV-I and -II carriers seroconverted, for an incidence rate (IR) of 0.6 transmissions/100 person-years (py) (95% confidence interval [CI], 0.2–1.6). This includes 2 HTLV-I transmissions/219 py (IR, 0.9 transmissions/100 py [95% CI, 0.1–3.3]) and 2 HTLV-II transmissions/411 py (IR, 0.5 transmissions/100 py [95% CI, 0.06–1.8]), with no significant difference by HTLV type. There were 2 male-to-female (IR, 1.2 transmissions/100 py [95% CI, 0.1–4.3]) and 2 female-to-male (IR, 0.4 transmissions/100 py [95% CI, 0.05–1.6) transmissions. HTLV-I or -II proviral load was 2 $\log_{10}$ lower in newly infected partners than in index positive partners who transmitted HTLV ($P = .007$).

Conclusions. The incidence of sexual transmission of HTLV-II may be similar to that of HTLV-I, and female-to-male transmission may play a more important role than previously thought. HTLV-I and -II proviral load may be lower in sexually acquired infection, because of a small infectious dose.

Human T lymphotropic virus (HTLV)–I and HTLV-II were the first retroviruses to be identified in humans [1, 2]. HTLV-I is associated with adult T cell leukemia/lymphoma [3, 4] and HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [5, 6]. There have been few studies of HTLV-II disease outcomes, but recent evidence suggests that HTLV-II infection is also linked with HAM/TSP [6]

HTLV-I is found primarily in persons originating from or having sexual contact with individuals from endemic areas, such as Japan or the Caribbean basin. Sexual transmission of HTLV-I has been widely reported in these and other populations, including in the United States and west Africa [7–10]. Some research indicates that HTLV-I may be transmitted more efficiently from males to females than vice versa [7, 11]. In the United States, HTLV-II is found largely among injection drug users (IDUs) and their sex partners [12, 13]. HTLV-II has also been found to be endemic among several native Indian tribes in North, Central, and South America [14–16] and in some pygmy populations in central Africa [17, 18].

Epidemiological data has established that HTLV-II shares similar routes of transmission with HTLV-I; however, sexual transmission of HTLV-II has been less well studied. Several cross-sectional studies have iden-

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tified sexual contact as an important risk factor for HTLV-II infection, particularly among indigenous populations in whom injection-drug use is rare, thus pointing strongly to evidence of sexual transmission [19–22]. Because of a lack of long-term follow-up of these non-IDU populations, an incidence rate (IR) of sexual transmission of HTLV-II remains unknown. For HTLV-I and -II, male-to-female transmission has been associated with a longer length of relationship, more episodes of unprotected sex, and higher proviral load [11]. However, the behavioral risk factors that increase the efficiency of sexual transmission of HTLV-II are still poorly characterized.

Most longitudinal studies of sexual transmission of HTLV-I have focused on high-risk populations, such as prostitutes or individuals attending sexually transmitted disease (STD) clinics, and, to date, there have been no published prospective studies on sexual transmission of HTLV-II. Information regarding incidence and behavioral risk factors would be useful in counseling HTLV-positive individuals and their sex partners on transmission and prevention. We now report on data from a prospective analysis of sexual transmission in a cohort of HTLV-I– and -II–positive blood donors and their sex partners, who were enrolled in the HTLV Outcomes Study (HOST), which was formerly known as the Retrovirus Epidemiology Donor Study (REDS) HTLV Cohort.

SUBJECTS AND METHODS

Study design and population. The study design included a prospective cohort of HTLV-I/II–positive blood donors and their seronegative sex partners, with the main objective of evaluating incidence and risk factors associated with sexual transmission. The Committee on Human Research at the University of California, San Francisco, approved the study protocol, and informed, written consent was obtained from all subjects. The details of the screening and enrollment criteria of HTLV-positive blood donors and their sex partners have been described elsewhere [11, 23]. Briefly, 130 HTLV-positive blood donors and their stable ($\geqslant$6 months) sex partners were enrolled in the sex partner substudy of HOST at baseline (1990–1992); subjects were recruited from 5 participating REDS blood centers: American Red Cross Blood Services centers, in Baltimore, Detroit, and Los Angeles; Blood Centers of the Pacific, in San Francisco; and the Oklahoma Blood Institute, in Oklahoma City. Among 130 couples enrolled at baseline, 32 partners tested positive for HTLV-I or -II [11]. We have continued to prospectively follow the remaining 98 serodiscordant couples, from visits 1 to 6 (1990–2003).

Subjects who met the following inclusion criteria were included in this analysis: positive with known HTLV type, HTLV-negative heterosexual partner at baseline, and completion of visit-1 interview and phlebotomy. Of the 98 couples examined, 85 met the inclusion criteria. Reasons for exclusion included the following: unknown HTLV type of index positive partner ($n = 1$), lack of baseline interview ($n = 6$), false-positive HTLV test result of donor ($n = 5$), and same-sex couple ($n = 1$).

At biannual visits, the sex partners of index positive partners were tested for HTLV-I/II antibodies, and index positive partners were interviewed about their sexual history, including frequency of condom use and whether they had remained monogamous with their sex partners since the previous visit. Corresponding data were obtained from sex partners at selected visits.

Laboratory methods. HTLV seropositivity of the index positive partners had been previously established by testing serum for the presence of HTLV antibodies, by use of an ELISA; positive ELISA results were confirmed by use of Western blot and radioimmunoprecipitation assay (RIPA), as described elsewhere [24]. Specimens demonstrating reactivity to *gag* p24 and *env* gp46 or gp61/68, by Western blot or RIPA, were considered to be positive for HTLV-I/II. HTLV-I and HTLV-II subtypes were distinguished either by polymerase chain reaction (PCR) or by type-specific serologic testing [24]. Partners were tested by use of the same methods, and the laboratory technicians were blinded to the identity of the donors of the specimens tested.

For the quantitation of HTLV proviral DNA, serum and peripheral blood mononuclear cell (PBMC) samples were stored at −70°C until being used. PBMCs were digested in a PCR solution with proteinase K. Quantitation of HTLV-I and HTLV-II proviral DNA was performed by use of real-time PCR, as described elsewhere [25]. The use of a common primer pair from a highly conserved sequence of the HTLV-I and HTLV-II *tax* regions assured that quantitation of proviral load was comparable for both viruses. To determine the proviral load of each sample, the number of copies of virus was divided by the cellular input, as established by the DQ-α copy number. The lower limit of detection of the assay was 1 copy/10^5 cells.

Statistical analysis. To estimate IRs of HTLV-I and HTLV-II, person-years (py) of observation were computed individually for each partner as the time between baseline and the most recent visit, with the exception of the seroconverters, in whom py were computed as the time between baseline and the midpoint between the last seronegative visit and the first seropositive visit. The IR was then calculated as the number of seroconversions divided by py of observation, with 95% confidence intervals (CIs) derived from the binomial distribution. Subset analyses by HTLV-I versus HTLV-II and by sex attributed both the seroconverters and py to each subset. *P* values were determined for comparisons of proviral loads of subjects who transmitted HTLV-I or HTLV-II with those of subjects who did not transmit HTLV-I or HTLV-II and were calculated by use of pooled *t* tests. Paired *t* tests were used to compare the proviral loads between index positive and seroconverting partners. Data

analysis was performed by use of SAS statistical software (version 8.12; SAS Institute).

RESULTS

Characteristics of the study population are described in table 1. Our analysis included 85 heterosexual couples (30 HTLV-I–positive donors [35%] and 55 HTLV-II–positive [65%] donors and 85 seronegative sex partners). Female HTLV-I/II–positive donors outnumbered males by greater than 2 to 1. At baseline, enrolled subjects ranged in age from 21 to 72 years old; however, most (>80%) were between 30 and 50 years old.

Four new cases of HTLV infection were detected among previously seronegative sex partners, including 2 cases of sexual transmission of HTLV-I and 2 cases of sexual transmission of HTLV-II. An equal number of transmissions occurred in either direction, with 1 case each of male-to-female transmission and female-to-male transmission, for both HTLV-I and HTLV-II. All 4 index-partner pairs were determined to be seroconcordant by HTLV type, by use of PCR. Table 2 summarizes IRs of sexual transmission of HTLV-I and HTLV-II. The IR of sexual transmission of HTLV-I was higher than that of sexual transmission of HTLV-II, but the difference was not statistically significant. Similarly, for directional transmission, the incidence of male-to-female transmission was higher than that of female-to-male transmission; however, the difference was not significant.

Data on the couples in which transmission occurred are shown in table 3. Risk factors for sexual transmission of HTLV (other than heterosexual contact with an enrolled index positive partner) were examined and ruled out. All 4 sex partners denied any history of injection-drug use, blood transfusion, tattooing, or other parenteral exposure. Furthermore, all sex partners reported being monogamous with their index positive partners during the observation period, whereas 3 of the 4 index positive partners reported the same. The median length of relationship reported by couples in which transmission did not occur was 72 months (range, 6–516 months). Similarly, couples A, B, C, and D reported lengths of relationships of 78, 120, 36, and 24 months, respectively (median, 57 months). Because so few seroconversions were observed among serodiscordant couples, it was not possible to formally evaluate the factors that differed between couples in which transmission occurred and couples in which transmission did not occur.

The 4 couples stated that the use of condoms during follow-up was rare. At baseline, the vast majority of all couples (>80%) reported never or rarely using condoms during follow-up, whereas very few couples (<5%) reported usually or always using condoms. Visit-2 data showed that, in couples still together, there was a small increase in the frequency of condom use (data not shown). At visit 2, ~12% of couples reported usually or always using condoms, which was increased slightly from 5% at visit 1. Female seronegative partners were more likely to report an increase in condom use between visits 1 and 2 than were male seronegative partners (increase of 8%–27% for female partners vs. 3%–9% for male partners). At baseline, length of relationship was examined for couples in which transmission occurred and for couples in which transmission did not occur.

Analysis of quantitative proviral load showed a higher proviral load in index positive partners who transmitted HTLV-I or HTLV-II than in those who did not transmit HTLV-I or HTLV-II, although, due to the small number of seroconversions detected, the difference was not statistically significant. For HTLV-I, the mean $\log_{10}$ copy numbers were 4.46 for index positive partners who transmitted HTLV ($n = 2$) and 2.91 for index positive partners who did not transmit HTLV ($n = 28$) ($P = .19$); both measures are per million nucleated cells. For HTLV-II, the mean $\log_{10}$ copy numbers were 3.20 for index positive partners who transmitted HTLV ($n = 2$) and 1.59 for index positive partners who did not transmit HTLV ($n = 53$) ($P = .11$). In a comparison of the HTLV proviral loads within couples in which transmission occurred, a significant difference was seen between those of the index positive partners and those of the newly infected partners. For HTLV-I and HTLV-II transmissions combined, index positive partners had a mean proviral load 2 $\log_{10}$ higher than that in their newly infected partners ($P = .007$) (figure 1). Because of small numbers, this difference was not significant when examined separately by HTLV type.

DISCUSSION

The reporting of data on the incidence of sexual transmission of HTLV-I varies among different populations studied. The IR of 0.9 transmissions/100 py observed in the present study was lower than that reported in the Miyazaki study (2.5 transmissions/100 py), which followed a similar cohort of serodiscordant couples in Japan; however, the 95% CIs around these 2 IRs overlap [26]. The lower rate in the present study may be explained either by chance or by the relative makeup of the 2 cohorts. Compared with the Miyazaki cohort, which included 100 HTLV-I–serodiscordant couples, our cohort included a combination of 30 HTLV-I– and 55 HTLV-II–serodiscordant couples. In addition, couples in the Miyazaki cohort were, on average, much older (50–70 vs. 30–50 years of age) and had been in their relationships much longer (>360 vs. 72 months), compared with the couples in the present study [7]. Several studies have suggested a correlation between older age and risk of infection, particularly for women, whose increased susceptibility may be attributed to a thinning of the vaginal epithelium after menopause [7, 27] and exposure to an increasingly infectious male partner. Stuver et al. have documented a 12-fold higher risk of infection in wives of seropositive husbands >60 years old, possibly because of increased viremia with age [7].

Other prospective studies that examined sexual transmission of HTLV-I focused primarily on high-risk populations, such as

Table 1. Baseline characteristics and risk factors of the study population.

Characteristic	Index positive donor infected with		Initially negative sex partner (n = 85)
	HTLV-I (n = 30)	HTLV-II (n = 55)	
Sex			
Male	7 (23)	17 (31)	61 (72)
Female	23 (77)	38 (69)	24 (28)
Age, years			
<30	3 (10)	6 (11)	10 (12)
30–39	7 (23)	26 (47)	33 (39)
40–49	18 (60)	19 (35)	18 (21)
50–59	0 (0)	2 (4)	12 (14)
>60	2 (7)	2 (4)	4 (5)
Missing	0 (0)	0 (0)	8 (9)
Race/ethnicity			
White	16 (54)	23 (42)	45 (53)
Black	6 (20)	11 (20)	17 (20)
Hispanic	1 (3)	16 (29)	13 (15)
Asian/other	7 (23)	5 (9)	10 (12)
Education			
High school or less	9 (30)	23 (42)	35 (41)
Some college	13 (43)	28 (51)	37 (44)
College graduate	8 (27)	4 (7)	13 (15)
Annual income			
<$30,000	4 (13)	16 (29)	25 (29)
$30,000–$50,000	13 (43)	17 (31)	18 (21)
>$50,000	13 (43)	22 (40)	42 (49)
Blood center study site			
Baltimore/Washington, DC	6 (20)	6 (11)	12 (14)
Detroit	7 (23)	7 (13)	14 (16)
Oklahoma City	4 (13)	6 (11)	10 (12)
San Francisco	7 (23)	12 (22)	19 (22)
Los Angeles	6 (20)	24 (44)	30 (35)
Frequency of condom use with partner			
Never	11 (37)	37 (67)	46 (54)
Rarely	8 (27)	11 (20)	25 (29)
Sometimes	9 (30)	5 (9)	10 (12)
Usually	2 (7)	2 (4)	3 (4)
Always	0 (0)	0 (0)	1 (1)
Lifetime injection-drug use			
Yes	0 (0)	16 (29)	7 (8)
No	30 (100)	39 (71)	78 (92)
Lifetime sex with an IDU			
Yes or likely	2 (7)	33 (60)	20 (24)
No or unlikely	25 (83)	20 (36)	53 (62)
Don't know	3 (10)	2 (4)	12 (14)
Lifetime female partners, for men[a]			
1 partner[c]	1 (14)	1 (6)	4 (7)
2–10 partners	4 (57)	6 (35)	22 (36)
>10 partners	2 (29)	10 (59)	35 (57)
Lifetime male partners, for women[b]			
1 partner[c]	1 (4)	0 (0)	5 (21)
2–10 partners	22 (96)	26 (68)	16 (67)
>10 partners	0 (0)	12 (32)	3 (12)
Sex with a prostitute			
Yes	3 (10)	9 (16)	32 (38)
No	27 (90)	46 (84)	52 (61)
History of STDs			
Yes	3 (10)	3 (5)	9 (11)
No	27 (90)	52 (95)	76 (89)

NOTE. Data are no. (%) of subjects. Because of rounding, some percentages may not total 100%. HTLV, human T lymphotropic virus; IDU, injection drug user; STD, sexually transmitted disease.

[a] Percentages are based on 7 HTLV-I–positive, 17 HTLV-II–positive, and 61 HTLV-negative men.

[b] Percentages are based on 23 HTLV-I–positive, 38 HTLV-II–positive, and 24 HTLV-negative women.

[c] Only lifetime sex partner was enrolled study partner.

Table 2. Incidence rates (IRs) of sexual transmission of human T lymphotropic virus (HTLV)–I and HTLV-II.

Variable	Variable transmissions/py (IR/100 py [95% CI])
HTLV type	
HTLV-I	2/219 (0.9 [0.1–3.3])
HTLV-II	2/411 (0.5 [0.06–1.8])
Direction of transmission	
Male to female	2/169 (1.2 [0.1–4.3])
Female to male	2/461 (0.4 [0.05–1.6])
Overall	4/631[a] (0.6 [0.2–1.6])

NOTE. Because they had 0 person-years (py) of follow-up, 7 couples were excluded from calculation of IR. CI, confidence interval.

[a] Because of rounding error, the 2 entries do not exactly sum to this number.

prostitutes or individuals attending STD clinics, rather than on serodiscordant couples. A study that followed prostitutes over the course of a 2-year period in Japan revealed an IR of 0.8 transmissions/py for sexual transmission of HTLV-I [28]. Similarly, a study of individuals attending STD clinics in Jamaica reported an overall IR of 0.9 transmissions/100 py [29]. These IRs are comparable to those observed in our analysis, despite differences in the type of sexual exposure.

Several cross-sectional studies support sexual transmission of HTLV-II, yet incidence data are lacking. The high seroprevalences among indigenous tribes in the Amazon region of Brazil are some of the most compelling evidence of sexual transmission, since injection-drug use is virtually absent in these isolated communities and transmission is presumed to occur primarily through sexual contact and breast-feeding. Sexual transmission is further supported by studies showing a gradual increase in HTLV-II seropositivity with age, perhaps as a result of exposure to more sex partners throughout life [19, 30]. Moreover, a survey of Kayapo Indian communities found similar seroprevalences among men and women (31.4% vs. 34.2%; $P < .05$), suggesting that sexual transmission may be equally efficient between the sexes [30]. In the present study, the incidence of sexual transmission of HTLV-II was comparable to that of sexual transmission of HTLV-I (CIs overlap) and, overall, was similar to IRs of sexual transmission of HTLV-I reported elsewhere.

Although the overall IR of male-to-female transmission in the present study was higher than that of female-to-male transmission, the difference was not statistically significant. Since transmission of HTLV-I is cell associated, male-to-female transmission is believed to occur more efficiently via infected cells present in semen [31, 32]. Female-to-male transmission, on the other hand, is postulated to occur through injured mucous membranes resulting from penile sores or ulcers [8]. Neither of the 2 men who seroconverted in the present study reported a history of penile sores, ulcers, or urethritis. It is possible that these conditions were underreported or that female-to-male transmission of HTLV may be facilitated by other factors related to susceptibility. For HIV, another sexually acquired retroviral infection, lack of circumcision in males was identified as a risk factor for infection [33]. One of the 2 males who seroconverted in the present study had been circumcised.

Data on directional transmission were consistent with rates reported in a study of individuals attending STD clinics in Jamaica, which also found similar IRs of HTLV-I between men and women [29]. In contrast, our findings on directional transmission were much lower than rates among couples in the Miyazaki cohort (4.9 transmissions/100 py for male-to-female and 1.2 transmissions/100 py for female-to-male transmission) [26]. However, this discrepancy may be the result of differences in age, length of relationship, or contraceptive practices of the 2 populations studied. Clearly, if age and length of relationship are major risk factors for infection, then we may see an increasing number of seroconversions as the median age of our cohort increases.

Previous studies have found a link between length of relationship and risk of HTLV infection, perhaps as a result of accumulated exposure to an infected partner [7, 11, 12]. Such an association was not seen in the present study and may have been missed because of the small number of seroconversions observed. Moreover, although couples reported lengths of relationships ranging from 6 to 516 months, the distribution was skewed, with most couples reporting a length of relationship of <100 months. Therefore, the length of relationship may have been too short or too homogeneous to observe any such correlation.

Although most couples in the present study did not report regularly using condoms, no transmissions were observed among couples that did, which provides indirect support for the current US Public Health Service recommendation that using condoms may be protective against HTLV infection. Counseling couples at baseline appeared to have a small positive effect on increasing condom use. Women were more likely to increase condom use than were men, perhaps because of a perceived higher risk of infection in women, compared with that in their male counterparts. Since our present findings indicate that men and women may be at equal risk for acquiring HTLV by sexual contact, future counseling may need to take this into account.

Previous studies have found higher proviral load to be a possible risk factor for sexual transmission of HTLV-I/II [7, 11]. We also observed higher proviral loads in index positive partners who transmitted HTLV than in index positive partners who did not transmit HTLV, although, because of the limited number of seroconversions detected, this association was not significant in our cohort. Instead, a significant 2-$\log_{10}$ difference in proviral load was seen between index positive partners and their newly infected partners. The lower proviral load in newly infected partners may be reflective of a "dose effect," in which

Table 3. Characteristics of couples with a seroconverting partner.

Seroconcordant couples	Seroconversion detected	HTLV type	Age, years	Sex	Race/ ethnicity	Condom use	History of STD	History of penile sores, ulcers, or urethritis (men)	Circumcision (men)	Menopause (women)
Couple A										
Index positive partner		HTLV-II	35	Female	Hispanic	Rarely	Yes (gonorrhea)[a]			…
Sex partner	Visit 2	HTLV-II	28	Male	White		No	No	Yes	
Couple B										
Index positive partner		HTLV-I	41	Female	Japanese	Rarely	No			…
Sex partner	Visit 3	HTLV-I	41	Male	Japanese		No	No	No	
Couple C										
Index positive partner		HTLV-I	56	Male	Black	Never	No	…	…	
Sex partner	Visit 4	HTLV-I	53	Female	Black		No			Yes
Couple D										
Index positive partner		HTLV-II	39	Male	Hispanic	Never	Yes (gonorrhea)[a]	…	…	
Sex partner	Visit 6	HTLV-II	40	Female	Hispanic		No			No

NOTE. HTLV, human T lymphotropic virus; STD, sexually transmitted disease.

[a] Before relationship with enrolled sex partner.

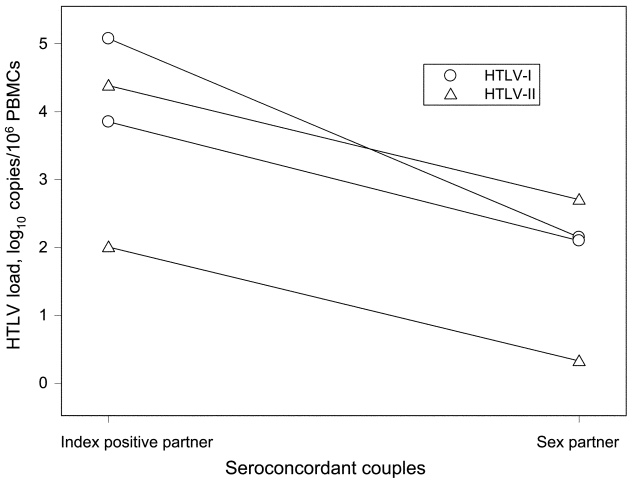

Figure 1. Proviral load in human T lymphotropic virus (HTLV)–I– and HTLV-II–concordant couples. Index positive partners had, on average, a 2 $\log_{10}$ higher proviral load than did their newly infected partners ($P = .007$, paired t test). PBMCs, peripheral blood mononuclear cells.

exposure to a small quantity of sexually acquired inoculum influences the number or size of lymphocyte clones with integrated HTLV provirus [34]. Alternatively, the lower proviral load could be due to a shorter duration of infection in newly infected partners, although HTLV proviral load has been found to be relatively stable over the course of years of infection. Studies examining the relationship between modes of transmission and proviral load are lacking, but a recent analysis of baseline samples from the larger HOST cohort showed that, for HTLV-II, female sex ($P = .01$) and more lifetime sex partners ($P = .06$) were associated with a lower proviral load, even after adjustment for age, injection-drug use, and sex with an IDU, suggesting that sexually acquired infection may result in a lower proviral load [35].

Some shortcomings must be considered when interpreting the IRs and findings of the present study. The study population exclusively comprised blood donors, who, by self-selection and health deferrals, were not representative of the general population. In addition, the number of seroconversions and py were both modest for the low IRs observed. Therefore, IRs in the present study should be interpreted in the context of their CIs. Finally, the default rate must be considered, since ~45% of the couples were lost to follow-up between visits 1 and 6. Given the small number of couples included, even a few seroconversions among couples lost to follow-up could alter IRs considerably.

In conclusion, sexual transmission continues to be an important route of infection for HTLV-I, and the present study has provided incidence data on how often this may be occurring in stable heterosexual relationships. The present study has also offered the first prospective data that support the notion that sexual transmission of HTLV-II is occurring at a frequency similar to that of HTLV-I. Furthermore, our data on directional transmission suggest that female-to-male transmission may play a more important role than previously thought, and, finally, low proviral load in newly infected partners may indicate that sexually acquired infection is associated with a small infectious dose and a persistently lower proviral load. Future studies are needed to confirm these findings and to better understand the factors that contribute to the risk of sexually acquired HTLV infection, particularly in female-to-male transmission, for which the pathophysiologic mechanism remains elusive.

THE HTLV OUTCOMES STUDY (HOST)

HOST is presently the responsibility of the following persons:

Study headquarters—University of California, San Francisco, San Francisco: E. L. Murphy (principal investigator) and J. Engstrom.

Blood centers—American Red Cross Blood Services Greater Chesapeake and Potomac Region, Baltimore, Maryland: C. C. Nass and J. Gibble; American Red Cross Blood Services Southeastern Michigan Region, Detroit: B. Newman; American Red Cross Blood Services Southern California Region, Los Angeles: G. Garratty, S. Hutching, and A. Ziman; Blood Centers of the Pacific, San Francisco, California: M. P. Busch; and Oklahoma Blood Institute, Oklahoma City: J. W. Smith and E. Moore.

Medical coordinating center—Westat, Rockville, Maryland: G. B. Schreiber, D. Ameti, and B. Wang.

Central laboratory: Blood Systems Research Institute, San Francisco, California: M. P. Busch and L. H. Tobler.

Diagnostic review panel—E. L. Murphy, R. Sacher, and J. Fridey.

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