Female-to-Male Transmission of Human Immunodeficiency Virus

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Objective.—To examine rates of heterosexual transmission of human immunodeficiency virus (HIV) and associated risk factors and to determine the relative efficiency of female-to-male and male-to-female transmission.

Design.—Survey of infected individuals and their heterosexual partners recruited since 1985.

Setting.—Participants were recruited from various HIV counseling and testing sites throughout California but were generally interviewed and tested in their homes.

Participants.—Data from 379 couples at entry to the study are reported: 72 male partners of infected women and 307 female partners of infected men. The infected index case had a well-established source of risk; couples were eliminated if the direction of transmission could not be established. The majority of couples were monogamous since 1978, white, and in their 30s. Most partners did not know their serostatus at entry into the study.

Main Outcome Measure.—HIV serostatus in the exposed sexual partner.

Results.—We observed one probable instance (1%) of female-to-male transmission compared with 20% transmission rates in the female partners of infected men. All couples were sampled in the same way. Male index cases were more likely to be symptomatic than female index cases.

Conclusion.—The odds of male-to-female transmission were significantly greater than female-to-male transmission. The one case of female-to-male transmission was unique in that the couple reported numerous unprotected sexual contacts and noted several instances of vaginal and penile bleeding during intercourse.

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AS OF April 1991, a total of 7048 (4%) of the cases of acquired immunodeficiency syndrome (AIDS) among adults and adolescents that were reported to the Centers for Disease Control was attributed to heterosexual contact with a high-risk or infected partner.[1] Seventy percent (4948) of these cases occurred among women and 30% (2100) among men. These cases among men represent 1.4% of all reported male cases in individuals over 13 years of age compared with 29% of all cases in women. Cases involving heterosexual contact constitute the only risk category of AIDS cases in which the number of female cases exceeds the number of male cases.[2] This excess, which has been noted since early in the epidemic,[3] may simply be due to the fact that more men than women have been infected and therefore can potentially infect their female partners. However, it could also reflect differences in the efficiency of male-to-female compared with female-to-male transmission.

See also pp 1657 and 1695.

The most effective method to investigate the efficiency of the heterosexual transmission of human immunodeficiency virus (HIV) is through studies of heterosexual partners that enable researchers to evaluate direct viral transmission and associated risk factors between specific individuals. Table 1 shows the results of a number of such studies that have examined the male partners of infected women according to the risk groups of the women.[4-19] When there is insufficient information to specify the risk group, or when the women are from a variety of risk groups, the risk group in Table 1 is labeled "mixed." Variation between studies is evident from the table. The proportion of infected men ranges from no transmission among men whose wives became infected through artificial insemination to greater than 70% in partner studies in "type II" countries where heterosexual transmission is the major mode of spread. Because of these discrepant findings, controversy still exists as to the efficiency of female-to-male transmission; hypotheses that explain this variation are discussed below. This study examines male partners of women from a variety of risk groups. Our main objective is to study HIV serostatus and risk factors for transmission in

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Table 1.—Female-to-Male Transmission of Human Immunodeficiency Virus

Risk Group*	No.† (% Infected)	Reference
Artificial insemination	4 (0)	4
Transfusion-associated	25 (8)	5
	4 (0)	6
Intravenous drug use	49 (4)	7
	18 (5)	8
	19 (5)	9
	13 (15)	10
	14 (50)	11
Mixed-risk group	11 (0)	12
	65 (11)	13
	100 (11)	14
	64 (16)	15
	15 (33)	16
	17 (65)	17
Haiti	38 (61)	18
Central Africa	78 (73)	19

*Risk group or area of residence of infected female index case.
†Number of male partners of human immunodeficiency virus–infected women in each risk group.

Table 2.—Risk Group of the Index Case

Risk Group	Female Partners of Infected Males (n=307), No. (%)	Male Partners of Infected Females (n=72), No. (%)
Bisexual	125 (41)	...
Hemophiliac	36 (12)	...
Intravenous drug user	73 (24)	21 (29)
Transfusion-associated infection	14 (4)	12 (17)
No identified risk*	28 (9)	10 (14)
Bisexual + intravenous drug user	31 (10)	...
Heterosexual partners	...	29 (40)

*All of these couples were discordant for human immunodeficiency virus infection. If both partners were infected, they would have to be eliminated from the analysis because we would not be able to determine the direction of transmission.

heterosexual partners of HIV-infected individuals and to determine the relative efficiency of female-to-male compared with male-to-female transmission.

SUBJECTS AND METHODS

Sample

Since 1985, we have been conducting a study of the heterosexual transmission of AIDS in which we enroll the opposite-sex partners of individuals infected with HIV. Entry-level results are presented herein for participants recruited through March 1991. The study protocol has been approved by the University of California–San Francisco Committee on Human Research. We report herein on 72 male, non–drug-using partners of infected women; 307 non–drug-using female partners of infected men are presented for comparison. Detailed results from the latter group have been presented elsewhere.[20-22]

Couples were recruited without regard to the gender of the index case, and over 75% of the sexual partners did not know their serostatus at entry into the study. More than 70% of recruited couples have been monogamous since 1978, and more than 90% of participants reported only one partner in the 6 months prior to enrollment.[20] The direction of transmission in concordantly infected couples was determined through risk histories; in all couples the infected index case had a well-established source of risk. If the source of transmission, and hence the direction of infection, could not be established with certainty, couples consisting of two infected partners were eliminated from the study. Fourteen such couples were recruited but have been excluded from the analyses presented herein.

Infected individuals were passively recruited from a variety of sources throughout California (confidential test sites, local departments of public health, clinics, physicians, and research studies). They were counseled to refer their heterosexual partners for HIV testing and counseling and were informed about the study. At the time of recruitment, the serostatus of the presumed originally uninfected partner was ascertained together with a retrospective risk history of sexual practices between the partners. After the risk assessment, couples received extensive counseling and education about HIV risk reduction. Participants were interviewed in their homes or in local clinics. Study protocol and data collection methods have been previously described.[21]

Statistical Analysis

Statistical comparisons of infection rates were based on the binomial distribution. A summary odds ratio comparing direction of transmission and associated confidence limits was computed using exact (conditional maximum likelihood) methods stratifying by number of contacts.

RESULTS

Table 2 presents the risk group of the index case for all couples according to gender. Most of the female index cases (40%) were infected from heterosexual partners. These represent those HIV-positive women who had originally acquired their infection from other male partners but who had subsequently acquired new partners. Table 3 compares the distribution of risk factors associated with risk of heterosexual transmission of HIV[3-22] between couples with men as the index case and between couples with female index cases. All of the risk factors refer to sexual practices engaged in by the couple except for index diagnosis (AIDS or symptomatic) and index case CD4 level less than or equal to 200/mm^3. These factors refer to the status of the index case at recruitment and therefore do not necessarily reflect the disease status of the index case at the time sexual contacts occurred between the partners. Nevertheless, when the index case meets these criteria, it is possible that a larger proportion of contacts between the partners occurred when the index case was at a more advanced state of HIV disease. One significant difference in risk factor distribution emerged: infected men were more likely to be symptomatic than infected women ($P<.01$).

There were no significant differences in demographic factors according to the gender of the index case except that we recruited more Latino couples with an infected male index case. All but 15 couples in the study were concordant for race. Sixty-nine percent of couples consisting of female partners of infected men were white, 12% were black, and 16% were Latino, compared with 77%, 10%, and 4%, respectively, of the couples consisting of male partners of infected women. The remaining couples were from a variety of backgrounds. The ages of participants ranged from 17 to 71 years, and more than 50% of couples (regardless of the gender of the index case) were between 30 and 40 years of age.

Sixty-one (20%) of the female partners of infected men and one (1%) of the male partners of infected women were infected at the time of the study. The crude odds ratio comparing the odds of occurrence of male-to-female transmission compared with occurrence of female-to-male transmission was 17.5, (90% confidence interval, 3.5 to 353; $P<.0001$). Odds ratios remained elevated when stratified by number of contacts. To perform this analysis, we calculated the number of episodes of vaginal or anal intercourse taking place after the estimated date of infection for the index case.[22] For example, when the number of contacts was stratified by six categories (<10, 11 to 100, 101 to 200,

Table 3.—Risk Factor Distribution (Couples With Each Risk Factor)*

Risk Factor	Female Partners of Infected Males (n=307), No. (%)	Male Partners of Infected Females (n=72), No. (%)	P
Anal intercourse	112 (37)	26 (36)	NS
Bleeding during sex	44 (14)	15 (21)	NS
No condom use	184 (60)	40 (56)	NS
Sex during menstruation	223 (73)	45 (63)	NS
No. of contacts (mean, median)	405, 225	388, 289	NS
Index diagnosis (% symptomatic or having AIDS)	155 (50)	23 (32)	<.01
Index case CD4 ≤200/mm³	36 (12)	10 (14)	NS

*NS indicates not significant ($P>.05$); and AIDS, acquired immunodeficiency syndrome.

201 to 500, 501 to 800, >800) the adjusted odds ratio was 18.7, (90% confidence interval, 3.7 to 378; $P<.0001$). Thus, any difference in the efficiency of transmission cannot be explained by differences in the number of exposures.

Small numbers make further stratification on such variables impractical. Similarly, because we observed only one instance of female-to-male HIV transmission, statistical comparisons cannot be made between this couple and those in which transmission did not occur, and thus associated risk factors could not be evaluated. Nonetheless, several factors are worthy of note in this couple.

Case History

The female index case of the infected male partner became infected through heterosexual contact. She knew of exposure to at least three prior partners (none of whom was her husband) from identified risk groups. She participated in a "swinging singles" club and, over the 5 years prior to entry in the study, had over 600 male partners, including over 2000 contacts with a bisexual man, an unidentified number of contacts with an intravenous drug user, and over 1000 contacts with a person she knew to be HIV-infected. Her husband (the male partner in the study) had only three female partners over the same time period, none of whom he knew to be at risk. To verify the accuracy of the interview, the couple was interviewed by three different interviewers at different times using a modified form of our standard risk questionnaire.

The couple reported an average of 15 sexual contacts a month for the last 7 years. Almost all of these contacts consisted of unprotected vaginal-penile and oral intercourse. The couple practiced anal intercourse twice. The couple never used condoms. This couple also had some unique sexual practices. As part of their "swinging" activity, the woman would frequently have sexual intercourse with another partner while her husband first observed and then had intercourse with her immediately after the other partner.

This couple reported both vaginal and penile bleeding during intercourse. Among all partnerships, observed bleeding during sex was usually either of vaginal or rectal origin. However, there were six other couples with a female index case in the study that reported penile bleeding during sexual intercourse over the last year, and the average number of times this was observed among these couples was four, with a range of one to 20 times. In contrast, this couple reported over 100 episodes of both vaginal and penile bleeding. The cause of this bleeding could not be established. Medical data were available only by history, and over the last 5 years, the woman reported four cases of vaginal yeast infections, both reported one case of trichomoniasis, and the man reported one case of urethral gonorrhea. In addition, the woman reported a history of endometriosis and had a hysterectomy during the year prior to entry in the study. The bleeding was not associated with menses as both partners reported vaginal-penile intercourse only rarely when the woman was menstruating.

COMMENT

Although we were able to examine female-to-male transmission only through a single case history, several factors emerged that are consistent with hypotheses about heterosexual transmission of HIV and that may be relevant in explaining prevalent female-to-male transmission in type II countries. Most important is the observation of repeated bleeding during intercourse. This is consistent with theories that postulate that open lesions from sexually transmitted diseases facilitate transmission.[23] In this couple, bleeding may have been related to endometriosis or hysterectomy, although it is unclear how these conditions could have affected penile as well as vaginal bleeding. The importance of sexual intercourse with one partner immediately following intercourse with another, high-risk partner is noteworthy. To account for HIV transmission from female prostitutes, early in the epidemic Wykoff[24] speculated that the vagina could act as a receptacle for infected semen from one man that could then infect subsequent partners. Although we are not speculating about the plausibility of this mechanism, we cannot discount it as a possibility.

The odds ratio for male-to-female compared with female-to-male transmission was significant and is unlikely to be explained by differences in the distribution of risk factors (Table 3). One risk factor (disease stage in the index case) differed in that more male index cases were symptomatic. Although disease stage has not been a significant risk factor for male-to-female transmission in our study,[20-22] it has been significant in other studies (eg, reference 16).

Even though we have no reason to suspect the accuracy of our risk histories, because both partners in this case history were not monogamous, we cannot be absolutely certain that we correctly classified this case as female-to-male transmission. Thus, it is possible that the discrepancy between the efficiency of male-to-female compared with female-to-male transmission in this study could be even greater. Of course, because we are relying on risk histories, the same caveats apply to classification of male-to-female cases of transmission as well. In other studies[25-28] that have compared the efficiencies of male-to-female and female-to-male transmission in type I countries, male-to-female transmission was always more efficient, although not to the extent observed herein (odds ratios range from 2.9 to >5.0); however, these estimates overlap with the lower bounds of our confidence interval.

There are several explanations for differences by study, risk group (Table 1), or gender. First, individual variations in infectiousness and/or susceptibility may confound transmission rates between studies. Per-contact infectivity rates are likely heterogeneous[22] and their distribution may vary. Likewise, the distribution of other cofactors that may facilitate transmission (eg, stage of HIV disease, sexually transmitted diseases) may also differ depending on the study. In addition, studies may not have adequately controlled for other confounding nonsexual routes of transmission such as risks associated with intravenous drug use. At first blush, cases that appear attributed to heterosexual transmission may, after in-depth inter-

viewing, actually be linked to other sources of risk.[29,30]

Finally, because partner studies are by definition not random samples, and most reported results are based on retrospective or cross-sectional analyses,[31] some studies may overselect couples in which both partners in a couple are infected because such couples may be more easily identified, thus biasing transmission rates. Furthermore, it is often difficult to establish the source of infection in such couples. When few prospective data are available, enrolling monogamous couples in which the serostatus of the partner is unknown, as was the case for most couples in this study, is one of the only ways to control for this bias.

Because we observed only 72 couples with women as infected index cases, results are difficult to generalize. These women and their male partners were recruited in a fashion identical to recruitment of the female partners of infected men in the study, thus reducing the chance of selection bias affecting the comparison of male-to-female with female-to-male transmission. The small sample size is a reflection of the relatively small reservoir of infected women compared with infected men. Low rates may be attributed to what is as yet a relatively early phase of the epidemic among heterosexuals (especially women) and may explain why we observe fewer symptomatic female index cases. Finally, a distinction must be made between low risk and no risk, and caution must still be exercised with unknown partners regardless of their gender.

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