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**ORIGINAL CONTRIBUTIONS**

**Sexual Risk Behavior and Risk Factors for HIV-1 Seroconversion in Homosexual Men Participating in the Tricontinental Seroconverter Study, 1982-1994**

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Trends in sexual behavior associated with incident infection with human immunodeficiency virus (HIV) type 1 are described and a case-control study was conducted to examine risk factors for HIV seroconversion in homosexual men who became infected with HIV between 1982 and 1994 from four geographic sites: Amsterdam, the Netherlands; San Francisco, California; Vancouver, Canada; and Sydney, Australia. Changes in sexual behaviors were evaluated from cohort visits in the preseroconversion, seroconversion, and post-seroconversion intervals and were further examined over three time periods: 1982-1984, 1985-1987, and 1988-1994. In a case-control study, sexual behaviors, substance use, and presence of sexually transmitted disease were compared between 345 HIV-positive cases and 345 seronegative controls matched by visit date and site. Receptive anal intercourse was the sexual behavior most highly associated with seroconversion. The odds ratio (OR) per receptive anal intercourse partner increase was 1.05 (95% confidence interval (CI) 1.02-1.09). To more carefully examine risk associated with receptive oral intercourse, analyses were done in a subgroup of men who reported no or one receptive anal intercourse partner. The risk (OR) associated with receptive oral intercourse partner increase was 1.05 (95% CI 1.0-1.11). In multivariate conditional logistic regression analyses, presence of sexually transmitted disease (OR = 3.39, 95% CI 1.95-5.91) and amphetamine use (OR = 2.55, 95% CI 1.26-5.15) were independently associated with seroconversion. Although the prevalence of major risk factors has decreased over time, the associations of these behaviors and HIV infection persist, suggesting that these risk behaviors remain important avenues for public health interventions. *Am J Epidemiol* 1997;146:531-42.

acquired immunodeficiency syndrome; HIV; homosexuality, male; risk factors; sex behavior

Infection with the human immunodeficiency virus (HIV) type 1 is dependent on several determinants including behavioral, social, and biologic. Transmission and acquisition probability may also vary due to

the inherently variable nature of sexual behavior, e.g., the duration or type or exposure, the presence of other factors such as sexually transmitted disease (STD) or drug and alcohol use, as well as the degree of infec-

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Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IAI, insertive anal intercourse; OR, odds ratio; RAI, receptive anal intercourse; ROI, receptive oral intercourse; STD, sexually transmitted disease; TCS, Tricontinental Seroconverter Study.

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tivity and susceptibility of partners. Among homosexual and bisexual men, receptive anal intercourse (RAI) is known to be the sexual behavior that carries the highest risk of infection (1–9). Epidemiologic and case studies support the hypothesis that receptive oral intercourse (ROI) carries some risk for HIV infection (9–11). The protective effect of condom use has been demonstrated among young men with prevalent infection (12) and more recently in a case-control study of incident seroconverters (7). However, this effect is not consistent in other studies of incident infection (5, 9), possibly due to differences in study design and to both methodological and confounding problems. HIV infection in homosexual men has been associated with the use of recreational and illicit drugs, particularly amyl nitrites, amphetamines, cannabis, and cocaine (3, 7, 13, 14). Prevailing thought is that these associations are primarily due to confounding between high risk sexual activity and drug use behavior (14–17), although drug use may also influence host susceptibility to infection (14, 18). Susceptibility to HIV infection is now believed to be facilitated by coincident infection with ulcerative STD (4, 17, 19, 20). The relation to nonulcerative STD is less clear, but evidence supports the hypothesis for higher risk of HIV infection with gonorrhea in studies of heterosexual transmission (21) and between rectal gonorrhea and HIV infection in homosexual men (22). As with drug use, confounding effects make these relations difficult to evaluate fully (23).

Homosexual men in industrialized countries are well informed about the dangers of sexually acquired HIV infection; and in the face of the acquired immunodeficiency syndrome epidemic, numerous studies have documented longitudinal declines in numbers of partners and in practices that carry a high risk of HIV transmission (6, 7, 20, 24–28). In particular, declines in the number of sex partners, RAI partners, and unprotected RAI partners are believed to have had significant impact on HIV incidence rates (24–26) and are attributed to the combined effects of several preventive education efforts (29–34). Less is known, however, about the patterns of sexual behavior in homosexual men relative to the period of exposure or seroconversion, due in part to the lack of adequate amounts of serial sexual data in seroconverters. Kuiken et al. (6), in the Netherlands, examined behaviors in the 3 years before and after seroconversion and over time from 1984 to 1988. The authors of the study reported that before seroconversion, there appeared to be a peak in sexual activity followed by a decline in risk behavior after infection, which more than likely was due to knowledge of infection status. This peak or period of “hypersexual” behavior is an important phe-

nomenon to study. It has been suggested by Jacquez et al. (35) that such a “high contact” period may play an important role in dissemination of the HIV epidemic during the primary infection phase, since newly infected people may be more infectious than those in whom infection is in a more stable phase.

This paper investigates risk factors and sexual behaviors in incident HIV seroconverters and has two aims. First, we offer a descriptive analysis of sexual behavior before, during, and after seroconversion in homosexual men who became infected with HIV between 1982 and 1994. Trends in sexual behavior are further examined over time, to focus on the combined effects of seroconversion and the progression of the epidemic on behavior patterns in homosexual men. Second, we conducted a case-control study to evaluate sociobehavioral and clinical risk factors for seroconversion and to consider whether such factors have changed over time. The Tricontinental Seroconverter Study (TCS) pools incident seroconverters from longitudinal studies of HIV infection conducted in homosexual men from four geographic areas (36, 37). Whereas the TCS is designed to study primarily the natural history of HIV infection, we designed a case-control study to examine risk factors for incident HIV infection. In the TCS data set, longitudinal data are compiled from visits before and after documented HIV infection. Because there are no consistent seronegative individuals in the TCS data set, we could use these seronegative visits as controls. Although much is known about sexual behavior and risk factors for HIV infection in homosexual men, by combining similar populations in four geographically distinct sites, this study provides new information on risky sexual behaviors and other risk behaviors based on substantial numbers of incident infections while affording an opportunity to examine trends in risk behaviors from an international perspective.

## MATERIALS AND METHODS

### Study population

The TCS follows homosexual/bisexual men with well-documented dates of HIV seroconversion who were enrolled in five prospective studies of the natural history of HIV infection in four internationally distinct sites: Amsterdam, the Netherlands; San Francisco, California; Sydney, Australia; and Vancouver, Canada. This collaborative study with details of the participating cohorts is described in detail elsewhere (36, 37). Participants were enrolled from the Amsterdam Cohort Study (26), the San Francisco Men’s Health Study (25), the San Francisco General Hospital Cohort (24), the Sydney AIDS Prospective Study (38), and the

Vancouver Lymphadenopathy-AIDS Study (39). Common protocols between the studies provide comparable data on a variety of behavioral, clinical, immunologic, and demographic factors. At all sites, participants completed detailed questionnaires and underwent clinical examinations at enrollment and at subsequent intervals ranging from 3 to 12 months. Physical examinations included routine blood draws from which HIV serostatus and coincident immunologic status were obtained. All participants had HIV status ascertained by repeated enzyme-linked immunosorbent assay and Western blot confirmation. As of January 1, 1995, a total of 422 seroconverters have been pooled from the four geographic sites. Of these, 378 participants (90 percent) have an interval of 2 years or less between their last negative and first positive HIV type 1 test. All analyses conducted are restricted to these men.

### Seroconversion intervals

For all study participants, three exposure intervals associated with seroconversion—pre-, during, and postseroconversion—were defined, using the last negative and first positive HIV test as reference points. First, the seroconversion or exposure interval was delineated as the period between the date 30 days before the last HIV-negative test and the date of the first HIV-positive test. This modification (+30 days) of the seroconversion interval was adapted to capture visits in which respondents had completed behavioral assessments when they might in fact have been recently infected but still tested negative for HIV and when visits were more apt to be associated with the true exposure period. The preseroconversion interval captured any visits in the 15-month (450-day) period before the seroconversion interval as described above, and the postseroconversion interval captured visits in the 15-month period after the first positive test. This time period (15 months) was chosen in an effort to obtain a comparable number of participants for all intervals and from all sites who were interviewed within a reasonable period relative to their exposure interval. Not all cohorts scheduled cohort visits at 6-month intervals. In Amsterdam, for instance, participants had 3-month visits for several years; and men at San Francisco General Hospital were seen at 1-year intervals. Therefore, for all participating cohorts, questions on sexual behaviors and substance use were adjusted to reflect behavior or events in the 6 months before the visit. This has been described in more detail previously (37). Data from individuals with more than one visit in the interval of interest were aggregated and mean values were computed that reflected mean 6-month recall. Data were extracted from cohort visits

for each exposure interval, pre-, during, and postseroconversion.

### Risk factor analysis: case-control study

To study risk factors associated with seroconversion, a case-control design was used. All participants who had a seroconversion interval of 2 years or less were eligible to be a case as they all were seroconverters. Since the TCS study is composed of longitudinal data obtained from cohort studies and data (behavioral and other) are available for participants before HIV infection, controls were sampled from participants' seronegative visits. For each case, a control was chosen from the same geographic site who had a seronegative visit with behavioral assessment within the case's seroconversion interval and who did not become seropositive within 6 months of the case's first positive HIV test. Controls were sampled with replacement; for example, a control drawn at one point in time ( $t$ ) may on a different visit date ( $t_i$ ) be selected as a control a second time for a different case and may at a later time ( $>t_i$ ) become a case. A total of 164 unique individuals were used as controls. Of those, 95 (58 percent) had more than one visit selected from all possible preseroconversion visits and were used as controls. Since bias could result from overrepresentation of individuals repeatedly sampled as controls, we compared median number of sexual partners for various sexual behaviors between those who had a single control visit with a sample of individual visits of those sampled more than once. No significant differences were noted in median number of sexual partners between those sampled once compared with those representing multiple samples. All cases and controls had to have completed behavioral assessments. For cases, this was required during the seroconversion interval or, lacking that, during the preseroconversion interval (as defined above). Cases and controls were compared on the basis of individually matched, not aggregated, visits.

### Variables

Data assembled in the TCS included measures of recalled sexual behavior, substance use, and clinical data, in this case STD, gathered during the same visit. In this study, STD diagnoses were ascertained somewhat differently at all sites. In Amsterdam and Sydney, diagnoses were made by the physician attending the study or were obtained from medical records. In Vancouver, medical records were obtained from the participant's clinic or physician. In San Francisco, men were asked to report whether the event had been "diagnosed" and "had they seen a physician" for the

problem—if so, they were coded as “yes.” In this way, a decision was made a priori to control for site differences. Data on several STDs were available from clinical interviews, from laboratory reports, or by physician reports. These included syphilis, gonorrhea, genital herpes, and hepatitis B virus infection. Gonorrhea and herpes diagnoses reflect any possible anogenital site infection. These variables were coded dichotomously “yes/no” to reflect whether the participant had been diagnosed with the disease in the preceding 6-month interval. These data were assembled for the three exposure intervals associated with seroconversion as described above. Sociodemographic variables including age, race, and education were available from both baseline and subsequent study visits.

Pooled sexual behavior data included number of partners with whom the participant had engaged in the following: sex, RAI, insertive anal intercourse (IAI), ROI, and insertive oral intercourse. The number of partners with whom participants had used condoms during RAI and IAI was available from most cohorts after 1986. These data were used to compute the proportion of partners with whom the respondent had unprotected sex and were further dichotomized to reflect condom use with *all* versus *some/none* partners. The risk of seroconversion associated with irregular (some/none) condom use was assessed among men who reported at least one RAI partner. Sexual behavior data (numbers of partners) were used both as continuous variables and collapsed into categories. The TCS compiled data on the following five measures of substance use: cannabis (marijuana or hashish), amyl nitrite, amphetamines, cocaine, tobacco, and alcohol. These data were dichotomized to reflect use/nonuse for the 6-month interval before the visit.

## Statistical analyses

Descriptive statistics and tests for mean and median differences were done using the *Statistical Package for the Social Sciences* (40). Mean differences in age across sites were tested using one-way analysis of variance and further compared using Scheffé's range test. Differences in proportions between sites were tested using Mantel-Haenszel chi-square tests for trend and Fishers's exact test. Nonparametric tests were used to test for differences among variables with non-normal distributions, including year of seroconversion and number of sexual partners. Tests were considered significant at a level of  $p \leq 0.05$ . The *Epidemiological Graphics Estimation and Testing* package was used to assess case-control differences with regard to seroconversion (41). Conditional logistic regression models were developed using variables found to be significant in univariate analyses. Numbers of sexual partners for separate sexual behaviors were entered into the models as continuous variables and, for some analyses, collapsed into categorical variables. All variables that were categorized into more than two levels were entered as indicator variables. Odds ratios (ORs) and 95 percent confidence intervals (CIs) were computed for both univariate and multivariate associations using conditional likelihood estimation methods. Finally, because of the possible confounding effect of matching by visit date and to assess whether associations between behavior and seroconversion might change due to temporal trends in both behavior and seroconversion occurrence, risk factors were further analyzed for separate time periods using 1987 as a cutpoint.

## RESULTS

The 378 men with seroconversion intervals of 2 years or less are described in table 1 by group and site.

TABLE 1. Demographic and site information of 378 seroconverters, the Tricontinental Seroconverter Study, 1982–1994

	Age at seroconversion* (years)		Postsecondary education†,§		Seroconversion after 1900¶		No. of lifetime partners	
	Mean	(SD)†	No.	%	Median	IQR†	Median	IQR
All sites (n = 378)	35.3	(7.7)	130	38	85.6	84.8–87.4	300	80–750
Vancouver (n = 121) (32%)	32.7	(6.9)	29	26	84.8	84.0–86.0	300	60–750
Sydney (n = 67) (18%)	36.0	(8.5)	37	56	85.3	84.9–86.5	500	68–997
Amsterdam (n = 130) (34%)	36.1	(7.6)	51	42	86.5	85.5–90.0	250	100–800
San Francisco (n = 60) (16%)	37.8	(7.0)	13	30	86.0	84.9–87.0	200	81–500

\*  $F = 7.8$ ,  $p < 0.001$ . Vancouver is significantly younger than all other groups.

† SD, standard deviation; IQR, interquartile range.

‡ Educational level available on  $n = 342$ .

§  $\chi^2 = 40.7$ ,  $p < 0.001$  for differences in educational level.

¶ Nonparametric (median) tests show that Amsterdam cohort has a significantly later year of seroconversion than all others. San Francisco has a significantly later year than Vancouver.

# At baseline entry.

Included are 121 men (32 percent) from Vancouver, 67 (18 percent) from Sydney, 130 (34 percent) from Amsterdam, and 60 (16 percent) from San Francisco. Mean age was 35.3 years at seroconversion for the entire group, although seroconverters from Vancouver were significantly younger than men from other cohorts, with a mean age of 32.7 years. Accordingly, Vancouver had the lowest proportion of men with higher (postsecondary) education compared with other sites and had earlier dates of seroconversion. The Amsterdam cohort, which is an open cohort, has a later mean and median date of seroconversion compared with all others. The majority (95 percent) of seroconverters from all cohorts were white.

### Sexual behavior: by seroconversion interval and time period

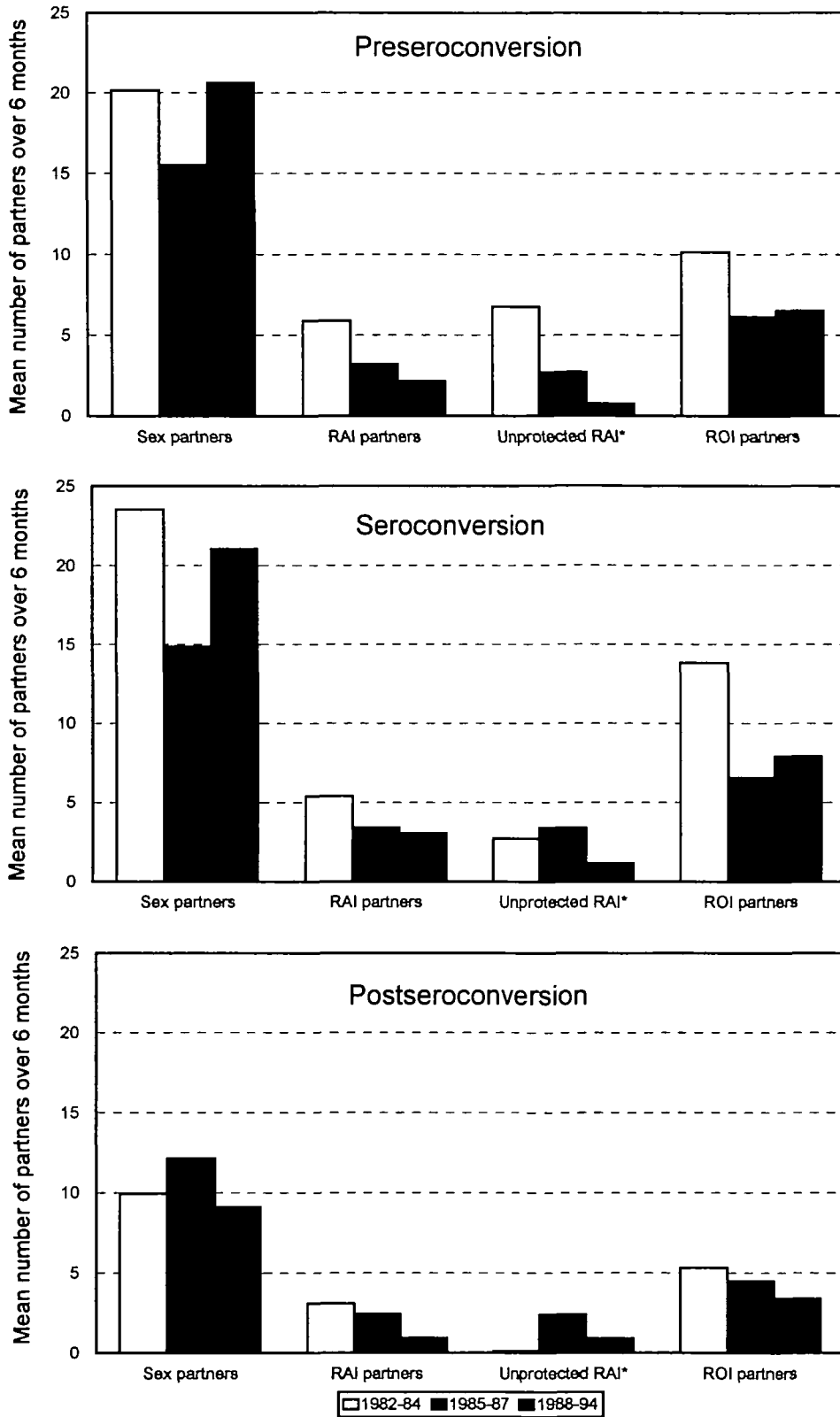
Two hundred thirty-nine men (64 percent) had completed behavioral assessments in their preseroconversion interval, 324 (86 percent) during the seroconversion interval and 312 (83 percent) in the postseroconversion interval. In figure 1 are shown the 6-month mean numbers of sexual partners overall and for specific sexual behaviors by seroconversion interval (pre-, during, and postseroconversion) and over calendar period (1984 and before, 1985–1987, and 1988–1994). The median numbers (and interquartile ranges) of sexual partners overall for pre-, during, and postseroconversion periods were 9 (4–22), 9 (5–21), and 5 (2–12), respectively. Median numbers (and interquartile ranges) of RAI partners were 1 (0–4), 1 (0–4), and 1 (0–2) in the pre-, during, and postseroconversion intervals. A decline is present over calendar time in the number of partners with whom RAI, unprotected RAI, and ROI were practiced. With the exception of unprotected RAI (higher preseroconversion in the 1984 and before interval), there are no differences in total number of partners, RAI partners, or ROI partners between the preseroconversion and seroconversion interval. After seroconversion, there is a marked decline in the number of sexual partners overall as well as for all specific sexual behaviors.

### Risk factors for seroconversion

Of the 378 men eligible for the risk factor analysis, 355 (94 percent) were matched with a negative control. Men who were not matched included early (1984 and before,  $n = 11$ ) and recent (after 1990,  $n = 12$ ) seroconverters for whom no negative control could be found. These men did not appear to differ from men who were matched in terms of demographics. Of the 355 who were matched, 315 (88 percent) had completed behavioral assessments in the seroconversion

interval. Behavioral assessments were available on 30 additional cases from the preseroconversion interval. Since few differences were found between sexual behaviors in the seroconversion interval and the preseroconversion interval in the initial descriptive analyses, univariate and multivariate analyses were carried out for the 315 (using cases' seroconversion interval data only) and 345 pairs (using cases' seroconversion interval data and preseroconversion interval data). Similar results were found for both analyses; therefore, all analyses presented are with the 345 pairs. Cases and controls were similar in age (34.3 and 35 years, respectively) and educational level. No differences are seen with respect to the number of lifetime sexual partners reported at entry into their respective study.

Descriptive statistics, frequencies, unadjusted and adjusted odd ratios for sexual behaviors, and other variables assessed as risk factors for seroconversion are presented in table 2. Cases were more likely to have more sexual partners in general, as well as for specific sexual behaviors, RAI, IAI, and ROI. Cases were significantly more likely to have reported multiple RAI partners, and the estimated OR for an increase in one RAI partner was 1.05 (95 percent CI 1.02–1.09). Seroconversion was also significantly associated with number of ROI partners (OR = 1.01, 95 percent CI 1.00–1.08). Analyses using number of partners collapsed categorically (0, 1, 2–9,  $\geq 10$ ) also showed that risk increased for both RAI and ROI: 1.23 (CI 1.06–1.45) and 1.24 (1.07–1.44), respectively. Number of IAI partners was not associated with seroconversion. Among those in whom clinical data were available during the corresponding visit, cases were more likely to have had several STDs. Significant risk was associated with having had any STD (OR = 3.23, 95 percent CI 2.08–5.02) and specifically syphilis (OR = 2.36, 95 percent CI 1.26–4.4), gonorrhea (OR = 5.0, 95 percent CI 2.7–9.3), and genital herpes (OR = 1.43, 95 percent CI 0.97–2.1). A significant association (OR = 2.73, 95 percent CI 1.67–4.45) was found for amphetamine use and seroconversion. No associations were found for risk of seroconversion and other substance use, including amyl nitrite (OR = 1.34, 95 percent CI 0.91–1.98) in the overall group. Amphetamine use was greatest among participants from San Francisco (38.7 percent), followed by Sydney (25 percent), Vancouver (18.2 percent), and Amsterdam (3 percent). Cocaine use and risk of seroconversion could not be assessed as there were no discordant pairs. Data on intravenous drug use were not available from all cohorts and could not be assessed.



**FIGURE 1.** Sexual behaviors in the preseroconversion interval, seroconversion interval, and postseroconversion by time period, the Tricontinental Seroconverter Study, 1982–1994. RAI, receptive anal intercourse; ROI, receptive oral intercourse; \*, among men with one or more RAI partners.

**TABLE 2. Descriptive statistics, frequencies, and odds ratios for HIV\* risk factors among cases and controls, the Tricontinental Seroconverter Study, 1982–1994**

Variables	Cases (n = 345)				Controls (n = 345)				Unadjusted		Adjusted for no. of RAI* partners	
	$\bar{x}$	Median	No.	%	$\bar{x}$	Median	No.	%	OR*	95% CI*	OR	95%CI
<b>Sexual behavior</b>												
Sex partners	19.2	9.0			15.5	6.0			1.00	0.99–1.01		
RAI partners	4.0	1.5			2.4	1.0			1.05	1.02–1.09		
IAI* partners	5.7	2.0			4.3	1.0			1.01	0.99–1.03	1.00	0.98–1.02
ROI* partners	9.4	3.5			6.1	2.0			1.01	1.00–1.03	1.01	1.01–1.08
<b>STDs*</b>												
Syphilis			36	13.1			19	6.7	2.36	1.26–4.40	2.26	1.19–4.29
Gonorrhea			79	28.8			33	11.7	5.00	2.70–9.29	4.88	2.60–9.20
Genital herpes			96	29.8			74	23.5	1.43	0.97–2.10	1.45	0.97–2.14
Hepatitis B			37	13.2			31	11.1	1.25	0.65–2.41	1.20	0.61–2.40
Venereal warts			3	3.6			5	5.6	0.60	0.14–2.51	0.63	0.15–2.70
Any STD†			151	51.5			92	31.2	3.23	2.08–5.02	3.10	1.98–4.84
<b>Substance use</b>												
Cannabis			230	74.0			209	74.6	1.23	0.81–1.88	1.24	0.80–1.90
Amyl nitrite			215	69.8			175	66.3	1.34	0.91–1.98	1.29	0.86–1.90
Amphetamines			78	26.9			35	13.3	2.73	1.67–4.45	2.64	1.61–4.32
Tobacco			116	61.7			71	58.7	1.04	0.59–1.85	1.04	0.58–1.84
Alcohol			220	90.9			193	86.5	1.67	0.88–3.16	1.73	0.90–3.45

\* HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; RAI, receptive anal intercourse; IAI, insertive anal intercourse; ROI, receptive oral intercourse; STD, sexually transmitted disease

† Only incident infections (syphilis, gonorrhea, genital herpes) were included.

After adjusting for number of RAI partners, significant predictors included the number of ROI partners, STDs including syphilis and gonorrhea, and amphetamine use (table 2). Number of ROI partners was not adjusted for condom use since this association would be restricted to only those with one or more RAI partners, and we believed that this model would not adequately include men who might practice other sexual behaviors. We did, however, investigate risk associated with ROI both as a continuous variable and categorically (none, one, two through nine, and 10 or more partners) among men who reported no RAI partner (cases:  $n = 113$ ; controls:  $n = 141$ ) or only one RAI partner (cases:  $n = 72$ ; controls:  $n = 71$ ). The OR for ROI (per partner) remained elevated at 1.05 (95 percent CI 1.0–1.11,  $p = 0.06$ ) in this group and did not change when controlling for number of RAI partners (no or one partner). The odds of seroconversion associated with having had 10 or more ROI partners compared with no ROI partners were 1.93 (95 percent CI 1.18–3.14) in the entire group and 5.06 (95 percent CI 1.66–15.4) in the subanalysis of those with no or only one RAI partner.

In table 3 are shown results of risk factor analyses, both unadjusted and adjusted for condom use in men with one or more RAI partners. Irregular condom use was reported more among cases (72.5 percent) than controls (68.6 percent), but the OR was not significant (OR = 1.44, 95 percent CI 0.62–3.38). Syphilis, gonorrhea, STD, amyl nitrite, and amphetamine use all showed significantly elevated ORs in unadjusted analyses. After controlling for condom use and RAI, the

occurrence of any STD was marginally associated (OR = 2.51, 95 percent CI 0.95–6.7,  $p = 0.067$ ) with seroconversion in analyses controlling for RAI and condom use (table 3). These analyses were restricted to 105 pairs of men who reported at least one RAI partner, and numbers are low due primarily to missing condom data among early seroconverters.

### Risk factors over time

Risk estimates changed little, although confidence intervals widened when analyses were stratified by time period—1987 and before and 1988 and later (table 4). Risks associated with number of RAI partners were essentially identical: 1.05 (95 percent CI 1.02–1.09) and 1.06 (95 percent CI 0.96–1.17) for the two periods, respectively. In table 4, it can be seen in models 4–7 that the risk associations calculated for risk behaviors are significant (condom use, ROI, amphetamine use, and STD) after adjustment for RAI using conditional logistic regression methods. Each model reveals the independent risk of each behavior, adjusted for the other. Risk associated with unsafe condom use could be assessed only for the later time period and remained nonsignificant. Risk estimates for amphetamines (adjusted for RAI) also declined and became nonsignificant (ORs = 2.74 and 2.08, respectively) compared with the overall period. Risk estimates for individual STDs remain elevated when analyzed by time period; however, after adjusting for number of RAI partners and/or condom use, they become nonsignificant (data not shown). Risk associ-



**TABLE 3. Odds ratios (unadjusted and adjusted for RAI\* and condom use) for risk factors among cases and controls with one or more RAI partners, the Tricontinental Seroconverter Study, 1982-1994**

Variables	Unadjusted OR*	95% CI*	Adjusted OR	95% CI
<b>Sexual behavior</b>				
RAI partners	1.03	0.99-1.07	1.03	0.97-1.09†
Condom use: some/none vs. always	1.44	0.62-3.38	1.52	0.64-3.62‡
<b>STDs*</b>				
Syphilis	2.38	1.04-5.40	1.23	0.36-4.23
Gonorrhea	7.20	2.83-18.4	2.68	0.83-8.59
Genital herpes	1.40	0.82-2.40	1.24	0.53-2.91
Hepatitis B	2.25	0.69-7.30	NC*	NC
Venereal warts	3.00	0.31-28.8	2.79	0.28-27.2
Any STD§	3.82	1.97-7.42	2.51	0.94-6.69
<b>Substance use</b>				
Cannabis	1.53	0.83-2.82	1.20	0.46-3.10
Amyl nitrite	1.83	1.03-3.26	1.27	0.46-3.45
Amphetamines	1.88	1.02-3.44	1.27	0.46-3.45
Tobacco	1.57	0.61-4.05	0.94	0.32-2.77
Alcohol	1.75	0.51-5.98	0.67	0.40-7.08

\* RAI, receptive anal intercourse; OR, odds ratio; CI, confidence interval; STD, sexually transmitted disease; NC, not calculable.

† Adjusted for condom use.

‡ Adjusted for number of RAI partners.

§ Only incident infections (syphilis, gonorrhea, genital herpes) were included.

**TABLE 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for risk associated with sexual behaviors\* overall and over two time periods in the Tricontinental Seroconverter Study,\* 1982-1994†**

Model	1982-1992		1982-1987		1988 and later	
	OR	95% CI	OR	95% CI	OR	95% CI
1 RAI‡	1.05	1.02-1.09	1.05	1.01-1.08	1.06	0.96-1.17
2 ROI‡	1.01	1.00-1.03	1.01	1.00-1.03	1.03	0.99-1.07
3 Irregular condom use§	1.44	0.62-3.38	NC†	NC	2.33	0.66-9.02
4 RAI	1.03	0.97-1.09	NC	NC	1.01	0.88-1.16
Irregular condom use§	1.52	0.64-3.62	NC	NC	2.32	0.60-8.98
5 RAI	1.04	0.99-1.10	1.05	1.01-1.08	1.03	0.92-1.15
ROI	1.01	1.01-1.08	1.01	0.996-1.02	1.02	0.98-1.07
6 Amphetamine	2.64	1.61-4.32	2.74	1.60-4.65	2.08	0.49-8.84
RAI	1.04	1.01-1.08	1.04	1.01-1.08	1.14	0.94-1.38
7 STD‡	3.10	1.98-4.84	4.25	2.44-7.39	1.36	0.60-3.08
RAI	1.05	1.01-1.09	1.05	1.01-1.10	1.03	0.93-1.14

\* Sexual behaviors include receptive anal intercourse and receptive oral intercourse.

† Risk measures in multivariate associations calculated by conditional logistic regression methods, adjusting for variables shown.

‡ RAI, receptive anal intercourse; ROI, receptive oral intercourse; NC, not calculable; STD, sexually transmitted disease.

§ Calculated among men with one or more RAI partners.

ated with STD is elevated in the earlier time period but becomes nonsignificant among more recent seroconverters (table 4).

### Multivariate models

Multivariate conditional logistic regression models developed from those variables found to be significant

in univariate analyses are shown in table 5. Increased risk of seroconversion is predicted by number of RAI partners having an incident STD and amphetamine use. Risk associated with RAI in a multivariate model controlling for ROI partners, STD, and amphetamine use is also shown and remains marginally significant (OR = 1.04, 95 percent CI 1.00-1.09). Multivariate

**TABLE 5. Conditional logistic regression models with risk factors\* for HIV† seroconversion in the Tricontinental Seroconverter Study, 1982–1994**

Model	Variable	OR†	95% CI†
1	RAI† (per partner)	1.05	1.01–1.09
	STD† (yes vs. no)	3.34	1.93–5.80
	Amphetamine use (yes vs. no)	2.50	1.24–5.04
		1.04	1.00–1.09
2	RAI (per partner)	1.01	1.00–1.02
	ROI† (per partner)	3.39	1.95–5.91
	STD (yes vs. no)	2.55	1.26–5.15

\* Sexual behaviors include receptive anal intercourse and receptive oral intercourse.

† HIV, human immunodeficiency virus; RAI, receptive anal intercourse; STD, sexually transmitted disease; ROI, receptive oral intercourse.

models could not be converged for the latter time period (1988 and later) and are therefore not presented for the separate time periods. Controlling for education and age had no significant effects on risk estimates. No significant interactions were found for any of the risk factors in the logistic models.

## DISCUSSION

In these analyses, the men who were studied were pooled from different cohort studies and reflect the infection demographics of the HIV epidemic in the Western industrialized world from the early and mid-1980s: white, educated, homosexual men in their mid-thirties. Beyond demographic similarity, these men were similar behaviorally; they were sexually active and reported large numbers of sexual partners before entry into their studies. General patterns of sexual behavior associated with HIV seroconversion are characterized as follows: sexual risk-taking behavior is greatest in the preseroconversion and seroconversion intervals studied here. Risky sex declines after seroconversion, with fewer numbers of sexual partners for specific high risk activities, including both RAI and IAI and unprotected anal sex. At all sites, participants were informed of serostatus shortly after their first positive test, so declines after seroconversion can probably be attributed to that knowledge. The results of the case-control study reconfirm that RAI is the sexual practice most highly associated with HIV infection in homosexual men. There also appears to be a slightly elevated, but significant, risk associated with ROI. Additionally, STD and amphetamine use were found to be discrete and persistent predictors of seroconversion in multivariate analyses. Unlike others, no associations were found between nitrite or cocaine use in these men and risk of seroconversion (7). Although the association between STD and risk of seroconversion

after controlling for RAI partners and condom use is marginal, these results (in men with one or more RAI partners) tend to support the hypothesis that a coincident STD facilitates acquisition of HIV infection.

The observation of high levels of sexual activity before and during the seroconversion interval followed by distinct declines in risk behavior after seroconversion are not surprising. High sexual activity during the seroconversion interval is especially important since this is the early infection period, when infection status is generally not known. Viral load can be high immediately after infection, and this period is likely one of high infectivity that can play a significant role in the dissemination of the HIV epidemic (42–45).

In this study, number of RAI partners remains a significant risk factor for seroconversion after controlling for STDs, amphetamine use, and number of ROI partners. Since this variable was entered in the model continuously, it demonstrates that even small increases in numbers of partners can have significant risk effects. Indeed, this risk estimate has an exponential interpretation: the risk associated with having one partner (as opposed to none) is 1.05. The risk associated with having five partners is 1.28, and having 25 partners is 3.39. The validity of this linear interpretation was examined in several ways, including log transforming the number of partners, truncating the outliers, and adding a quadratic term to the logistic model. The results of these analyses showed that we did not have a significant departure from linearity, justifying the use of RAI as a continuous variable in the model.

In a recent study of seroconverters, Ostrow et al. (7) document lower incidence of risky sexual behaviors over time and suggest that these declines are reflected by a lower risk association between RAI and seroconversion. In contrast, in our risk factor analyses, the ORs for RAI and ROI remain stable over the two time periods. Although risk associated with irregular condom use is higher for the later time period, it remains nonsignificant. However, risk associated with STD decreases. These changes may occur as a result of changes in the background prevalence of HIV and STD.

ROI has a slightly elevated but significant association with seroconversion in these men. This association remains stable independent of the number of RAI partners. Although the risk estimate is small, we believe precision is afforded by the design (cases and controls are all seroconverters) and the assessment of risk on a per partner basis. Acquisition of HIV infection from unprotected ROI has been recognized as a potential risk factor in several case studies and brief

reports (5, 10, 11, 46). However, statistical confirmation of this practice is difficult since most homosexual men engage in multiple sexual behaviors. However, by limiting analyses to only those men with one or no RAI partners, we have shown an increase in risk of HIV seroconversion associated with multiple ROI partners, suggesting that some infections may in fact have occurred through this route. Although we did not evaluate condom use during orogenital sex, it is not likely that condom use increased substantially over time. A recent study in San Francisco documents that in 1992, only 6.3 percent of male patients at an STD clinic reported using condoms during orogenital sex (47). Irregular condom use (some/none vs. always) among men with one or more RAI partners was not shown to be significantly associated with higher risk of HIV infection, although a greater proportion of cases reported using condoms irregularly compared with controls. The nonsignificant risk measure may be due to small numbers resulting both from lack of condom data before 1987, when most men became infected, and as a result of paired analyses. Cases were more likely to report more than one RAI partner; however, if not matched to a control, they were excluded from the analysis. Risk associated with condom use and seroconversion is difficult to evaluate because condom use is act specific and can be evaluated only among men who report having partners. Recently, among incident seroconverters, Ostrow et al. (7) reported that unsafe condom use is four times more likely among seroconverters than seronegatives. Lack of power may partially explain why an association could not be established in our study. For the same reason, risk could not be compared over the two time periods; however, condom use increased at all sites over time.

The validity and reliability of self-reported sexual risk behaviors are always subject to question and consideration of possible bias that might occur as a result of under- or overreporting. Generally, if a high risk behavior such as RAI is underreported due to recall bias or reluctance, infected cases are more likely to be classified as nonexposed, influencing the risk measure toward the null. The OR for RAI in these analyses, although low, is within the range reported by others in analyses using RAI as a continuous variable (7), as well as within the range seen in populations that include more low risk people and studies that group partners categorically (17). The risk of ROI, however, may be overestimated if RAI is underreported. Our analysis of ROI as a risk factor, limited to men who report minimal or no RAI, is vulnerable to this bias. An examination of the data revealed that very few men consistently reported no or one RAI partners but that

in fact, behaviors varied over time. Of those with multiple visits who report no or one partner, 82 percent report more partners at other preseroconversion visits. The consistency of the findings of sexual behavior trends as well as the factors described above lead us to believe that inaccurate reporting of sexual risk behaviors does not contribute to bias the results significantly.

The association between amphetamine use and risk of seroconversion was strong in our analyses, even after controlling for number of sexual partners. This relation may possibly be explained by improper use of condoms or increased duration of sexual exertion resulting in an increased risk of breakage or rectal trauma, although no data are available in the TCS to verify this. Other explanations for the risk associated with amphetamine use and HIV infection may be related to type of partner selection or possibly increased susceptibility to infection due to a drug-related effect on the immune system or the sharing of injection equipment. Although data on intravenous drug use were not pooled in this data set, needle sharing was not very common among men in our cohorts; and in the site with the highest prevalence of amphetamine use (San Francisco), only one of 47 seroconverters reported this behavior. Amphetamine use and other drugs have been reported to be risk factors in studies of incident HIV infection (7, 13, 14). Even though other drugs such as nitrites and cocaine were not found to be associated in our study, drug use prevention strategies should be incorporated in HIV prevention and education formats for homosexual and bisexual men.

Two associations were found with respect to STD that are important to discuss. First, gonorrhea was found to be a risk factor for seroconversion after controlling for RAI. Second, having had any incident STD (syphilis, gonorrhea, or genital herpes) was significant in multivariate analyses and marginally significant in analyses controlling for RAI and condom use. Since all men except those from San Francisco were clinically diagnosed for STDs at the time of their visit, these results are not likely to be caused by misclassification or underreporting bias. In addition, failure to report prevalent STDs would lead to an underestimation of the effect, making the estimate of STD risk conservative. Strong evidence exists that STD treatment leads to significant declines in HIV incidence (48). The positive, albeit marginally significant association found between incident STD and HIV seroconversion in this study, after controlling for RAI and condom use, lends support to the theory that STDs are more than epidemiologic markers for behavioral risk and may in fact facilitate HIV transmission.

In conclusion, these data further support the importance of STD prevention and treatment in reducing HIV infections among homosexual and bisexual men.

It is interesting to note behavior after seroconversion. Again, although there are longitudinal declines, substantial numbers of men report continuing to engage in unsafe sexual behavior after having been informed of their change in serostatus. Of interest in this period is the number of men who engage in unprotected IAI, the behavior that is associated with transmission to an uninfected partner (17). Between 1985 and 1987, 40 percent of men with more than two sexual partners reported unprotected IAI. Only a small decline is reported in the later group, 36.5 percent of whom reported having unsafe sex after seroconversion. It is important to point out that the partners' serostatus is not known in these men. Nevertheless, this finding raises the question of whether targeted prevention efforts should be undertaken in HIV-positive men.

The numerous epidemiologic studies investigating risk factors and the natural history of HIV infection begun during the early to mid-1980s enrolled homosexual and bisexual men at risk for what we have come to know as one of the most devastating epidemics in modern times. Public health strategies aimed at reducing risk behaviors in this population have been successful to some extent, as evidenced by the reductions in high risk sexual behaviors seen in this study and others. New studies have shown, however, that younger homosexual and bisexual men are still at risk in many of the same areas that are represented in this study (12, 49-51). To date, prevention of HIV infection is possible only through education programs, behavioral modification, and STD prevention. Recognizing the patterns of risk behavior over time as presented here serves to further increase our knowledge of human sexual behavior and risk factors for transmission and to adapt our prevention programs accordingly.

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