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HIV Infection among Female Partners of Seropositive Men in Brazil

Mark D. C. Guimarães,[1,2] Alvaro Muñoz,[3] Cynthia Boschi-Pinto,[2] and Euclides A. Castilho[2]
for the Rio de Janeiro Heterosexual Study Group[4]

A heterosexual partner study was carried out in Rio de Janeiro, Brazil, from August 1990 to December 1991. The main objectives were to determine the rate of male-to-female transmission of human immunodeficiency virus (HIV) and to determine risk factors. Male index cases were recruited according to the following criteria: 1) confirmed HIV positivity, 2) 18 years old or older; 3) heterosexual contact within the past year. Only female partners who reported not to have other risk factors but to have had sexual contact with the index case were invited to participate. Couples were interviewed for risk factors and had blood collected for laboratory studies. The overall prevalence of HIV infection was 45 percent among 204 female partners in the study. Using logistic regression, the authors found the following factors to be independently ($p < 0.05$) associated with HIV infection: 1) anal sex (odds ratio (OR) = 3.74, 95% confidence interval (CI) 1.87–7.45); 2) condom use during vaginal sex sometimes (OR = 1.45, 95% CI 1.07–1.96), rarely (OR = 2.10, 95% CI 1.15–3.83), or never (OR = 3.04, 95% CI 1.23–7.50) as compared with always; 3) frequency of sexual contacts in the year prior to interview (100+) (OR = 2.00, 95% CI 1.03–3.91); and 4) oral contraceptive use (OR = 2.04, 95% CI 0.97–4.29). In addition to a borderline significance of oral contraceptive use, there was a strong suggestion of an interaction with history of sexually transmitted diseases. *Am J Epidemiol* 1995;142:538–47.

developing countries; HIV infections; risk factors

The acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV) has become a major public health problem in several countries around the world (1). Sexual transmission is the major mode of spread of HIV infection, with close to 80 percent of all AIDS cases worldwide attributed to either homosexual or heterosexual contact (2–7). In Brazil, a steady change among the risk categories has been observed in more recent periods with a worrisome increase in the heterosexual group. The proportion of new cases attributed to homosexual transmission dropped from 47 percent from the initial period of the epidemic (1980–1986) to 24 percent by 1991. The bisexual transmission group changed from 22 percent to 10 percent, and the heterosexual category increased from 5 percent to 20 percent. The male:female ratio has dropped significantly from 28:1 in 1985 to 10:1 in 1987, 8:1 in 1989, and 5:1 in 1992 (8). Finally, the proportion of newly diagnosed adult female AIDS cases has increased from 4 percent in the period 1980–1986 to 11 percent in 1988 and 15 percent in 1991–1992. The increase in the heterosexual transmission group can also be seen when stratifying the AIDS cases by sex. Among women, the proportion of new cases attributed to heterosexual transmission increased from 32 percent in the period 1980–1986 to 38 percent in 1989 and 51 percent in 1991–1992, while among men these increases were 4 percent, 12 percent, and 16 percent, respectively (8).

Risk factors for male-to-female HIV transmission have been analyzed in several published papers (9–18). Examples of factors related to the male index case and found to be statistically associated with HIV infection are 1) clinical stage of the infection; 2) immunologic and/or virologic parameters (e.g., p24 antigenemia and low T helper cell counts); 3) the risk group; and 4) history and/or diagnosis of sexually transmitted diseases (STDs), particularly the presence of genital ulcerative lesions. Among the factors found to be associated with increased susceptibility of the noninfected female partners are 1) history and/or diagnosis of STDs, also with special reference to genital ulcerative lesions, which may disrupt vaginal, anal, or penile mucosa cells; 2) estrogen use as an oral contraceptive; 3) parity; and 4) history of pregnancy and abortions. Behavior-related factors found to be associated with HIV transmission include 1) anal sex, 2) lack of condom use during vaginal sex, 3) number of partners, and 4) frequency of sexual contacts.

Although some consistency has been found with regard to these factors, it is not clear whether they similarly increase the probability of acquiring HIV through heterosexual contact in different geographic regions. To date, no analytical heterosexual transmission study has been carried out in Brazil, where heterosexual spread of HIV infection is of increasing concern. The present multicenter study was aimed at assessing how different sexual activities, among other factors, may affect the efficiency of HIV transmission in Rio de Janeiro, Brazil.

MATERIALS AND METHODS

Population

The study design consisted of selecting a group of women exposed to HIV-infected men through sexual contact from the following seven AIDS referral centers in the city of Rio de Janeiro: 1) Gaffree & Guinle University Hospital from the University of Rio de Janeiro, 2) University Hospital from the Federal University of Rio de Janeiro, 3) an outpatient unit from the National Institute of Medical Care, 4) Pedro Ernesto University Hospital from the State University of Rio de Janeiro, 5) Evandro Chagas Hospital, 6) Santa Catarina Hemophiliac Center, and 7) Pneumology Institute from the Federal University of Rio de Janeiro. These are public hospitals/units for AIDS care, and they have similar clientele. The main purpose of the study was to compare HIV-positive women and those found to be negative with regard to several factors including sexual behavior, socioeconomic characteristics, and reproductive history.

The eligibility criteria for the male index cases were 1) any heterosexual contact, i.e., vaginal, oral, or anal penetration, within the year prior to the interview; 2) positive diagnosis for HIV; 3) 18 years of age or older; and 4) agreement to participate in the research study. Men already diagnosed with AIDS/HIV infection who were under follow-up as well as those newly diagnosed cases were included. Female partners were eligible according to the following criteria: 1) at least one sexual contact, i.e., vaginal, oral, or anal penetration with one of the HIV-positive men (index case) within the year prior to the interview; 2) 18 years of age or older; 3) agreement to participate in the research study. In addition, female partners were excluded if 1) they used intravenous drugs or had shared needles or other equipment with another person, including the index case; 2) they had a known previous sexual contact with an infected man other than the index case; and 3) they had recent (after 1980) transfusion or hemodialysis and were found to be HIV positive.

Two methods of recruitment for the index cases were developed: 1) passive referral, which comprised patients referred by physicians/clinics and self-referrals in response to extensive publicity; and 2) active search through direct contact with potential participants. Although the index cases could refer any female partner, in 99 percent of the cases they were in steady relationships, and in only two cases the index cases referred two women. A standardized procedure was established so that the study visit was scheduled for the couple on the same day. This visit consisted of collecting 20 ml of blood for laboratory studies and conducting a 50-minute interview. Participation in the study was completely voluntary, and confidentiality was assured.

A standard pretested questionnaire was administered to all couples enrolled in the study by trained interviewers. Information on sociodemographic, reproductive, and sexual history variables was obtained. To minimize possible response bias, the couple was interviewed the same day and the individuals were interviewed in separate rooms by different interviewers. The index case interviewer had no access to his partner's answers and vice versa. Individuals interviewing the female partners were blind to their HIV status at the time of the interview. All interviewers were trained following detailed manuals of instruction, and questions had closed structured answers. The exposure variables presented herein were based on the women's answers, unless specified otherwise. Operational definitions for selected variables were as follows: 1) Sexual practice in the past year was defined as vaginal only, vaginal and oral, vaginal and anal, and vaginal, oral, and anal; 2) condom use in the past year was defined as always, sometimes (i.e., >50 percent), rarely (i.e., <50 percent), or never; 3) oral contraceptive use was defined as ever or never; 4) frequency of sexual contacts in the past year was defined as a range (0, 1–25, 26–50, 51–75, 76–100, 101–125, 126–150, 151–200, 201+). The range was further categorized as <100 and ≥100 for analysis purposes, given that approximately 50 percent of the answers were <100.

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Abbreviations: AIDS, acquired immunodeficiency syndrome; CD4, T helper lymphocyte; CD8, T suppressor lymphocyte; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; SE, standard error; STD, sexually transmitted disease.

[1] Department of Preventive and Social Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil.
[2] Oswaldo Cruz Foundation, Ministry of Health, Rio de Janeiro, Brazil.
[3] Department of Epidemiology, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, MD.
[4] The Rio de Janeiro Heterosexual Study Group includes Luiz A. Alves Lima from Santa Catarina Hematologic Center; Victor Berbara from National Institute of Medical Care; Solange Cavalcante from Evandro Chagas Hospital, Oswaldo Cruz Foundation; Valéria Gomes from Pedro Ernesto Hospital, State University of Rio de Janeiro; Mariza Morgado from The Immunology Laboratory, Oswaldo Cruz Foundation; Eleonora Quinhões and Dário Signorini from Gaffree & Guinle University Hospital, University of Rio de Janeiro; Andrea Sereno from Federal University of Rio de Janeiro.
Reprint requests to Dr. Alvaro Muñoz, Department of Epidemiology, 624 North Broadway, Room 797, Baltimore, MD 21205.

Reliability analysis indicated reasonable agreement when comparing female partner answers with index case answers regarding sexual practices in the past year. Percentages of agreement were 100 percent for vaginal sex, 81 percent for oral sex, 87 percent for anal sex, and 83 percent for lack of condom use during vaginal sex, with Kappa statistics of 1.0, 0.63, 0.70, 0.63, respectively.

Of the 302 index cases initially screened, 46 (15 percent) were ineligible (four were HIV negative, 21 did not have heterosexual contact in the past year, 11 were exclusively homosexual, three shared their needles with their partners, and seven had other conditions). Fifty-two index cases (17 percent) did not participate (23 did not show up for scheduled visits, 14 could not be located, seven (along with five female partners) refused to participate, and three had other conditions). The exclusions left 204 couples (68 percent) available for final analysis. No statistically significant difference among participants and nonparticipants was found with regard to center, type of cases (new vs. ongoing), and age.

Laboratory examinations

Blood was collected using Vacutainer® tubes (Becton-Dickinson, Franklin Lakes, New Jersey), and two slides were prepared for leukocyte differential count. The material was then prepared for examination and/or stored in a −70°C freezer according to standard procedures. HIV-1 antibody tests were carried out using enzyme immunosorbent assay (19) and Western blotting (20) techniques. Purified blood mononuclear cells were isolated from heparinized whole fresh blood, and enumeration of total T cell and subpopulation numbers (CD4 and CD8) was performed using monoclonal antibodies. The number of cells was determined by flow cytometer (Coulter, Hialeah, Florida) with the following specifications: Epics 751, Laser 488 nm, Voltagen Photomultiplier 120–1,300 v. The results were expressed as percentages relative to total differential lymphocyte counts and absolute numbers (cells/mm^3).

Statistical analysis

The prevalence of HIV infection among sexual contacts of HIV-positive men was determined by the number of positive women divided by the total number of women tested. The risk factor assessment was carried out retrospectively. Odds ratios were used to quantify the association between single putative risk factors and HIV infection. Categorical data were analyzed using chi-square and Mantel-Haenszel procedures, and continuous data were analyzed using the Student's t test.

Multiple logistic regressions were fitted to obtain estimates of the risk of infection, adjusted for multiple factors that might have contributed to the occurrence of HIV infection. A variable was entered into the model only if its addition had a significant contribution to the model at a p value of <0.05. Each variable was assessed through the Wald test; the models were compared using the likelihood ratio test, and final model goodness of fit was assessed by the Hosmer-Lemeshow test (21, 22). Ninety-five percent confidence intervals were computed on the odds ratios derived from the regression coefficients and their respective standard errors.

RESULTS

Descriptive statistics

Overall, 45 percent of the 204 women were found to be HIV positive, with none of them having reported any other risk factor other than sexual contact with the index case. Descriptive statistics of selected characteristics of the female partner, of the couples' sexual activity, and of the index cases are listed in table 1. Most of the couples were in long-term and steady relationships but only recently (within 6 months prior to the interview) had learned the index case HIV status. Regular oral contraceptive use (ever) was reported by 74 percent of the women, and only 19 percent had sexual partners other than the index case in the past year. In addition to vaginal sex, anal sex was reported by 8 percent of the women, and oral and anal sex was reported by 23 percent. Condom use during vaginal sex in the past year was rarely or never used by 74 percent of the women. Among those practicing anal sex (n = 63), a condom was rarely or never used by 83 percent. Most of the index cases were >30 years of age (76 percent), were in advanced stages of HIV infection (60 percent), and had low CD4 counts (51 percent with <200 cells/mm^3). Index case risk groups reported were bisexuals (47 percent), intravenous drug users (16 percent), hemophiliac/transfusion recipients (10 percent), and other combinations (18 percent).

Univariate analysis

Table 2 shows the prevalence of HIV infection among female partners of HIV-infected men, the univariate analysis of the risk of infection as measured by the odds ratio, and the estimated 95 percent confidence interval according to selected characteristics. Analysis of sexual behavior characteristics showed that women practicing anal sex in addition to vaginal sex had a fourfold increase in the risk of HIV infection (odds ratio (OR) = 4.14, 95 percent confidence interval (CI) 1.33–12.90). Similar results were seen when anal sex was practiced in addition to vaginal and oral sex (OR = 4.44, 95 percent CI 2.09–9.40). An important observation is that oral sex in addition to vaginal sex did not change the risk of being HIV infected when compared with those practicing only vaginal sex (OR = 0.91, 95 percent CI 0.42–1.95). Condom use during vaginal sex showed a significant trend when comparing those who sometimes, rarely, or never used condoms with those who always used them. The respective ORs were 1.96, 3.10, and 3.91, with a χ^2 for linear trend being highly significant (χ^2 = 9.25, p = 0.002). Condom use during anal sex was always/sometimes used by only 17 percent of the couples, with small numbers for proper risk assessment. Finally, women reporting ≥100 sexual contacts with the index case in the past year were at increased risk of HIV infection (OR = 2.63, 95 percent CI 1.46–4.73). Other variables related to sexual behavior (i.e., sexual partners other than the index case, sexual intercourse during menses, and vaginal bleeding), although showing higher HIV prevalences, were not statistically associated with HIV infection. Women reporting past STDs also had a higher prevalence; however, it was not significantly associated with HIV infection.

Univariate analysis of reproductive aspects showed that ever use of oral contraceptive was found to be associated with HIV infection (OR = 2.01, 95 percent CI 1.04–3.88). Few women used other contraceptive methods such as a diaphragm (1 percent) and an intrauterine device (5 percent). Other variables assessed, (i.e., age at first intercourse, age when regular sexual life began, past pregnancy, and induced abortion) were not associated with infection.

Among the characteristics of the index cases, only advanced clinical stage (AIDS) (OR = 2.28, 95 percent CI 1.19–4.38) was statistically associated with HIV infection among their partners. Although higher prevalence rates were found for bisexual and intravenous drug-using index cases, as compared with hemophiliacs/blood recipients, these were not statistically significantly different. The risk group "other" included multiple categories, except intravenous drug use. Other index case characteristics (i.e., age, circumcision, current diagnosis of genital ulcers, past STDs) were not associated with HIV infection in the female partner. Although not statistically significant, the CD4:CD8 ratio and the CD4 cell counts were positively associated with HIV infection among the female partners of the index cases.

TABLE 1. Selected descriptive statistics among 204 participant couples including HIV*-seropositive men in Rio de Janeiro, 1990–1991

Characteristic	N	%
Female partner		
Duration of relationship (25+ months)	162	79
Learned index case HIV status (<6 months)	135	66
Age (30+ years)	127	62
Race (white)	130	64
Education (8+ years)	102	50
Monthly family income (≥US $250)	116	59
Oral contraceptive use (ever)	152	74
Sexual partners other than index case	38	19
Sexual practice		
Vaginal only	98	48
Vaginal and oral	43	21
Vaginal and anal	16	8
Vaginal and oral and anal	47	23
Vaginal sex with condom		
Always	31	15
Sometimes	22	11
Rarely	59	29
Never	92	45
Anal sex with condom		
Always/sometimes	11	17
Rarely/never	52	83
≥100 contacts	71	35
Index case		
Age (30+ years)	156	76
Hemophiliac/transfusion recipients	21	10
Bisexual	96	47
Intravenous drug user	32	16
Other risk groups	37	18
Diagnosis of acquired immunodeficiency syndrome	123	60
CD4 count† <200	92	51

* HIV, human immunodeficiency virus.
† Missing in 25 participants.

Multivariate analysis

The independent effect of sexual practices on the risk of HIV transmission from infected men to their female partners was assessed through logistic regression modeling using the manual backward stepwise method (21). The choice of variables to start with was based on whether a characteristic was considered a potential confounder for the association between sexual practices and HIV infection, the univariate analysis, and biologic/epidemiologic considerations. The following variables were chosen to start as a full model, and then their importance by sequential deletion was assessed: 1) anal sexual practice; 2) lack of condom use in vaginal sex in the past year; 3) frequency of sexual contacts in the past year; 4) oral contraceptive use; 5) clinical stage of the index case, i.e., AIDS or AIDS-related symptoms; 6) sexual partners other than the index case in the past year; and 7)

TABLE 2. Univariate analysis of HIV* infection among female partners of infected men according to selected characteristics, Rio de Janeiro, 1990–1991

Variable	N	% HIV positive	OR*	95% CI*
Sexual practice				
Vaginal only	98	35	1.0	
Vaginal and oral	43	33	0.91	0.42–1.95
Vaginal and anal	16	69	4.14	1.33–12.90†
Vaginal and oral and anal	47	70	4.44	2.09–9.40†
Vaginal sex with condom				
Always	31	23	1.0	
Sometimes	22	36	1.96	0.58–6.57
Rarely	59	48	3.10	1.16–8.29†
Never	92	53	3.91	1.53–9.96†
Sexual contacts				
100+	71	61	2.63	1.46–4.73†
<100	133	37	1.0	
Other sexual partners				
1+	38	58	1.89	0.93–3.83
Only index case	166	42	1.0	
Sex during menses				
Yes	63	48	1.13	0.62–2.05
No	139	45	1.0	
Vaginal bleeding				
Yes	34	50	1.26	0.60–2.63
No	167	44	1.0	
Past STDs* ever				
Yes	58	50	1.32	0.72–2.43
No	146	43	1.0	
Oral contraceptive use				
Yes	152	49	2.01	1.04–3.88†
No	52	33	1.0	
Age of first intercourse (years)				
<19	95	52	1.64	0.94–2.85
19+	109	40	1.0	
Age began regular sex (years)				
<19	66	55	1.76	0.97–3.17
19+	138	41	1.0	
Past pregnancy ever				
Yes	173	46	1.36	0.62–2.98
No	31	39	1.0	
History of abortion ever				
Yes	79	50	1.71	0.74–3.96
No	32	38	1.0	
IC* clinical stage				
Asymptomatic	59	32	1.0	
AIDS*-related symptoms	22	41	1.46	0.53–4.00
AIDS	123	52	2.28	1.19–4.38†
IC risk group				
Hemophiliac/transfusion	21	29	1.0	
Bisexual	96	42	1.79	0.58–5.69
IDU*	32	50	2.50	0.67–9.59
Other	37	57	3.28	0.91–12.23
IC age (years)				
<30	48	48	1.16	0.61–2.22
30+	156	44	1.0	
IC circumcision				
Yes	35	57	1.78	0.86–3.71
No	166	43	1.0	
IC current genital ulcers				
Yes	29	52	1.37	0.63–3.03
No	169	44	1.0	
IC CD4:CD8 ratio				
<0.8	158	48	1.74	0.88–3.43
0.8+	46	35	1.0	
IC CD4 count				
<200	92	47	1.08	0.60–1.95
200+	87	45	1.0	
IC past STDs ever				
Yes	162	46	1.27	0.64–2.53
No	42	40	1.0	

* HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; STD, sexually transmitted disease; IC, index case; AIDS, acquired immunodeficiency syndrome; IDU, intravenous drug user.
† Statistically significant.

duration of the relationship. The study center was included in all of the models. The outcome of interest (HIV infection among the women) was coded as 1 for those who were HIV positive, and as 0 for those who were HIV negative. Sexual practice was fitted as a dichotomous variable where anal sex (code = 1) was compared with vaginal sex (code = 0) regardless of whether oral sex was practiced, since, as shown in the univariate analysis, oral sex was not more likely than vaginal sex alone to increase transmission. Most covariates were also dichotomous and were coded as 0 for the reference category and 1 for the presence of risk factor, while condom use during vaginal sex was fitted as a continuous variable with one unit change from each category. Gaffree & Guinle University Hospital and Federal University Hospital (centers with the highest recruitment) were included as dummy variables and compared with "others" as reference.

Table 3 shows the adjusted ORs and the 95 percent CIs. The ORs in the multivariate analysis were smaller than the univariate ORs due to partial confounding; however, the directionality and significance were unchanged. In particular, the adjusted OR = 3.74 of anal sex (95 percent CI 1.87–7.45) was similar to the estimates derived from the univariate analysis in direction but slightly lower than the univariate OR = 4.44 for anal, vaginal, and oral sex and OR = 4.14 for vaginal and anal sex, indicating a reasonable consistency of the association. Similarly, the adjusted OR of sometimes using condoms during vaginal sex (OR = 1.45, 95 percent CI 1.07–1.96), rarely (OR = 2.10, 95 percent CI 1.15–3.83), and never (OR = 3.04, 95 percent CI 1.23–7.50), as compared with always, were consistent with the trend shown in the univariate analysis (ORs = 1.96, 3.10, and 3.91, respectively). Frequency of sexual contact in the year prior to interview (100+) also showed an independent effect (OR = 2.0, 95 percent CI 1.03–3.91) with a 24 percent decrease compared with the univariate analysis (OR = 2.63). Although presenting a borderline significance, ever use of oral contraceptive (adjusted OR = 2.04, 95 percent CI 0.97–4.29) was also independently associated with HIV infection. Goodness of fit was assessed through the Hosmer-Lemeshow test, which compares observed with predicted probabilities estimated from the model and has a χ^2 distribution with 8 degrees of freedom (21). The test statistic was 4.14 ($p = 0.844$), indicating that the model provided an adequate fit.

The association between oral contraceptive use and HIV infection was further investigated using stratified analysis (table 4). Pointing to possible interactions, stratum-specific odds ratios indicated that oral contraceptive users were more likely to be HIV positive if they practiced anal sex (OR = 3.08), infrequently used condoms during vaginal sex (OR = 2.08), had more frequent sexual contacts (OR = 2.86), had no past STDs (OR = 2.74), and whose index cases were asymptomatic (OR = 4.09). However, except for STDs, the Breslow-Day test of homogeneity did not indicate statistical significance.

TABLE 3. Estimated odds ratios with 95% confidence limits of variables included in the final logistic model among female partners of HIV*-seropositive men in Rio de Janeiro, 1990–1991

Variable	OR*	95% CI*
Anal sex	3.74	1.87–7.45
Condom use in vaginal sex		
Sometimes	1.45	1.07–1.96
Rarely	2.10	1.15–3.83
Never	3.04	1.23–7.50
100+ sexual contacts	2.00	1.03–3.91
Oral contraceptive use	2.04	0.97–4.29
Gaffree & Guinle Hospital	2.52	1.17–5.45
Federal University Hospital	1.69	0.80–3.59

* HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval.

DISCUSSION

The present study has provided evidence and clear documentation for the role of sexual behavior in the risk of heterosexual transmission of HIV in Brazil. The prevalence of HIV infection among the women (45 percent) is higher than in most partner studies carried out in the United States (median = 19 percent, range 5–57 percent) (5, 9, 13–15, 23–26), Europe (median = 22 percent, range 7–53 percent) (17, 18, 27–31), or Africa (median = 25, range 4–89 percent) (12, 16, 32–36)). Sources of variation include heterogeneity with regard to study design; great variation in sample sizes, risk group, and clinical stage of index case; sexual behavior; and possibly different virus strains.

The major factors independently associated with prevalent infection among the female partners reported herein were practice of anal sex, lack of condom use during vaginal sex, and frequency of sexual contacts, whereas oral sex was not important for HIV transmission in this population. The strength of the association between anal sex and prevalent HIV infection in this population was of considerable magnitude, suggesting that it may be a major route of heterosexual transmission of HIV in Brazil, in addition to unprotected vaginal sex. The rate of anal sex practice was high (31 percent in the past year) and in most cases was without the use of condoms (83 percent). Similarly, most couples rarely or never used condoms during vaginal sex in the past year (74 percent). Taking as reference women who did not practice anal sex and always used condoms during vaginal sex, estimates of attributable risk for this exposed population of female partners indicate that 63 percent of the infections could be explained by anal sex or inconsistent condom use during vaginal sex (sometimes, rarely, or never) (22).

Albeit limited information is available regarding the clinical diagnosis of STDs, none of the variables related to STDs assessed in the present study (past history, current diagnosis of ulcerative lesions among the index cases, and serology for syphilis and hepatitis B) were independently associated with HIV infection among the female partners. This may be partially explained by the nature of the present study, i.e., partner study with known infected index cases. STDs have been shown to be important cofactors for heterosexual transmission, especially genital ulcerative lesions (32–34). However, the effect of STDs may be more clearly seen in areas with higher prevalence of HIV infection and in studies with unspecified index cases, where the number of different partners also becomes an important risk factor due to a greater likelihood of finding an infected person. Thus, in addition to an increase in susceptibility, STDs may act as an indicator of degree of partner exchange (37, 38). In the present study, the number of sexual contacts with the index case, but not sex with other partners, was independently associated with HIV infection. This is consonant with the partner study design in which the likelihood of infection is almost certain. More important for the current analysis, however, is the fact that frequency of contacts may act as a confounder variable for other factors (e.g., anal sex and condom use). In addition, the lack of association between HIV infection and sex with other partners may be an indicator that the index case was in fact the source of infection for the female partners.

The high prevalence among the women could be partially explained by the advanced clinical stage of most index cases as demonstrated by the increasing HIV infectivity with duration of infection (10, 27, 37, 39). Increasing virus load as well as emergence of more virulent strains of virus throughout the course of infection are possible reasons for this change in infectivity (27, 40). Although dates of infection among the index cases were not available, HIV clinical course and immunologic markers could be used as indirect indicators of time since infection, as shown by several authors (9, 10, 41–43). Most infected women were asymptomatic (72 percent) with higher CD4 counts (median = 420 cells/mm^3), as compared with their male partners (71 percent were symptomatic and median CD4 count was 179 cells/mm^3). A CD4:CD8 ratio <0.8 corresponded to an odds ratio of 1.74 (table 2). The strength of association was less (OR = 1.08) for CD4 <200 cells. Although both markers are strongly associated with the onset of AIDS, which was significantly associated with infection in the female partners, the differences of the strengths of association of these markers are related to the larger measurement error of the count compared with the ratio. In addition, the complete blood count, and hence the CD4 cell count, was missing in 19 (13 percent) and six (10 percent) of the symptomatic and asymptomatic index cases. To identify those who were severely immunosuppressed, we used 100 instead of 200 cells as the cutoff for the CD4 cell count. As expected, the association was strengthened (OR = 1.31); however, the inferences were unchanged (95 percent CI 0.71–2.40).

Multicenter studies are more likely to suffer from selection bias. The centers from which the couples were recruited represent the most important AIDS referrals in the city of Rio de Janeiro and were statistically similar with regard to most exposure characteristics assessed (frequency of contacts, condom use during vaginal sex, anal sex, sex with other partners, duration of relationship, age, oral contraceptive use, socioeconomic indicators). However, a statistically significant difference was found for the index cases' clinical classification. Hospital referral centers are more likely to include symptomatic index cases, as is the case at four of the centers used in this study. One possible consequence of this selection is a higher estimate of the overall prevalence of HIV among the female partners.

Another aspect that should be mentioned with regard to the multicenter nature of the study is the inclusion of one outpatient hemophiliac center. It has been shown that HIV prevalence among partners of HIV-infected hemophiliac index cases is generally lower than other risk groups (23, 24). Indeed, the lowest prevalence was found to be in the hemophiliac center (12 percent). One consequence of this lower prevalence was the independent association between Gaffree & Guinle University Hospital and HIV infection detected in the multivariate model, given that the hemophiliac center was included in the reference category (others). To check this finding, we refitted the final model, excluding the hemophiliac center. The

TABLE 4. Prevalence of HIV* infection among female partners of HIV-infected men according to oral contraceptive use, stratified by selected characteristics, Rio de Janeiro, 1990–1991

Variable	OC* use	N	% HIV positive	OR*	95% CI*	OR_{MH}*	95% CI	χ^2	p value†
Anal sex									
Yes	Yes	49	76	3.08	0.89–10.58	1.96	0.99–3.86	0.705	0.401
	No	14	50	1.0					
No	Yes	103	37	1.64	0.72–3.74				
	No	38	26	1.0					
Vaginal sex with condom									
Always/sometimes	Yes	36	31	1.35	0.38–4.84	1.89	0.97–3.68	0.231	0.631
	No	17	24	1.0					
Rarely/never	Yes	116	55	2.08	0.96–4.53				
	No	35	37	1.0					
Sexual contacts									
100+	Yes	54	67	2.86	0.93–8.75	1.99	1.03–3.88	0.592	0.442
	No	17	41	1.0					
<100	Yes	98	40	1.65	0.71–3.82				
	No	35	29	1.0					
Past STDs*									
Yes	Yes	48	48	0.64	0.17–2.40	1.94	0.96–4.02	3.33	0.068
	No	10	60	1.0					
No	Yes	104	50	2.74	1.26–5.95				
	No	42	26	1.0					
IC* clinical stage									
Symptomatic	Yes	108	54	1.70	0.75–3.89	2.06	1.05–4.04	0.966	0.326
	No	37	40	1.0					
Asymptomatic	Yes	44	37	4.09	0.73–30.00				
	No	15	13	1.0					

* HIV, human immunodeficiency virus; OC, oral contraceptive; OR, odds ratio; CI, confidence interval; OR_{MH}, Mantel-Haenszel odds ratio adjusted by variable in column 1; STD, sexually transmitted disease; IC, index case.
† Breslow-Day χ^2 test for homogeneity.

odds ratios obtained for Gaffree & Guinle University Hospital and Federal University Hospital were 1.80 ($p = 0.155$) and 1.13 ($p = 0.746$), respectively, while the remaining associations did not change significantly (ORs = 3.71, 1.45, 1.63, 2.42, for anal sex, condom use, frequency of contacts, and oral contraceptive use, respectively). This way, we concluded that the center should be considered a nuisance factor, and it was kept in the model for the purpose of controlling for this factor.

Another aspect suggested by the analysis is a positive association between ever use of an oral contraceptive and HIV infection. The current state of the art regarding this point is still controversial (10, 16, 31–33, 35, 39, 44, 45). One suggested explanation for the positive association of oral contraceptive use and HIV infection is a confounding effect of behavior factors (e.g., frequency of sexual practices and condom use). While some of these factors have been taken into account by Simonsen et al. (32) and Plummer et al. (33), confounding may still be present due to incomplete adjustments.

The present analysis of oral contraceptive use and HIV infection was controlled for many factors with more complete data. The association detected in the univariate analysis was confirmed by logistic modeling and stratification analysis, including condom use, though its significance remained borderline. These results should be taken with caution. Aspects such as dose, brand, type (hormonal concentrations), and more precise dates of use should be included in studies designed to specifically assess this association. In addition, small numbers may have generated unstable ORs with lack of adequate power for reaching statistical significance. Nevertheless, the apparent interaction between oral contraceptive use and anal sex, lack of condom use during vaginal sex, frequency of sexual contacts, STDs, and index case clinical stage, despite the absence of statistical heterogeneity, are intriguing findings.

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