



Per-Contact Risk of Human Immunodeficiency Virus Transmission between Male Sexual Partners

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The risk of human immunodeficiency virus (HIV) transmission from various types of homosexual contact, including oral sex, is of biologic, epidemiologic, and public health importance. The per-contact risk of acquiring HIV infection from specific acts was estimated in a prospective cohort study of 2,189 high-risk homosexual and bisexual men, conducted in San Francisco, California; Denver, Colorado; and Chicago, Illinois, in 1992–1994. During 2,633 person-years of follow-up, 60 seroconversions were observed. The estimated per-contact risk of acquiring HIV from unprotected receptive anal intercourse (URA) was 0.82 percent (95% confidence interval: 0.24, 2.76 percent) when the partner was known to be HIV+ and 0.27 percent (95% confidence interval: 0.06, 0.49 percent) when partners of unknown serostatus were included. There was heterogeneity in per-contact risk, with nine seroconversions occurring after only one or two episodes of URA. The per-contact risk associated with unprotected insertive anal and receptive oral sex with HIV-positive or unknown serostatus partners was 0.06 and 0.04 percent, respectively. URA accounted for only 15 percent of all reported sexual activity by seroconverters. As lower-risk practices become more common, they may play a larger role in propagating the epidemic and should also be addressed by interventions targeting high-risk homosexual and bisexual men. *Am J Epidemiol* 1999;150:306–11.

HIV infections, transmission

Homosexual transmission of human immunodeficiency virus (HIV) continues to play an important role in the acquired immunodeficiency virus epidemic, accounting for approximately one quarter of the estimated 41,000 new HIV infections occurring annually in the United States (1). Numerous studies of homosexual and bisexual men have shown that unprotected receptive anal intercourse (URA) predicts HIV seroconversion. However, most studies have not found significantly elevated risk in association with other types of contact, including protected receptive anal intercourse (PRA), unprotected and protected insertive anal intercourse (UIA and PIA, respectively), and unpro-

tected receptive oral intercourse (URO) (2). Furthermore, only sparse data are available on the per-contact risk of URA, and there are no published estimates of the per-contact risk of these other common sexual practices.

Knowledge of relative per-contact risk may help in designing interventions and projecting their impact. For example, such information might be of use in deciding what exposures should qualify for postexposure prophylaxis and in gauging the importance of risk to the insertive partner in designing rectal microbicides. More-reliable information about per-contact risk may also be of use in counseling homosexual and bisexual men. The risk of URO is particularly controversial, since this practice is often seen as a “safe” alternative to URA, in spite of case histories suggesting infection by this route (3–13).

Estimation of per-contact risk is complicated by complex patterns of exposure among high-risk homosexual and bisexual men. Per-contact risk estimates for vaginal sex have been provided by partner studies of serodiscordant monogamous couples. However, serodiscordant monogamous couples are rare in cohorts of high-risk homosexual and bisexual men, who commonly report multiple partners and multiple types of contact. In imputing the probable route of HIV transmission for homosexual and bisexual men

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Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PIA, protected insertive anal intercourse; PRA, protected receptive anal intercourse; STD, sexually transmitted disease; UIA, unprotected insertive anal intercourse; URA, unprotected receptive anal intercourse; URO, unprotected receptive oral intercourse.

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with multiple types of contact, it has generally been assumed that the highest risk type of contact accounted for infection. This may usually hold, but does not rule out infection via a lower-risk route. In this analysis, we use a modified Bernoulli regression model to obtain information about the per-contact risk of various types of sexual contact from seroconversions in a prospective cohort of high-risk homosexual and bisexual men with complex patterns of exposure. The model also provides information about significant modifiers of per-contact risk, including condom failure.

MATERIALS AND METHODS

Centers for Disease Control and Prevention Collaborative Seroincidence Study

The multisite Centers for Disease Control and Prevention Collaborative HIV Seroincidence Study was a prospective study of high-risk, HIV-uninfected homosexual and bisexual men. Three large cohorts were recruited in 1992 in Chicago, Illinois; Denver, Colorado; and San Francisco, California, and followed for up to 18 months at semiannual intervals. Eligibility criteria included report of anal sex, sexually transmitted disease (STD), and, in San Francisco, unprotected receptive oral sex with ejaculation within the previous year. At baseline and each follow-up visit, pretest counseling and HIV-antibody testing were carried out, and questionnaires were administered to ascertain sexual risk behaviors over the preceding 6 months. We excluded those who reported any injection drug use, since this had been found to be a significant independent predictor of seroconversion (14).

Statistical model

A modified Bernoulli model was used to estimate per-contact risks. The likelihood of remaining uninfected, q , is the product over types of contact of $(1 - p_j)^{n_j}$, where n_j is the number of contacts of type j and p_j is the per-contact risk of transmission for this type of contact. For seroconverters, it is generally not possible to identify which sexual contact first transmitted HIV. However, the infective contact is likely to have taken place in the 12 months before the visit at which seroconversion was documented. Thus, for a seroconverter, the likelihood is $1 - q$, with the values of n_j summed over contacts reported for the two 6-month periods preceding the seroconversion visit. For seroconverters who first tested positive at the third or fourth visit, contacts more than 12 months before the seroconversion visit enter the analysis in the same way as contacts for nonseroconverters. A version of this model has been used previously to estimate per-partner rather than per-contact risk of HIV

seroconversion in an earlier cohort of high-risk homosexual and bisexual men (15).

Counting of contacts

Study questionnaires ascertained the numbers of receptive and insertive anal contacts, URO contacts with ejaculation, and condom failures for the 6-month period preceding each study visit. For each type of contact, these numbers were ascertained separately for a primary partner, the nonprimary partner with whom the study participant had most frequent sexual contact, and all other partners combined. Partner HIV serostatus was reported as positive, unknown, or negative. However, multiple other partners could only be classified as positive or negative if all were positive or negative; otherwise, contacts with these partners were counted as unknown serostatus. Contacts with seronegative partners were excluded from the analysis. Including these contacts would have resulted in substantially lower estimates of per-contact risk.

The proportion of anal contacts partners in which condoms were used was ascertained for each type of contact, partner, and reporting period as a categorical variable with levels "never," "rarely," "some," "about half," and "most," "almost all," and "always." In turn, the number of protected contacts was estimated to be 0, 5, 25, 50, 75, 95, or 100 percent of all such contacts, respectively. Modifications of this schema did not substantially affect results. Episodes of condom failure (breakage or slippage) were reported as protected sexual episodes, along with an aggregate tally of total condom failures. As a result, report of condom failure in a reporting period was treated as a modifier of the per-contact risk of PRA. In exploratory models, no effect of condom failure on the per-contact risk of PIA was found.

Risk and infectivity

Infectivity is usually defined as the per-contact probability of transmission, given that the partner is HIV positive. However, in this high-risk cohort, the great majority of contacts with either HIV-positive or unknown serostatus partners were with the latter group. The relatively high risk of URA made it possible to estimate infectivity with HIV-positive partners separately, but other types of contact with HIV-positive partners were too few, and their risk was too low to provide stable estimates for each of these two partner categories. As a result, we estimated average or pooled per-contact risk, the per-contact probability of transmission with a high-risk partner, which includes HIV-positive and unknown serostatus men.

To the extent that unknown serostatus partners are uninfected, per-contact risk may be substantially lower than per-contact infectivity. However, compared with direct estimates of infectivity from serodiscordant couples, per-contact risk may be of greater use in estimating aggregate transmission risk in high-risk populations in which unknown serostatus partners are common.

Heterogeneity

We addressed heterogeneity in per-contact risk by using a fixed-effects Bernoulli model that allows the per-contact risk p_i to depend on covariates, some of them specific to reporting period, through the logistic transformation. The covariates considered were study site; age; interval history of gonorrhea, chlamydia, and nonspecific urethritis; use of alcohol and recreational drugs, including poppers, cocaine, hallucinogens, and amphetamines; numbers of partners; and condom failure. A qualitative statistical test for unmodeled heterogeneity in per-contact risk of URA and PRA was also implemented in exploratory models by allowing per-contact risk to depend on the log number of contacts of each type. While it is unlikely that per-contact risk systematically depends on number of contacts reported, this augmentation makes it possible to model relatively high cumulative risk after a few contacts and relatively low cumulative risk after many, a previously reported pattern characteristic of heterogeneity (16–18).

Model verification

We carried out a series of simulations to assess the adequacy of the model. Of particular concern was its capacity to estimate relatively small per-contact risks in the presence of much larger risks and its robustness against unmodeled heterogeneity. An additional concern was systematic underreporting of the number of contacts among participants reporting relatively few, in conjunction with overreporting among those reporting many, which has been implicated as another potential source of model inadequacy (19). Simulated seroconversions were generated based on the reported numbers of contacts and per-contact risks reflecting our actual estimates. Heterogeneity in overall respondent susceptibility as well as the risk of individual contacts was modeled by random effects on the logit scale for the per-contact risk of each type of contact. Reporting error was simulated by generating outcomes according to “true” numbers of contacts obtained by shrinking the nonzero reported numbers toward their geometric mean; the model was then fit to the reported numbers. For each pattern of fixed and random effects, 100 simulated datasets were fitted, and then average

per-contact risk estimates were compared with the average of the true values.

RESULTS

The Collaborative HIV Seroincidence Study followed 2,189 homosexual and bisexual men, of whom a total of 60 seroconverted during 2,633 person-years of follow-up. A total of 1,915 men had at least one follow-up visit and reported no injection drug use; there were 52 seroconversions in this group. We analyzed data for 1,583 men, including 49 seroconverters, who reported at least one sexual contact with an HIV-positive or unknown serostatus partner.

Several established risk factors were seen significantly more often among seroconverters, including URA with HIV-positive or unknown serostatus partners, having at least one HIV-positive partner, and condom failure (table 1). Most participants reported multiple partners in at least one reporting period, and monogamous partnerships with an HIV-positive partner were rare. Among seroconverters, only 14 percent reported URA with HIV-positive partners, while an additional 31 percent reported URA with unknown serostatus partners. Provided that subject reporting was accurate, this implies that a majority of new infections took place via other types of contact, which may have included episodes in which condoms were used but failed.

Table 2 shows numbers of contacts included in the analysis. PRA and PIA were the most commonly reported types of contact, followed by UIA and URO. Compared with nonseroconverters, a much larger proportion of the URA contacts reported by seroconverters were with HIV-positive partners. Furthermore, median and mean numbers during periods with at least one contact were uniformly larger for seroconverters.

TABLE 1. Risk factors in the Collaborative HIV* Seroincidence Study cohort, 1992–1994

Risk factor	Seroconverters (%)	Nonseroconverters (%)	<i>p</i> value
Any HIV+ partner	37	22	0.02
URA* with HIV+ partner	14	1	0.001
URA with HIV+/?* partner	45	28	0.01
Multiple partners	96	85	0.03
Monogamous partnership with HIV+ partner	0	7	0.07
Condom failure			
Any	49	32	0.01
In period with PRA*	47	24	0.001

* HIV, human immunodeficiency virus; URA, unprotected receptive anal intercourse; HIV+/?*, HIV-positive or unknown serostatus partner; PRA, protected receptive anal intercourse.

TABLE 2. Numbers of sexual contacts reported by seroconverters and nonseroconverters in 6-month reporting periods in which at least one contact was reported, Collaborative HIV* Seroincidence Study, 1992–1994

Type of contact	Seroconverters				Nonseroconverters			
	Reporting periods	No. of contacts			Reporting periods	No. of contacts		
		Total	Median	Mean		Total	Median	Mean
URA HIV+*	9	169	6.0	18.8	63	395	2.0	6.3
URA HIV+/?*	30	268	2.5	8.9	657	3,507	1.0	5.3
UIA HIV+/?*	30	436	2.5	14.5	1,059	7,124	2.0	6.7
URO HIV+/?*	22	254	3.5	11.5	859	6,387	2.0	7.4
PRA HIV+/?*	62	671	5.0	10.8	2,019	13,126	3.0	6.5
PIA HIV+/?*	58	1,059	4.0	18.3	2,678	20,382	3.0	7.6

* HIV, human immunodeficiency virus; URA HIV+, unprotected receptive anal intercourse with an HIV-positive partner; URA HIV+/?*, unprotected receptive anal intercourse with an HIV-positive or unknown serostatus partner; UIA HIV+/?*, unprotected insertive anal intercourse with an HIV-positive or unknown serostatus partner; URO HIV+/?*, unprotected receptive oral intercourse with ejaculation with an HIV-positive or unknown serostatus partner; PRA HIV+/?*, protected receptive anal intercourse with an HIV-positive or unknown serostatus partner, including episodes with condom failure; PIA HIV+/?*, protected insertive anal intercourse with an HIV-positive or unknown serostatus partner, including episodes with condom failure.

TABLE 3. Estimated per-contact risks for six types of sexual contact between men, Collaborative HIV* Seroincidence Study, 1992–1994

Type of contact	Per contact risk (%)	95% CI*
URA HIV+*	0.82	0.24, 2.76
URA HIV+/?*	0.27	0.06, 0.49
UIA HIV+/?*	0.06	0.02, 0.19
URO HIV+/?*	0.04	0.01, 0.17
PRA HIV+/?*	0.18	0.10, 0.28
PIA HIV+/?*	0.04	0.01, 0.11

* HIV, human immunodeficiency virus; CI, confidence interval; URA HIV+, unprotected receptive anal intercourse with an HIV-positive partner; URA HIV+/?*, unprotected receptive anal intercourse with an HIV-positive or unknown serostatus partner; UIA HIV+/?*, unprotected insertive anal intercourse with an HIV-positive or unknown serostatus partner; URO HIV+/?*, unprotected receptive oral intercourse with ejaculation with an HIV-positive or unknown serostatus partner; PRA HIV+/?*, protected receptive anal intercourse with an HIV-positive or unknown serostatus partner, including episodes with condom failure; PIA HIV+/?*, protected insertive anal intercourse with an HIV-positive or unknown serostatus partner, including episodes with condom failure.

Estimated per-contact infectivity of URA with HIV-seropositive partners was 0.82 percent (table 3), while per-contact risk of URA with HIV-positive and unknown partners combined was 0.27 percent. In contrast, per-contact risk of PRA with HIV-positive or unknown partners was 0.18 percent, although a substantial proportion of this risk may be due to condom failure. Estimated per-contact risk for UIA, PIA, and URO in each case was 0.06 percent or less, substantially lower than the risk for URA or PRA.

Our multivariate model also identified several covariates that were significantly associated with heterogeneity in per-contact risk for given types of contact. For URA with HIV-positive or unknown serostatus partners, per-contact risk was significantly higher in periods in which some of the contacts were with

HIV-positive partners (odds ratio (OR) = 13.8, 95 percent confidence interval (CI): 2.4, 78, $p = 0.003$) or when gonorrhea, chlamydia, or nonspecific urethritis was reported (OR = 12.7, 95 percent CI: 2.4, 66, $p = 0.003$), and among men less than age 25 years at recruitment (OR = 6.3, 95 percent CI: 1.2, 34, $p = 0.03$). Estimated per-contact risk of PRA was also increased in periods in which condom failure was reported (OR = 4.5, 95 percent CI: 1.6, 12, $p = 0.004$). No risk modifiers were found to be significant for UIA, PIA, or URO. In addition, no evidence was found for an effect of study site or numbers of partners on per-contact risk.

Further evidence for heterogeneity in per-contact risk was suggested by nine seroconversions that occurred after only one or two URA contacts with HIV-positive or unknown serostatus partners. In addition, a qualitative statistical test indicated heterogeneity not accounted for by covariates included in the final model. This test suggested similar degrees of heterogeneity for URA and PRA with HIV-positive and unknown serostatus partners, although the result was statistically significant ($p = 0.002$) only in the latter case, owing to the relatively small number of URA contacts.

The simulations showed that if seroconversions occur according to the Bernoulli model, then large and small per-contact risks can be simultaneously estimated with only slight inflation (positive bias) of approximately 10 percent in both. However, in simulations in which susceptibility to HIV infection was allowed to differ between subjects, estimated per-contact risks were too small (negative bias); the degree of this bias increased with the degree of heterogeneity for both the smaller and larger risks and was about 50 percent in a simulation in which heterogeneity was severe.

Differential under- and overreporting of numbers of contacts also caused negative bias of a similar magnitude and in proportion to the degree of misreporting. However, even severe heterogeneity in risk between individual contacts induced no bias.

DISCUSSION

Our results are consistent with earlier epidemiologic findings and confirm that unprotected receptive anal sex is the riskiest of sexual practices for homosexual and bisexual men by an order of magnitude. Our data suggest that this practice remains common among high-risk homosexual and bisexual men; an earlier analysis of these data found that the attributable risk was 47 percent (14). The nine seroconversions that occurred after only one or two URA contacts suggest that if behavioral reporting is accurate some men are at very high risk from URA. Prevention messages must continue to emphasize the importance of avoiding this type of contact.

Our estimate of 0.82 percent for the per-contact infectivity of URA with HIV-positive partners is also consistent with earlier estimates of 0.8–3.2 percent (16). This estimate is roughly twice the estimate of 0.33–0.50 percent for needlestick injuries involving exposure to known HIV-seropositives (20, 21). Furthermore, when contacts with unknown serostatus partners were taken into account, the 0.27 percent per-contact risk of URA remained comparable with the risk of needlestick with a known HIV-positive. This suggests that interventions such as postexposure prophylaxis should not be withheld from homosexual and bisexual men who reported URA with unknown serostatus partners on the mistaken perception that this risk is substantially lower than a needlestick with a known seropositive partner. In addition, domestic prevention programs and studies to evaluate prevention interventions should target homosexual and bisexual men with HIV-positive and unknown serostatus partners rather than focusing on serodiscordant monogamous homosexual couples.

After controlling for having a known HIV-positive partner, the risk of URA with HIV-positive or unknown serostatus partners also appears to depend strongly on age and interval report of STDs. Evidence for an effect of age on per-contact risk of URA with unknown serostatus partners may represent heterogeneity in susceptibility, in that older study participants will, on average, have escaped infection after larger numbers of contacts at the time of recruitment. It may also mean that the younger men are less skilled at learning the serostatus of infected partners and that their partners, also relatively young on average, are less likely to know whether they have been infected.

Increased risk of URA during periods when STDs were reported is consistent with many other reports (22, 23). Estimated per-contact risk of PRA with HIV-positive and unknown serostatus partners, including episodes in which condoms failed, was two thirds the risk of URA with the comparable set of partners. Condom failure does much to explain this finding; estimated per-contact risk of PRA during periods with at least one condom failure was elevated by a factor of more than four. The relatively high risk of PRA may also stem in part from higher HIV seroprevalence among PRA partners, both recognized and unrecognized, and from misreporting of URA as PRA, possibly as a result of stigmatization of URA by prevention campaigns. In addition, the receptive partner may sometimes be unaware of condom failure, which would lead to a spuriously elevated estimate of the per-contact risk of PRA in the absence of condom failure. The analysis shows that while condoms provide considerable protection when used correctly, condom failure poses substantial risk for the receptive partner in anal sex. This suggests that report of any receptive anal intercourse (URA or PRA) with an HIV-positive or unknown serostatus partner would be an efficient inclusion criterion for studies evaluating prevention interventions. Furthermore, the apparently large risks of URA and PRA suggest that high-risk homosexual and bisexual men should be encouraged to learn the serostatus of their sexual partners and take this risk into account in making decisions about sexual activity.

For UIA, PIA, and URO, estimated per-contact risk was lower than for URA by approximately an order of magnitude and was about equal for each of the three. On the basis of this analysis, zero risk cannot be ruled out, but case reports make it clear that seroconversions occur by at least one of these routes. The low risk of UIA suggests that risk to the receptive partner should be the primary consideration in the design of rectal and possibly vaginal microbicides in settings in which STDs are uncommon; however, penile or urethral inflammation caused by the microbicide or concurrent STD might increase risk to the insertive partner and must be evaluated in safety trials of microbicides. To the extent that UIA and URO become more common among high-risk, HIV-negative homosexual and bisexual men, substantial numbers of seroconversions could result. Thus, it is important to communicate clearly that these practices are not without risk.

The study has several limitations. In total, only 49 seroconversions were included in the analysis, the number of seroconversions associated with specific types of contact (in particular, URA with an HIV-positive partner) was small, and the risk of several types of contact appears to be low. In addition, most participants had

multiple kinds of exposure with multiple partners—there were no seroconversions among men reporting only URO—and these were ascertained by self-report, which may be both biased and imprecise. As a result of these limitations, we were able to estimate per-contact infectivity only for URA; for the other types of sexual contact, we could only estimate per-contact risk with HIV-positive and unknown serostatus partners combined, and the resulting estimates are imprecise. In addition, simulations showed that severe heterogeneity in susceptibility to HIV infection could induce substantial downward biases in our estimates of per-contact risk, although these were less than an order of magnitude and appeared to be uniform across types of contact.

While these biases should not seriously affect the absolute or relative order of magnitude of our estimates of the per-contact risk of various types of contact, we did find significant evidence of heterogeneity in the per-contact risk of URA and PRA and may simply have lacked power to detect analogous heterogeneity in the per-contact risk of UIA, URO, and PIA. Heterogeneity in per-contact risk may arise from factors affecting the infectiousness of the HIV-positive partner, including viral strain, disease stage, cell-associated or plasma viral burden, antiretroviral treatment, and concurrent infections, especially STDs. Similarly, the susceptibility of the seronegative partner may depend on recently discovered mutations in chemokine receptors (24, 25); HLA genotype (26); and considerations such as micro-trauma, bleeding, or STD in the receptive partner. It is important to point out that because of heterogeneity, per-contact risk for any individual may be considerably higher than the average. Thus, these estimates are useful for assessing population-based risk, but should under no circumstances be interpreted as absolute risks at the individual level.

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